FDA-AACR-ASTRO Clinical Development of Drug-Radiotherapy Combinations Workshop

Transcript: Introduction and Session I: Preclinical Considerations

T. Lawrence: 00:01:18 Okay. It's 8 o'clock. I think we're going to get started. We're going to try hard to run on time today. Good morning. On behalf of the American Association of Cancer Research, I want to thank everybody here and out in ethernet land for joining us today. I'm Ted Lawrence. I'm the immediate past chair of the AACR Radiation Sciences in Medicine Working Group which is a relatively recently formed group within the AACR that's helped to energize radiation research in both the clinical and basic science level.

00:01:47 The AACR is very proud to be co-sponsoring this workshop with the US Food and Drug Administration and the American Society for Radiation Oncology for ASTRO. Along with my co-chair from AACR, Dr. Steve Hahn whom I just saw and is here somewhere. There he is, over there. We are thrilled to co-chair this meeting with two co-chairs from ASTRO, Drs. Marka Crittenden and Phuoc Tran, and one co-chair from the FDA, Dr. Amanda Walker who I'm going to talk a little bit more about in a moment.

00:02:19 So the goal of this workshop is to bring awareness to the oncology community at large on the need to develop drugs in combination with radiation. As many of you know, drugs often get developed completely on their own and then after years of development, radiation therapy is finally able to be introduced in combination with these drugs when, in fact, some of their greatest effectiveness could be in combination with radiation. So, the goal of this workshop is to bring together academia, government and industry to figure out how we can introduce radiation sooner into the drug development pathway.

00:02:54 So, I'm happy to report that as of last night, we have nearly 400 people registered for this workshop, which I think is remarkable. In addition, there are 150 people registered to attend the workshop here in Bethesda. We have 250 people who are webcasting in. So, that's the total of 400. We're very excited about that.

00:03:13 So, in addition to AACR and ASTRO sponsoring this workshop with the FDA, this workshop has been supported in part by Cancer Research UK Combinations Alliance, Bayer Healthcare Pharmaceuticals Incorporated, and AstraZeneca. And we are extremely grateful for their contributions to this meeting which permits us to bring people together to make these kinds of advances to bring drugs and radiation together. The AACR is always looking for opportunities to engage on important regulatory issues, and the AACR looks forward to a continued productive partnership with the FDA.

00:03:48 So, I want to thank all of you for joining us today. Now I'm going to turn it over to my fellow workshop chair, Dr. Amanda Walker, after I say that she is an amazing power house who pulled this meeting together in a remarkable way from the AACR and ASTRO. You are a force of nature, Dr. Walker, and I thank you very much for pulling this meeting together.

Walker: 00:04:17 Thank you very much, Dr. Lawrence, for the kind introduction and good morning everyone. I'm Amanda Walker. I'm a radiation oncologist. I'm a medical officer in the Office of Hematology/Oncology Products at the FDA, and I'm also an acting associate director in the FDA's Oncology Center of Excellence. I'm truly pleased and honored to be here this morning.

00:04:36 So first, I'd just like to take a moment to thank AACR and ASTRO for co-sponsoring this workshop. I would also like to thank my co-chairs, Dr. Lawrence, Dr. Hahn, Dr. Crittenden, and Dr. Tran. Thank you for being so generous with your time and your expertise in putting this together. I would also like to thank Dr. Ricky Sharma for his guidance and his help in transforming this workshop really from what was just a conversation in the conventional hall at ASTRO into what is about to transpire over the next two days. Really, none of this would have been possible, again, without AACR, and from a logistical standpoint, Anna Sadusky, Sarah Martin, and Josh Britton have been phenomenal in sort of making all this happen. Having everything run so smoothly so far. So, thank you very much. Truly phenomenal.

00:05:24 So, why are we here today? So, as Dr. Lawrence mentioned, the purpose of this workshop is really to provide a forum to discuss some of the challenges, both real and perceived, in drug development with radiation. As most of you are aware, radiation is a critical component in the management of many types of solid tumors. For example, in the neoadjuvant setting for esophagus and rectal cancer, in the definitive setting for lung and head and neck cancer, and it's used in the adjuvant setting for a number of tumor types including breast cancer. And, of course, radiation is used as a palliative treatment in patients with metastatic disease. And in recent years, the field of radiation oncology has undergone a remarkable transformation with substantial improvements in treatment planning and delivery, including the use of stereotactic body radiation therapy and image guidance which allows us to insure the radiation is being delivered precisely where we intend for it to be delivered.

00:06:15 Medical oncology, at the same time, is also undergoing a remarkable transformation with the development of novel targeted therapies. As an example, our office at the FDA is really setting records in terms of new molecular entities entering the market each year, and the number of new indications that are granted. So while both fields, medical oncology and radiation oncology, have made significant advances in parallel, very little has changed in terms of the drugs that we use in combination with radiation. In fact, over the past ten years again, our office at the FDA has approved over 200 new indications and not a single one of those indications was for use specifically with radiation. So why is this a problem?

00:06:56 So keep in mind that in each of the prior clinical examples I provided. Radiations delivered as a component of curative therapy. Of course, as we all know, not every patient that receives treatment is not cured. Even when the radiation is delivered concurrently with chemotherapy. So, the bottom line is we can do better and our patients deserve better. Increasing the rates of cure shouldn't have to come at increasing the rates of toxicity. And one solution, although there may be many, is to develop drugs with radiation.

00:07:24 And what about in the metastatic setting where radiation therapy isn't necessarily part of a curative regimen? Well, there is a mounting body of evidence to suggest that a paradigm shift is on the horizon, whereby radiation can be used to enhance the effect of a systemic therapy and a drug-only approach to treating metastatic disease may not be the best approach.

00:07:43 Radiation drug combinations hold great promise, and I hope that over the next two days we can have productive conversations about the optimal paths forward. Because, again, we can do better and our patients deserve better.

00:07:55 So, this workshop begins with two standalone introductory presentations by Dr. Richard Lawrence and Dr. Sharma, followed by four major sessions that are going to take place over two days. Session I will focus on the considerations for non-clinical evaluation of radiation drug combinations, and Session II this afternoon will focus on the clinical considerations including trial design, radiation quality assurance, regulatory end points for approval, and patient reported outcomes. Tomorrow, we'll begin with Session III focusing on immunotherapy, followed by Session IV which will focus on other targeted agents with radiation. There's more to look forward to tomorrow with a debate, as well as an excellent standalone presentation on biomarkers.

00:08:35 As you can see on the agenda there are several panel discussions throughout the workshop. So, I want to emphasize these are intended to be interactive. Don't be shy. Ask questions. You can ask questions in person, obviously, but also folks can ask questions via the webcast.

00:08:51 So just a few housekeeping points. The restrooms are outside the door. Wifi password is on the table. We're trying to stay on time just for the courtesy of everyone on the room, but also for those on the webcast, as well, who might just be dialing in to see one presentation. And then lunch is on your own, unfortunately, our apologies, but coffee will be served during the break, at least the morning break for sure. So, with that very brief introduction, I want to say thank you again for attending and I'll hand it over to Dr. Richard Lawrence for his thoughts on improving collaboration with industry.

R. Lawrence: 00:09:33 Hi. Good morning. I'd like to thank Amanda and the other co-chairs for this certain invitation to talk. So, I slightly repositioned this talk, and I've renamed it Drug Radiation Combinations: Mixed Opportunity and How To Fix It.

00:09:57 Just say the ideas presented here represent only myself and these are my conflicts of interest. Here's an overview of what we're going to see. We're going to talk a little bit about the missed opportunity. We're going to talk about pharma-society interdependence, pharma-society difficulties, the life and death of the drug, previous government attempts to fix the situation, and then at the end we're going to concentrate on a new games theory approach to fixing this situation.

00:10:26 So this slide really encompasses what I call the missed opportunity. These are two studies you may well know. Two phase 3 studies of cetuximab. On left-hand side we see the role of cetuximab in metastatic colorectal cancer. On the right-hand side, cetuximab combined with radiation of treatment of head and neck cancer. In both studies, the addition of cetuximab improved median [inaudible 00:10:50] survival. However, on the left-hand side you can see that by the time we get to eighteen months, the two lines have come together and there's no impact on longterm survival. Whereas, on the right- hand side, the two lines stay apart and slightly come apart slightly more over time implying that cetuximab has actually induced a cure when combined with radiation. Whereas, in the metastatic setting it's merely a palliative agent.

00:11:17 If one looks over the past twenty years or so of radiation drug combinations, aside from esophageal cancer in the cross regimen which was just repurposing of known agents, the very last big piece of news is [inaudible 00:11:34] being applied with cetuximab in head and neck cancer. And just so we know, 2006 is in the pre-iPhone era. So all the time that we could've had 10 iPhones, but no new drug radiation combinations.

00:11:50 So, why is it that we don't have more combinations with radiation? Is it because radiation drug combinations don't work? I think the answer is no. I think it's simply because ... I don't want to say we're not trying hard enough, because all of us in this room are trying very hard, but we're just not ... Let's put it this way, the reason we're not hitting the target, or in darts the reason that we're not hitting triple 20, is simply because we're not throwing enough darts. You can see both in the Phase I and the Phase III settings these are analyses we did of clinicaltrials.gov, you can see that less than 10% of studies involve radiation. You know, there just aren't enough studies there so the chance of hitting the triple 20 is really rather low.

00:12:34 So let's talk about interdependence, the way that both pharma and society depend upon each other. We could be a little nostalgic and think about the good ole' days. This is what's called the Birth of Modern Medicine: The first randomized controlled study performed at 1948. A few words of history: 1948 Britain was bankrupt post WWII and tuberculosis was a significant public health problem. There were news from the United States there was a new drug called Streptomycin that had some effect but the drug was very expensive and the government couldn't really afford it. And they said, before we start paying for this drug for the population we need better proof that it really does something. So they went to this fellow called Austin Bradford Hill who later would become the Father of Medical Statistics and he designed, which at that time, was a new entity but what we now call a Randomized Controlled Study that showed that Streptomycin indeed improved overall survival, and hence it became indicated and given also in the United Kingdom.

00:13:32 If you look in the manuscript in the PDF, no word is mentioned about who supplied or who produced the drug. It seems to be a purely academic study. However, in reality, the drug was produced and supplied free of charge by Merck and Company. There has never been a Golden Age of academic medicine. There's always been an independence between society and the pharmaceutical company whether we disclosed it or not. So we need each other. On the one side, pharma definitely needs society and the academic community for the basic research. They need physicians to accrue the patients. They need the FDA to approve the drug. They need the physicians, once again, to prescribe the drug. Insurers have to pay for the drug. So, pharma definitely needs society, but we as society also need the pharmaceutical world, because it's the companies who really know how to do the drug [inaudible 00:14:21], discovering the chemical optimization. They know how to run high-level clinical trials, and to get good accrual, and how to produce the drug. Ultimately, we need each other.

00:14:32 However, in all good marriages, there are also difficulties and little frustrations between us. So, on the one hand industry is frustrated by the amount of regulation which adds to the high cost of developing new entities, and perhaps may also add to the fact that there's a low-level success of the face we know ... The so-called product drought. They're also frustrated by the short length of patents. On the other hand, in society there's frustration that the pharmaceutical world doesn't always push in the right direction. The so-called neglected areas: pediatrics, the elderly, rare orphan diseases, and what interests people in this room is radiation drug combinations that seem never to quite hit the limelight. Society is frustrated by the high cost of drugs. And our society also has frustrations not connected to the pharmaceutical industry. For instance, the fact that whenever society tries to put its foot down and say maybe this drug is too expensive, maybe this drug is not effective enough, that can cause outpourings of popular support, newspaper and television articles, etc, trying to persuade the regulators to approve a drug which in reality may have limited efficacy.

00:15:45 Just to say that the world is a little more complicated than I said, when I say society also actually reflects different entities. There's the government itself, there are physicians, patients, the payers or HMOs and, of course, big pharma. So really, each of these different entities is pulling in slightly different directions and each has their own agenda.

00:16:09 So, let's take a little understanding of the life and death of a drug because I think it's important to understand how pharma work. So, again, this is as little analysis we did of clinicaltrials.gov from a mathematical perspective. So, let's look at the bevacizumab of Avastin, and here on the Y axis you can see the number of new trials started each year, and on the X axis you can see the [inaudible 00:16:32]. You can see there's really a take off around 2004-2005. That's when they achieved FDA approval. It went up sharply and then it went down. And as you approach patent end really the interest in the drug really dies down and almost disappears. So, when I first did this I thought this was just something unique for Avastin. However, then we looked at four other agents, Alimptor, etc, and we see exactly the same pattern. There's always that spike at the time of or just after FDA approval and then the number of trials quickly drops down, and as we reach the patent end interests by the pharma company or whoever's sponsoring these trials really disappears almost completely. That's looking at all clinical trials.

00:17:18 What if we look at radiation? So this is the same graph but here the red tops of each of the bars is the number of radiation trials. You can see here that radiation starts at just about the time of FDA approval give or take a year and then ... You know I used to be a Boy Scout and we used to be about trying to get the fire going. You know there'd be kind of a little burn trying to get it into a big blaze. Well, the blaze never happens because we just kind of muddle along for a couple of years and then we die out with everybody else. We never really get there. A couple of years ago I tried to quantitate this with a talented medical student who's just now finishing his residency at Rush, Phillip Bloominfeld, and we looked at about 20 or 30 new agents and we analyzed the life and death of these drugs.

00:18:07 So, here from 0 years is the opening of the first Phase I study without radiation to patent expire age which is on median of 21 years after the first clinical study. And you can see here that, generally speaking, that they get FDA approval after 7 or 8 years. But happens with radiation? Now that we see the lower part of the figure, you can see that generally speaking that the first radiation Phase I study happens about 6-7 years after the first Phase I study without radiation. And then even if everything was to run to time and work very efficiently, we'd expect to get the first positive Phase III style approximately 15-16 years into the life cycle of this drug. The truth is it's too late because then the pharmaceutical companies only got a limited number of years to make any money out of that drug before patent expires. So the fact is, if you start a combinations radiation too late it's really nobody's interest to carry on. And that, unfortunately, is what happens too often.

00:19:14 Previous government attempts to influence the situation gets things going. So there's been a whole series of legislation. This is from a US perspective over the years. The most famous is the Hatch Waxman Act from '84, but there've been other attempts as well. And the bottom line of all these pieces of legislation by Congress have been to provide market exclusivity to promote public health goals. In other words, you do what we want you to do and we'll give you an extra "X" months or years of patent extension. For instance, in the pediatric exclusivity provisions it said if you do clinical trials in the realm of pediatrics, just to make the effort, wherever the results are, we'll give you an extra "X" years of patent extensive. So, all of these pieces of legislation were made with good intents, however, in reality, none of

these things really worked out the way they were intended. For instance, in the world of the pediatric indications, so pharmaceutical companies often tested drugs which weren't really relevant and they got their patent extension without really impacting medicine in any significant way.

00:20:25 For instance, I think Lipitor was tested in the pediatric population. Why? I'm not quite sure but they were awarded for that because that wasn't specified in the legislation. So, we got here a quote from the newbound quarterly: "These incentive programs have been characterized by misuse and may actually [inaudible 00:20:44] to the misuse or harmful secondary consequences."

00:20:49 Here's a fascinating paper for the New York Journal a few years back looking at cocca cine drug that our grandfathers knew about. Maybe also our grandmothers so that there's no discrimination here between men and women. Knew about cocca cine, however, there was this whole story about a couple of years ago that some of these companies started testing it and they got patent exclusivity, and the price zoomed up. Likewise, from an ecological perspective these are two papers from the ASCO Post and from blood saying, you can see one's called Subverting the Hatch Waxman Act. How pharmaceutical companies are taking these laws and they've applied them correctly. Nobody's breaking the law, but in the end the end consequences were not what was expected and really didn't deliver what we wanted to see.

00:21:33 There is some literature about how you can use persuasion in order to change companies, and I'm not going to go through the slide in detail, just myself and my team did some thinking and we came up with various techniques you could use to persuade pharmaceutical companies and I'm willing to discuss these over a cup of coffee and give you some details.

00:21:52 But what I really want to go on is talking about Game Theory. So, I'm really grateful for Amanda when she phoned me up ... It wasn't very long ago, actually ... About two months ago, and it gave me the emphasis really to do what I wanted to do a long time, and I just shot off some emails to people that I don't know at all in the Game Theory world and said can we sit down over a cup of coffee and discuss this situation. So, the first thing I learned is that if you want a good cup of coffee, a Game Theory academic may not be the correct person to go to. But I'm now going to teach Game Theory as I understand it from a clinician's perspective.

00:22:37 The first about Game Theory knowledge is that everyone has an objective and if you try to present everyone wants the world to be a better place you're not going to get anywhere. Everybody's got their own agenda. Companies are driven by their own benefit to make money and they exploit rules for their own benefit. And the job of governments or whoever creates the rules is to try and create a set of instructions and rules that will encourage companies to address societies needs to move from this situation to this situation.

00:23:09 So the world of pharma ... If we have any doubt about what pharma's all about we've got a quote here, so you've got a reference as well. "Pharmaceutical companies are in the business of making money by selling pharmaceuticals. Profit equals sales minus cost - this is 101 Economics. So, at the [inaudible 00:23:26] a socialist criticism of the western world is just the way that we work. So, I grew up on Margaret Thatcher. I'm a capitalist, right? But, I think if we ... The fact is that companies want to make profits and if, just to say, Pfizer was to

go bankrupt tomorrow it would be to nobody's benefit. It would be a complete disaster. So, we need companies to survive.

00:23:47 And just to say costs here don't just mean dollar costs. It can mean taking risks with new entities. It can be distractions, external expertise, etc, etc. So, what are the implications of this profit module? So, the way things are today, pharmaceuticals make money through selling tablets. I mean, it can be effusions, capsules, but let's say tablets because it's a nice word. So if companies make money selling tablets, then the pharmaceutical companies are going to make and want to sell an awful lot of tablets and they're also going to encourage people to prescribe tablets for long periods of time. To put it bluntly, the dream drug for pharmaceutical companies would be 40mg twice a day on an empty stomach for the next 30 years. That's the way you make money. So, can we see the implications of this in the real world. I wanted to show you two kind of silly little studies that I just did the other night. So, I looked over the New England Journal of Medicine, the last 8 or 10 Phase III studies of systemic agents that have been published over the last couple of weeks or months and just to see how long the drug was given. So here you can see this is the last 8 or 9 papers and this is the median duration of treatment. So you can say on average the median time is 12 months; 52 weeks. That's an awful lot of tablets being taken in these manuscripts. I didn't put in here the median advantage of taking the agents but I think it was rather small. So we're taking a lot of tablets.

00:25:15 Now, the next slide I'm a little embarrassed to show, but if you just keep it between ourselves and don't tell anyone. So, I went into PubMed and I did an analysis of how many times the word "beyond progression" appears. Beyond progression because when I was young we said if a drug stops working you should stop taking it. But now we've got a new concept. If it stops working, you should carry on taking it. It's called beyond progression. So how many times the word "beyond progression" appear in the titles of manuscripts in PubMed? Fifty-four times. How many times the word "cancer cure" appear in titles? Ninety-nine times. We're almost from society's point of view as interested in drug beyond progression as we are in curing cancer. Maybe it says a little bit about how the pharmaceutical companies are influencing academic medicine. Well that's PubMed.

00:26:05 What about another great database of oncology? The Asco Abstracts? Well, seven of them are interested in curing cancer. But, seventy-five want us to give drug beyond progression. Maybe that says something about the direction we're going in. Paul Ehrlich talked about the magic bullet for cancer, and we talk a lot in these meetings and dark rooms and all falling asleep about is it biologically possible to create a drug, a magic bullet for cancer. But I want to ask a different question. Is it economically viable? If I, tomorrow, made a drug that cures you of cancer, who would make money out of that? One thing for certain is everybody in this room, including myself, would be out of a job. So whose in the interest to create such an agent?

00:26:56 So, I talked to two Game Theory people. One is Sergey Hart at HEAP University and the other is Dr. Koby Glass who is into medical economics and Sergey Hart is in the Game Theory. I discussed the situation with them and they described what we have is a market failure. Not a product failure. Product failure is google glasses. A market failure is a specific term for the inefficient allocation of goods and services leading to net social loss. Everybody is working hard but maybe we're pushing in the wrong direction. And they said, well the problem is the acts of congress. The factors of the incentive. It was a good idea but the incentive was too far distant from the end point we really wanted. And this, perhaps, is my

most important slide. We created together what we called the individualized incentive module ... Actually, it was more Professor Hart. He said don't change anything. Keep the same regulation, the same pricing, just do one thing. Say to the pharmaceutical companies, if on an individual basis one patient stays progression free of the disease, say for three years. The details aren't important. Three years after he takes a tablet and nothing has happened to that patient then the company gets a substantial bonus payment that. Let's say $60,000. Again, I don't know the numbers. But there is a bonus payment for each individual success and that we called the individualized incentive module won't be the end point to such a model.

00:28:28 So, first off, we expect the companies will be more interested to create therapies that drive long-term progression free survival. There'd be more emphasis on locally advanced disease and, indirectly, companies may look for more radiation drug combinations. Of course, a number of questions that would have to overcome; who would drive this change? I've got a feeling it'd be Medicare or the payers. How big would that bonus have to be? Would the payers be willing to pay, etc, etc?

00:28:58 We'd also need to try to work out as you're doing Game Theory, what would the player change and how you'd overcome that change. But, nonetheless, it would seem this would be a driver for change. Who would benefit? I think everybody. Pharma would be happy. Government would be happy. Patients would be happy. Physicians would be happy. It would be a win-win situation improving long-term outcomes.

00:29:21 So, in summary ... My last 21 seconds ... We've described the essential, yet imperfect relationship between pharma-society. We've discussed previous attempts to correct the situation. We've proposed the individualized incentive model toward pharma based upon Game Theory principles that would be a win-win for everybody's benefit. Thank you very much.

T. Lawrence: 00:29:50 Any questions?

00:29:57 Before I ask my questions I have to tell you my mathematician joke [inaudible 00:30:00]. A mathematician is somebody who turns coffee into the equation.

T. Lawrence: 00:30:24 I think one of the key points of your talk, [inaudible 00:30:30], which we really have to focus on is that the 16-year lag between the first use of radiation and the first publication, I think, is a killer for not demonstrating the effectiveness of radiation therapy. So, do you have ideas of how we can potentially structure preclinical work or other studies to try to show the effectiveness earlier and earlier so that we can shrink that time so that the effects of radiation could be demonstrated earlier well before the patent expiration?

R. Lawrence: 00:31:08 You know, I just have to say in my understanding, I'm not sure how essential the preclinical work is. I mean you have to have some preclinical work, but I've been a little underwhelmed by the effectiveness in interview models, for instance, to demonstrate clinical outcomes. And I think it may actually slow things down. I think it needs some in vitro work, proof of principle. But I think one has to move from the clinic and perhaps skip some of the interviewer modeling. I think we have some disagreement here.

Speaker 4: 00:31:42 Yeah, so, to qualify both of those as somebody is both an academic radiology oncologist and then went to industry, and I'm very short, to offer some additional thoughts. Because the FDA does not require testing for an IND submission with new agents with radiation

Goldberg: 00:32:00 ...and for an IND submission with new agents with radiation therapy, some of the core basic biology is not done and therefore, it remains a problem and a gap. Having submitted many unsuccessful LOI's to the FDA and to CTEP on drug-radiation combinations earlier on, and being told that there's no pre-clinical evidence to justify, which is completely true, the FDA has a lever that it hasn't thought about or not to pull to create that basic information that then becomes available to support what you're showing on a lot of those early combinations are investigator initiated research. They're not often industry research. And those don't get approved in the absence of basic science that's been done. That's one thought.

00:32:56 That's a lot of the gap. Another sort of thing that is within academic's control having started a radiation based study from industry, is medical oncologists hold all of the research infrastructure at our academic institutions. It's very challenging to get a radiation-based study that's an international registrational global study up and running. The MedOnc's have the infrastructure, the MedOnc's have the relationships. Radiation Oncologists are not up and present and being as engaged, and that would certainly decrease that time that we spend.

00:33:40 Another thought on your game theory, just before I hand the mic over, it would be a whole lot more than 60,000. And you're going to actually figure out given number of treatments along that time window, whatever that time window would have to be, how that gets allocated across many different players. That's actually an interesting idea, but we can't even come up... I mean, those of us who have watched the debate in the United States, when in fact we got curative therapy for Hep-C, what kind of massive upheaval that caused for a drug that was unquestionably effective, unquestionably curative, relatively speaking not expensive, relative to the cost of treating the disease itself? And there was a lot of political cost to pay for that.

00:34:28 So, that's something, a reality check on the idea of changing the incentives model.

R. Lawrence: 00:34:33 Thank you.

Speaker 1: 00:34:34 I just wanted to say that was a lovely analysis of the oncology drugs, but it pales in comparison to the drugs used for rheumatologic diseases, so the anti-TNF's are given once a month, or once every two weeks for the life of the patient, so I think this really is a stunning finding, and I think it really discourages innovation and discourages companies from looking to cure. So it gets exactly to your point, but it's a huge problem, I think. So, thank you.

T. Lawrence: 00:35:11 I don't want to monopolize the microphone, I just can't let the assault on pre clinical work go unchallenged. Now I think if we're [inaudible 00:35:19] to understanding the mechanism for biomarker development for constructing rational clinical trials, you know, my brother, Dr. Lawrence, you don't want to argue against free clinical work, right?

R. Lawrence: 00:35:31 No, no. Lawrence versus Lawrence. We even both spell the name the correct way. Thank you very much.

Sharma: 00:35:54 Thank you, that was a great start to the morning, very stimulating. I'm going to be less controversial. My name's Ricky Sharma, I'm the Chair or Radiational Oncology, University College, London. As Amanda mentioned earlier, I was one of the people who helped build up some momentum in this field, with a paper that we published from the UK a couple of years ago now. You remember the UK, that small island geographically close to Europe, but maybe not so philosophically close? So, in terms of the recommendations that we came up with, I'm just going to give you a sort of top line overview of all of those. I'm not going to go in to any depth on any particular area, but I'm very happy to talk about those. Those are my disclosures.

00:36:39 And this is the paper, it's actually an open-access paper, so feel free to download it during the session. I'm not going to go into some of the specific examples, some of the boxes in that paper, so it might be worth getting hold of it. I think it will be a useful article to have at hand for this two day meeting. And it was hailed at the time by the NCRI as a landmark paper. It certainly helped increase our profile internationally.

00:37:08 In the U.K., we know from very reliable statistics that one in two people will get cancer during their lifetime, and the problem is increasing in magnitude, these are the projected figures. And I think there's a general feeling that drugs on their own have failed to make sufficient progress, certainly up to 2014, you can see that the improvement in median survival from 71 drugs that were approved by the FDA was only 2.5 months in PFS, and 2.1 months in overall survival. So that's why we need to rethink how we use those drugs. And one of the ways of using them is in combination with curative modalities. So we know, once again from the U.K., that radio-therapy and surgery remain the main curative modalities.

00:37:59 From work going back to the time of Gordon Steele and Mike Peckham in the 1970s, we know that if we combine drugs in the right way with radio-therapy, we can achieve synergy. This is a type of modeling that we use in the lab in terms of mathematical ways to work out whether something is truly synergistic or additive.

00:38:20 That has been born out in various combinations of drug post radio therapy. This is an example from the 90's, where for rectal cancer if you add 5FU to adjuvant radio therapy, the overall survival is better.

00:38:39 This is a very nice review by the previous speaker, which summarizes all the different cancers where we routinely use the combination of chemotherapy and radiotherapy to achieve cure, to achieve organ preservation, to improve outcomes for patients.

00:38:57 But it has been a bit of a rollercoaster with the newer drugs. This one's already been cited, the combination of Cetuximab with head-neck radiotherapy and I highlight the fact that there was very nice pre-clinical work done by Paul Harari and others in terms of the modeling. And this of course is another very nice example where the Swiss led a trial of combining Temozolomide plus radiotherapy for GBM and showed an improvement in overall survival. But importantly they developed a companion diagnostic at the same time and this became standard in terms of testing patients prior to offering them the combination of drug plus radiotherapy.

00:39:48 But there have been some failures since then. These are just three examples, all published in high impact journals, where the addition of a drug to the standard has failed to improve overall survival. And in the third one listed there, the esophageal cancer study, it actually

had a detrimental effect. So just adding a drug to the standard, which already might be chemoradiotherapy, doesn't seem to work.

00:40:15 And of course, the lung cancer study from the U.S., the RTOG0617, did not show benefit for dose escalation of 74 Gray versus 60 Gray for non-small cell lung cancer and did not show a benefit from adding Cetuximab in non-selected patients in addition to chemoradiotherapy.

00:40:36 But perhaps there can be some learning messages from studies like that where there was a retrospective study where they looked at potential biomarker selection that could have been done. And it showed that the result might have been different if there had been biomarker selection. Perhaps we don't think enough about the dose constraints for the critical organs when we're combining the drug plus radiotherapy. And we have to seriously think about just adding a drug to a combination therapy when we're already using one or two drugs plus radiotherapy as standard treatment.

00:41:11 How can we do better? From the pharma aspect Oslam [inaudible 00:41:17] has led a lot of this initiative in terms of drug radiotherapy combinations and here Oslam and Steve Wedge when they were AstraZeneca published a paper showing some of the problems from the pharmaceutical end of the spectrum. Until we thought within CTRad as an academic organization we were well placed to bring together academics, representatives from pharma and regulatory bodies together with consumer groups and patient groups in order to improve the outcomes for patients. In particular, the pharma industry emphasized to us that we have to have the regulatory bodies on board. So what's been lacking so far is the engagement with FDA, EMA and MHRA and we are very lucky to have champions like Amanda Walker from the FDA in terms of radiation oncology. Francesco Pignatti from the EMA and Dan O'Connor from the MHRA to really help with this communication.

00:42:29 So we brought together this group, mainly radiation oncologists, but also scientists and clinicians from pharma, a clinical radiologist, consumer representatives, medical statisticians, some medical oncologists with good relationships with pharma, scientists from academia and three regulatory experts.

00:42:51 And we held two workshops exactly a year apart. That happens to be my wedding anniversary so I was in trouble two years in a row. I'm still paying the consequences. So workshop one and workshop two, 2014/2015. And in the second workshop we divided the whole group into tables and everyone rotated around all the tables. So everyone could have a say on all the topics. As a result of that, I think we managed to achieve consensus in one day, which was quite an achievement.

00:43:28 So I'm not going to go through every single consensus statement but, what I'll do is just pick out a few points that might be useful for this two day workshop. So collaboration between industry and academia is essential. We already heard about that and some of the tensions that could exist. These combinations should occur as early as possible in drug development and you're going to hear later in the session from Kaye Williams in terms of RaDCom which is a pre-clinical alliance to try and push those combinations forward pre-clinically.

00:43:56 The robust scientific basis has to exist in pre-clinical models supporting the point that Ted just made. It's useful to have a line of sight to registration right from the beginning. Maybe not for specific cancer but in terms of the regulatory outcome. We need to consider drug-radiotherapy combinations as important as drug-drug combinations in terms of the early

development of a drug. So in terms of the basic science, Steve Wedge led this table and he pulled together the hallmarks of cancer and we tried to redefine them with regard to the drug classes that are currently very topical in industry. So on the outside of this circle you can see drug classes where there is a lot of pharma interest in development and in the middle you can see the hallmarks of cancer that are relevant to radiobiology.

00:44:58 And there have been two very nice papers already published and I strongly recommend you get a hold of these papers as well. One from the U.K., led by Kevin Harrington and one from the NCIRTOG group, led by the previous speaker. And so, in terms of the pre-clinical package there is a literature out there and as I've said already, Kay will be telling us in a bit more detail how we've tried to push that forward beyond those papers by actively collaborating with some of the pharma partners shown here in the U.K..

00:45:41 In terms of clinical endpoints, some of the questions that popped up at the table, as we rotated around, were which end points should we select to represent local control of disease? How do we best demonstrate the benefit for patients? And there's a very interesting session this afternoon on patient reported outcomes. How do we get the regulators to acknowledge organ sparing as an end point? Should we be considering composite and co-primary end points. Perhaps some of the more well established end points that the MedOnc community routinely use but with a co-primary of an end point that we wouldn't naturally think about. For example, organ preservation.

00:46:29 So in terms of the answers, yes we should include clinically relevant early and intermediate end points and the time scales could be different for drug-radiotherapy combinations compared to drug-drug combinations. The end points should be pragmatic, relevant to patients and applicable in a real world setting and we're seeing more of that in the U.K. now with registry based commissioning in terms of the real world setting. In terms of local regional control, it would definitely matter to patients so we need to try to engage with the regulators to show that. And in terms of secondary end points they should include normal tissue toxicity, which some radiation studies have failed to include in terms of longer term end points.

00:47:14 So I'm just going to touch on a couple of other areas. Changing the standard of care. We need to define the current standard of care but also predict how that standard of care might change during the long time scales required for these studies. At [inaudible 00:47:28] for example, last year I represented a study that we got the funding ten years previously and I took ten years to actually get to the primary end point. And the line of sight should take potential changes into account so that eventually when we do reach the primary end point that it is still clinically relevant.

00:47:51 So radiotherapy combinations with good biological therapeutic rationales should be considered in pre-clinical studies on the part of the design of early phase studies. And increasingly we're seeing that with window of opportunity studies, which is an interesting area in itself. Limited or no guidelines currently exist for drug-radiotherapy combinations. So I'm hoping that this workshop will help address that deficit. And we need discussion with early regulatory agencies ensuring access to new treatments in the shortest possible time frame.

00:48:25 And, in fact, that point about early discussion was emphasized by Amanda Walker in an article that she published. And here in this figure from the paper, we actually tried to define

some of the points where pharma should be talking to the regulators and they are shown here at the bottom of the diagram. So certain points where, for example, the core program for a drug might be reaching phase one, we're hoping that the drug-radiotherapy combination could be considering the design of the phase one study around the same time. And then there should be these discussions, as shown at the bottom of the diagram, with regard to engaging with the regulators FDA, EMA or MHRA.

00:49:14 And this is the article that Amanda published in which she said it is critical that sponsors engage with the FDA early and often in the process of drug development through meeting requests and special protocol assessments.

00:49:29 So in terms of existing regulatory guidance, these are the only documents we could find that refer to drug-radiotherapy combinations. Quite often it's just a small paragraph or just a couple of sentences. It isn't sufficient for investigators who are interested in this area.

00:49:47 And in terms of the proceed regulatory barriers, these were the things that came up on the post-it notes that we stuck on the board during the workshops. Lack of guidance on combination between a local regional therapy and a systemic therapy. Limited regulatory experience of this field. So sometimes the queries were not being answered in the right way pharma felt. Guidance on pre-clinical data packages required to be submitted and then specific case studies such as repurposing drugs where the drug might not still be produced by a pharma company. The dose of drug to be used using a sub-therapeutic dose for [inaudible 00:50:25] sensitization. Identifying sub-populations and companion diagnostics and the whole field of immuno-radio oncology, which tomorrow will be explored in more detail.

00:50:37 So finally I'd like to mention the value of having consumers involved. So we had Helen and Tom who are our consumer representatives in the workshop and Helen's here today and will be involved in some of the panels. In terms of patients, consumers they should be involved from the concept stage of these combinations and they should help define what will or will not be acceptable to trial participants including clear statements about the potential benefit for future patients. It's slightly tricky without conducing participation in a trial but, there should be some sort of clear statement about what this research might ultimately lead to.

00:51:26 So in conclusion, the NCRI CTRad group has brought together academics, industry, consumer groups and regulators and now having this workshop will build up even more momentum in this field, which is fantastic. But I think specifically there's an opportunity to build on our consensus statements and to think about the regulatory guidance that we need in this field both from the academic side but also from the pharma side. So I'd like to acknowledge CRUK and CTRad and RaDCom. This is my email address so, feel free to contact me with any queries.

00:52:06 Thank you for listening.

Dicker: 00:52:19 Hey Ricky, Adam Dicker.

00:52:22 So two other dimensions to your talk, one is diagnostics. So that's a whole different issue. We help the company with their FDA and CMS approval and those were two kind of separate issues for Genomics Signature in terms of the utilization of post-operative radiation therapy and it happened to be in prostate cancer. And that was a learning experience for us

about dealing with people at FDA as well as on the CMS side and the diagnostic and companion [inaudible 00:52:59] marker space has its own complexities.

00:53:02 And then it's the ... In terms of third party payers ... 'Cause in Europe sometimes when a drug is approved through NICE sometimes companies have taken a very innovative approach that they'll ... Only if the drug needs certain end points will they get payment et cetera. We don't have that situation exactly in the United States. We have insurance companies that will determine kind of whether you're on pathway or off pathway or if there are ten different ways to treat metastatic lung cancer. These are the six or the four that a particular insurance company may pay for. So, just another dimension to the complexity that you already raised.

Sharma: 00:53:49 Yeah, thank you for that. There are sessions in the program particularly, for example, Fei-Fei will be talking about some of the biomarker aspects and I think we'll definitely come back to those two points in the panel discussions later today.

00:54:02 Thank you.

Speaker 2: 00:54:04 [inaudible 00:54:04] Ricky, beautiful talk.

00:54:05 I think one thing that we talk about third party payer, FDA and stuff but, another very powerful body in this country is NCCN. When drugs get on NCCN guidelines sometimes people use it even before FDA approval. For example the [inaudible 00:54:24] adjuvant setting. So the question is whether there are thoughts in the future to bring in these powerful guideline group together as well as FDA and third party payers and CMS and such?

Sharma: 00:54:40 Yeah, absolutely I agree with that. I think NCCN guidelines are critical on so many counts. What I don't know, because I'm now over here, is I don't know what representation radiation oncology has on NCCN boards. Is it reasonable?

Speaker 2: 00:54:57 There's nobody. No radiation oncologist on board.

Sharma: 00:55:01 Right, so maybe we can come back to that in some of the panel discussions. That's a really useful point.

00:55:10 Great. Thank you very much.

Coleman: 00:55:33 We're ahead of schedule, what do we do? [crosstalk 00:55:37] The magician who walked down the street and turned into a drug store. Sorry.

00:55:52 Yaacov gets that one. [inaudible 00:55:57] Okay, that was existential. So, we'll get going early. We're pleased to chair this session so Kay and I will have just a couple of early words. I'm going to apologize. I have a 1:55 flight out of Reagan so at 11:45 I'm going to run away. It isn't the bad quality of these talks; it's because I have to catch a plane.

Williams: 00:56:19 It's also very dependent on our chairing abilities I guess for Norm to be able to go and get his plane on time.

00:56:26 I want to welcome you all to Session One, Pre-Clinical Considerations on behalf of myself and Norm. Clearly we've just had a gauntlet thrown down to us from the pre-clinical perspective from what Richard's just said. Hopefully, we can address that slightly within this session.

00:56:42 I guess from my own personal perspective, I work obviously focused in pre-clinical research, and I think it's about understanding the balance of what's required. It's about risk. It's about balance with benefit and obviously from all of the pre-clinical work we can do we're looking at likelihood of both of those things. So I think hopefully through these sessions this morning we'll be able to get to a point where we can understand what's the minimal package that's required that would give you the confidence. So actually if it was you who was going into one of those clinical trials do you think there would be a good foundation for the study that was going ahead.

00:57:16 Okay, so without further ado, I'd like to invite Paul Harari to give the first presentation on Past Successes and Failures of Radiation-Drug Combinations. Thank you.

Harari: 00:57:37 Thank you very much Kaye and Norm. And thanks to the group for organizing this meeting. I have high anticipation it's going to be very valuable for the field going forward.

00:57:51 So my task is to provide some commentary on past successes and failures in radiation-drug combinations and I'll make a few comments about that.

00:58:03 It was already alluded to the 1979 publication by Gordon Steele describing the Steele hypothesis for how drug-radiation combinations may work most effectively together. A number of years ago Soren Benson and colleagues published a nice modification of the Steele hypothesis trying to incorporate more of the modern drug therapy and how they may work ideally in concert with radiation. These are both valuable contributions that can help put in perspective some of the classic backgrounds for combining drug with radiation.

00:58:47 As we moved into the molecular era of drug therapy over the last two decades, the tremendous number of agents that emerged into the field, that in itself, represented a dilemma as to how do we study systematically so many different agents. Be that in pre-clinical setting and obviously even more complex in the clinical setting. One sobering reality that I think has already been alluded to in the preamble this morning, is that so far we haven't done it very frequently. This was a brief snapshot that one of our trainees at my institution did with me where we looked at the year 2014, all of the phase three randomized controlled trials in oncology, those that included radiation. The other category are predominantly drug related trials. You can see the molecular targeted agent trials and that very small sliver of green that is less than one percent were the combination radiation and molecular agent trials. So this tells us the magnitude of the problem that we are not studying this very often and not able to bring this successfully forward to phase three trials with high frequency.

01:00:09 So let's go through a few elements of the past to help illuminate thoughts for the future. If there's any area where we have studied radiation-drug a lot or hope to do so and still do so, it relates to oxygen. There is no better radio sensitizer known than oxygen. And dating back many decades, we have understood this impact of radiation with oxygen. This is that classic curve showing that if you have high oxygen levels you can induce more radiation cell killing. When you have hypoxia, you blunt or diminish the effect of radiation on cell kill.

01:00:55 When I Googled, the other day, Daiakshumi diagrams for radiation oxygen interaction, this was just as far as I could scroll to make one snapshot. There are literally hundreds and hundreds and hundreds of these diagrams and they're all interesting. We know them from text books and review articles about how radiation and oxygen work. If nothing else, just based on the sheer number you would think we would have dozens of trials where this has been shown to be effective. It was 1955, the publication from Tomlinson and Gray, that really first illuminated the issue of hypoxia in tumors. They did this with a lung tumor model and this led to the beginning of these beautiful diagrams. Where you're close to a blood vessel. You have high oxygen, better cell killing. As you move away from the blood vessel you have less oxygen tension, more hypoxia, more difficult to control those tumors with radiation and potentially with many, if not most, chemotherapy agents.

01:02:06 So here is some of the trial vignettes from yesteryear. This is a trial from about twenty years ago when anemia was recognized to be a potential adverse impacter on outcome with radiation. Saying well since we need oxygen to get the ideal radiation effect, let's take a tumor that is treated with radiation, in this case head and neck cancer. Where in the 1990's radiation alone was used for the majority of advanced head and neck cancers, if they are anemic, they have less oxygen, they are going to do worse with radiation. And the background data was clear; the anemic patients had worse outcomes. When you had low hemoglobin, you had lower survival. When you had low hemoglobin, you had higher local regional failure. So trials were mounted to increase oxygen and the erythropoietin trials were the classic ones that carried this forth. On the other side of the ocean, Henke and colleagues conducted the first epo trial on head and neck cancer to correct the anemia, increase oxygen tension and see if we could engender a higher cure rate with radiation.

01:03:28 Over 350 patients were enrolled in this trial. There was very high enthusiasm for this. I remember early in my training, the optimistic view of this approach and low and behold in all categories, the epo patients did worse. They recurred faster, they died faster, they had higher local regional failure rates and so, this was a conundrum. This was not the only example. We mimicked the exact same approach in the U.S. here through the RTOG. Epo for anemic ...

01:04:00 ... here through the RTOG, EPO for anemic patients with head and neck cancer. Virtually the identical result. Here we have higher local-regional failure rates. And here we have lower overall survival rates for those patients who received the EPO.

01:04:24 This was just a small part of a massive effort to use, develop drugs that would address this oxygen issue with radiation. A beautiful series of hypoxic radiosensitizers were developed and studied systematically in the laboratory in cell culture and animal models, and in clinical trials. Misonidazole serving as a prototype, but then increasingly more sophisticated, more bioavailable agents, and even those with selective hypoxic cytotoxicity. You know many of these names here. One of the most modern of the era was tirapazamine. This is a different class of sensitizer. And this was studied in head and neck and cervix and several other cancers, again with high promise that this may identify the hypoxic tumors, ameliorate the effect, and improve outcome. Unfortunately, this trial that enrolled over 800 patients, this was centered out of the TROG in Australia but had multiple institutions around the world, showed a negative result. The addition of tirapazamine to radiation platinum did not improve survival. If anything, there was just a hint that it may have a worse overall outcome.

01:05:53 Why so much pre-clinical promise that still exists today? The hypoxia, we're gonna be talking more about hypoxia today, the basic science is overwhelmingly powerful, that we should be able to make inroads here, and yet so little clinical trial success. I listed just a few. There are probably another 25 reasons why potentially these trials were unsuccessful, certainly in the anemia category. I think there came to be a realization that anemia may be a surrogate for patients with other comorbidities, and just correcting that anemia doesn't make a well patient, so to speak, and that that was just a tip of the iceberg that we may be addressing. Not every tumor or every aspect of every tumor is hypoxic.

01:06:49 Lot of issues with drug delivery distribution in the tumor. Possibly the drugs, some of the drugs weren't as effective as advertised. Certainly drug-related toxicities became an issue with the imidazoles, where at a highly effective concentrations there were more issues with neuropathy. The potential that the drug radiation selectivity for tumors was not as precise as we had hoped, and there were collateral damage effects on normal tissue. The notion that as tumors are shrinking during radiation, they are in fact potentially reoxygenating, and that with fractionated regimens we may not be able to realize the power of exploiting hypoxia. These are just a few of the reasons brought forth why so many of those clinical trials were negative.

01:07:45 And yet with strong science but weak confirmation in clinical trials, I feel obligated to comment that there are still strong believers and defenders, and Jens Overgaard and many others are among those, and Jens has been a champion of hypoxic, or exploiting hypoxia and looking at radiosensitization drugs. In fact, that is probably the one part of the world, in Denmark, where radiosensitization using nimorazole is still used, because they developed and carried out a phase III trial in head and neck cancer patients that showed a benefit and an increase in local-regional control and survival for the use of nimorazole. And so for many years since that trial, they have stuck to that result and used that for their head and neck cancer patients even off-study. And this meta-analysis that Jens put together does portray a powerful story, although the story of the basic science and the pre-clinical is so much more powerful than what came out when you look at the total distribution of clinical trials.

01:09:05 But let me flash forward to a so-called positive example, and then make a few summary comments. As the molecular era rolled forward, and in the receptor tyrosine kinase family, the EGFR, certainly during about 20-year period, has been a prototype example. This cartoon illustration shows the development of monoclonal antibodies and receptor tyrosine kinase inhibitors of the EGFR receptor tyrosine kinase, and suggests how they may interface with radiation. There were a beautiful set of pre-clinical studies looking at how EGFR inhibitors, signal inhibitors, may work in concert with radiation or drug. Here is looking at cell cycle effects. These are G1 arresting agents that inhibit the impact of p27 on cell cycle traverse, so that you accumulate cells in G1. That potentially has a very nice marriage with radiation, where using a G1 arrestor like an EGFR inhibitor with a G2 arrestor, radiation, attacking distinct cell cycle check points seem to be a powerful rationale for that combination. EGFR inhibitors, in this case the receptor tyrosine small molecule inhibitor erlotinib, combined with radiation, was very powerful in its ability to induce apoptosis in pre-clinical models. We even saw anti-angiogenic impact of EGFR inhibitors here, using a model system in mice, showing the ability of an EGFR monoclonal antibody to inhibit vascularization of human tumors growing in surrogate mice.

01:11:08 And as the pre-clinical data in xenografts matured, these are in the late 1990s, some of the early studies looking at the potency of combining EGFR inhibitors with radiation in terms of

head and neck tumor control in the animal model systems. And we had a beautiful story of EGFR inhibition plus radiation based on proliferation, cell cycle, apoptosis, DNA damage, even anti-angiogenic and metastatic effects. Which exactly was the one of these that served as a definitive rationale for EGFR inhibition with radiation as clinical trials were developed? I would put forward the following. We had absolutely no idea. And there was a smorgasbord of potential promising pre-clinical data, of which I was very invested, as were many other investigators around the world, but which was dominant, or were they all in play? To this day that remains quite ill-defined.

01:12:21 The radiation cetuximab trial that was alluded to earlier today was, as many successful trials, fairly simple in its design. You gave radiation with curative intent to advanced head and neck cancer patients, or you gave that radiation in combination with weekly cetuximab. 424 patients were enrolled during the time period as shown, and this was published in 2006. And this identified a 10% survival advantage. Not a delay in recurrence, not a delay in death, but a survival advantage, meaning more patients living without cancer for the rest of their life. As was also commented on earlier this morning, that at the five-year study, we're still seeing that 10% difference in survival favoring the addition of the molecular agent to radiation.

01:13:23 Why is this a significant trial? I don't think it's too challenging to comment that first of all, this is the first phase III trial demonstrating a survival increase using a molecular agent in concert with radiation. There were also other beneficial aspects of it as noted here. How many agents followed the cetuximab example for FDA registration? So radiation and cetuximab. Cetuximab received an FDA registration in combination with radiation for advanced head and neck cancer in 2006. I think I, and probably others in the room, thought this was just the beginning. This was going to open the floodgates for dozens of new agents to be married with curative radiation to improve curates.

01:14:14 Zero. Not one single drug has been FDA-registered in concert with radiation following the cetuximab trial. And we've heard some of the commentary about why this may be. How powerful was the early clinical data before this phase III randomized trial was developed? There was just one single phase I trial of 16 patients that preceded the phase III trial. There was no phase II trial. There were no confirmatory phase ones. In this case, industry in combination with the academia just made a considerable leap, particularly industry in terms of funding the trial to move it to phase III.

01:14:59 In fact, since that study, cetuximab is often heralded as a modern-day radiosensitizer. Are we even sure that it is a radiosensitizer? Well, virtually all head and neck cancer tumors, if you look at them carefully enough, express the EGFR. We don't even have a biomarker for response for cetuximab. All the tumors express it. We don't correlate the likelihood of response with the expression of EGFR. There are other factors still in play that may have impacted this outcome, not the least of which are immune effects that now a number are considering is the ADCC component of a monoclonal antibody like cetuximab, in part explaining some of the outcome results, even from the positive trials. Not all cetuximab studies are positive, as we know. Here, rapidly after that trial showing the augmentation of cure after radiation cetuximab, the RTOG added cetuximab to the combination radiation platinum, which had become the standard of care in the interim, and then compared that with cetuximab. Thousand patients were rapidly accrued, and there was no difference in either local-regional control or progression-free survival. In fact, the triple-arm patients experienced without question a higher toxicity level.

01:16:29 As we look back at the complexity of signaling and the complexity of the underlying effects that has caused further study as to how this molecular agent may be interfacing most effectively. And as the HPV era emerged during the late 1990s, early 2000s, we even began to uncover and are still unraveling, are the agents as successful in HPV-positive versus HPV-negative tumors? Because this effect is a powerful one. This retrospective look back at those who have HPV-associated tumors versus non-associated tumors. Fact the enhancement of radiosensitivity in HPV-associated tumors is still being defined at a molecular and genetic level.

01:17:22 So as immunotherapy advances so powerfully in the years at present, and we're seeing now in studying the effects of radiation on tumor-immune susceptibility, and how the rapidity or longer interface of radiation with immune modulatory drugs may be best exploited, we have a lot to learn. We are revisiting the abscopal effect that was first identified some 60 years ago, and seeing it now more frequently in certain studies. Here are two studies looking at radiation and immunotherapy where we're identifying tumors not treated with radiation generating powerful tumor responses a la abscopal effect.

01:18:08 So, again, just as with the EGFR story with radiation and immunotherapy, there are a lot of questions relating to timing, sequencing, dose fractionation, et cetera, that require careful investigation. Fortunately, as I close here in a moment, we are seeing at least from a quick look in mid- 2017 a slightly higher uptake of radiation immunotherapy trials than we did in the molecular-targeted era. This is a slide showing radiation and immunotherapy trials with an N of 125. It's still a very modest percent of the total trials when you look at those with immunotherapy and radiation. But considerably higher than it was just four years ago when we looked at the radiation molecular-targeted trials.

01:19:02 Why is it so challenging to study these new drugs with radiation? Few of the comments are here. The phase I paradigm was clearly designed for drug study. The fact that half of our patients are treated for cure means that we have to honor the prior standard of care, which is often radiation and drug. And so you're mounting new agents on top of complex backbones. And the simple fact that radiation yields local tumor responses most of the time makes it harder to isolate the effect of the new drug. So there are a lot of parameters of phase I design that present challenges for phase I radiation drug trials.

01:19:46 But I suppose the message that I want to convey in closing, and I mean it to be an optimistic message. I'm very optimistic person myself. We commonly don't know why trials fail. And, my goodness, we commonly don't know why trials succeed. In fact, most of the commentary and most of the highly passionate discussion only comes after the trials are done. No one hesitates to describe why there has been success or failure after the trials are published, but there is a relative dearth of that before the trials are mounted. So, personally, my own recommendation actually parallels something that the very first speaker said this morning. Although I'm a believer in robust pre-clinical testing, I think we need to increase the number of darts that we throw at the dartboard. More trials combining radiation drug are required. We have a paucity of studies being carried out. Where can we do this? Both where radiation plays a key treatment role, so many tumors where that is the case. And also there is a beautiful opportunity in oligometastatic disease to study radiation and new drug combinations.

01:21:12 So in conclusion, when to study radiation combined with drug in oncology? Far more frequently. That's the main message that I have today. We need to get out there and be

active players in every regard to increase the likelihood that we can identify and secure the advantage that is resting there, hidden right beneath our noses for radiation drug combinations. Thank you very much.

Coleman: 01:21:42 I'm gonna take some questions. Let me start with one, Paul. We had the cetuximab study. We had the platinum. We didn't have any pre-clinical data, and we put them together into a big clinical trial. Would you have made the decision to take those drugs and put them together at that point in time?

Harari: 01:22:09 Oh, it's a good question. So as the ... Actually, believe it or not, although modest, there was pre-clinical data. MD Anderson had very nice pre-clinical data of, it was sort of the Luka Milas era of animal studies. You add the platinum with the radiation, the cetuximab, you get a better response. But as you know, it can't always show toxicity quotients as well in beautiful animal models that we have greased the wheel for, as what happens in clinical trials. I guess I was, I will say I was a believer that maybe it was gonna benefit, but that was clearly a dead, negative trial with nothing but really adverse impact.

01:22:53 Ted.

T. Lawrence: 01:22:55 I'm not enjoying the theme that we're having here against pre-clinical studies.

Harari: 01:22:55 I didn't think you would.

T. Lawrence: 01:23:01 I wanna challenge a couple things. First of all, on your list of why the hypoxic cell sensitizers failed, I will respectfully challenge you to, I think you left out the most important potential, which is that we didn't select the right patients. So I think if, when the tirapazamine study, for instance, was reevaluated, as you know in that study I'm sure some of those patients underwent hypoxic evaluation, I think it was mainly by imaging. And if you looked at the subset of patients who had hypoxic tumors, there was a suggestion that those patients actually did better on that study when you did that subset analysis.

Harari: 01:23:35 Sure.

T. Lawrence: 01:23:35 So I think if we take a big step back and say, "If we had used trastuzumab, Herceptin, on all unselected breast cancer patients, we would've gotten a negative study." And they picked that group of patients because that was the marker from pre-clinical work, and those are the patients who benefited. I think if we had approached hypoxia the same way, we would have done better in those hypoxic studies.

Harari: 01:23:35 [inaudible 01:23:59].

T. Lawrence: 01:23:58 And then to go that, to your study that you participated importantly in, the cetuximab study, I think it's our failure that we haven't defined good biomarkers. At least in our laboratory work, the great majority that has neck cancer cell lines we work with, do respond to cetuximab. So I think that the conclusion is probably most of these tumors are EGFR, at least partially EGFR-driven, and we just haven't developed the right biomarkers just to test that. So I still think that defining biomarkers, defining the subset, and using a molecularly targeted agent in a molecularly targeted way, and I think hypoxic cell sensitizers are the same category.

Harari: 01:24:37 Sure.

T. Lawrence: 01:24:37 Has a much greater chance of success.

Harari: 01:24:37 [inaudible 01:24:39].

T. Lawrence: 01:24:39 And then David Raben had a negative study on combining cetuximab [inaudible 01:24:43] platinum radiation, a very negative study on it. So I think the pre-clinical data on that triple combination-

Harari: 01:24:49 Sure.

T. Lawrence: 01:24:49 ... was controversial.

Harari: 01:24:50 No, those are all good points, Ted. On the oxygen, I suppose, I would say now that we all, you and I lived through this era and participated in it. Over 10,000 patients have been randomized to trials, and we have one country in Europe that uses one-

T. Lawrence: 01:25:09 [crosstalk 01:25:09] in Denmark.

Harari: 01:25:09 ... agent. And so, no matter how we slice it and how much we want to believe in the science, and I think the science is strong, we have to acknowledge that we didn't make a significant impact on global oncology here. I would also say that if, as we go through this workshop today and tomorrow, we list as [inaudible 01:25:34] collectively for our field all of the things that we need to do to bring forth agents, then we will be part of the future failure to advance, because we basically have laid out a 20-year process for each drug to be studied carefully, and that's what we've done in the past, and that has not worked. I think we have to look for more streamlined ways, and one of those is to just accelerate the wheel, to test things more frequently. [crosstalk 01:26:06]-

Coleman: 01:26:06 Okay, 30-second question.

Speaker 3: 01:26:08 Yeah, you didn't ... Radiation only works if you point it at where it needs to be delivered. So, there's whole quality assurance piece in drug development and for the companies here to understand that if you don't have that as part of the trial design, you're as, you didn't show the TROG data, but-

Harari: 01:26:32 Sure.

Speaker 3: 01:26:32 ... that's one reason why that trial [inaudible 01:26:34] failed. And the other comment, both for you and Ricky, is, in order to increase the pipeline, you need to increase the number of trainees who are interested in drug development, and help foster their careers. You've done a great job, and others in this room. But we need more people to be able to throw the darts at the dartboard.

Harari: 01:26:52 Sure. Good point. Thanks.

Williams: 01:26:57 Thank you very much. Gives me great pleasure now to introduce Professor Tim Illidge from Manchester. How Can Pre-Clinical Data Inform Clinical Trials?

Illidge: 01:27:10 Thank you very much, Kaye. Thank you for the invitation. It's a pleasure to be here and to speak. I'm hoping that my talk will address Doctor Richard Lawrence's point, and that I can convince you that this is important. And I'm hoping that it will make Doctor Theodore Lawrence a little bit happier, as we do really want to do that. These are my disclosures.

Speaker 4: 01:27:34 Can you speak [inaudible 01:27:35]?

Illidge: 01:27:34 Yeah. My talk has been made a lot easier by the quality of the previous talks. We've heard already that the prevailing culture is to demonstrate toxicity and activity data in early-phase trials. And the whole focus of medical oncology has been on palliative metastatic disease, where downhill with the wind behind you, you can't really add a lot to human happiness when people are at that end of the spectrum. In stark contrast, of the, the majority of patients that are treated with radiotherapy in the societies that have the best outcomes, just under two-thirds of patients are treated with radiotherapy, and it's used as part of the curative treatment in around 40% of the patients. We've talked already about some of the differences, the erratically potentially curative treatments given over multiple fractions over six and seven weeks. It's long since been the North American way to try and bore the treatment to death. In Manchester, we've often pioneered the way for shorter courses of fractionation, and it's pleasing to see that other people around the rest of the world are joining in the game now with these hyper-fractionated approaches.

01:28:49 And we have other technologies, which we've talked about, which may have new rules. We've known for long time about the influence of the five R's, reoxygenation, repopulation, reassortment, redistribution, repair and radiosensitivity. And we've already had a very good image showing us the exploitable mechanisms when combining drugs with radiation. In particularly the one, the special cooperation where the radiation is treating the primary tumor, and the drug potentially treating metastatic disease or disseminated disease, cytotoxin enhancement [inaudible 01:29:25] DNA repairs with DDRIs, biological cooperation. A temporal modulation is actually very important for chemotherapy combinations as well, where we effect repopulation and reoxygenation. And the area of normal tissue protection, which is perhaps, had less attention. You've seen this picture already. It was from the Nature Reviews article that we put together, and Ricky's already brought this to your attention.

01:29:49 I'm now going to actually focus on just a few examples to focus our thoughts in these different areas. So in the manuscript, we looked at the minimum pre-clinical data set for justifying early-phase clinical development of a new drug radiation combination. And we thought that four areas in particular should be addressed, that these were important starting a clinical trial. Firstly to demonstrate that the novel drug improves efficacy in radiotherapy, in clinically relevant models. Of course that's the difficult bit, the clinically relevant models. Defining an effective dose schedule. Providing an assessment of normal tissue toxicity for the drug radiotherapy combination. To identify potential clinical risks. And identify potential responsive patient sub-populations and associated candidates' biomarkers that we've already alluded to.

01:30:46 But what can you get from the in vitro studies? Well, you can do the dose response curves, you can look at scheduling, you can look to see radiosensitization, identity or synergy, which is rarely seen but obviously exciting when you see it. And you can look preliminary at biomarker analysis. What about the in vivo models? How many tumor models do you need? What's the right end point? More of that in a moment. We'll come onto that. For

radiotherapy, you can give single fraction, or you conduct multiple fractionated doses. You may need both. For the drugs, we look at the radiation and the drug dose response. And we can look at scheduling issues of the radiotherapy and the drugs.

01:31:25 What sort of models do we have? And these tumor models, they're more likely to be informative than the in vitro studies, where we can look at dosing, we can look at mechanisms, we can look at scheduling, and we can begin to look at biomarkers. The tumors and the graph models remain the principal model assessing efficacy of drug radiotherapy combinations but now, these days, we have patient-derived xenografts, which are more molecularly diverse. We have genetically engineered models, or the so-called GEMs, that have more complex stromas. These models have considerable time considerations, and it's unclear, I think, at the current time whether they're providing substantially more information for the radiotherapy drug studies. That's a point that we might want to come back to. For my own area of particular interest, and my group has been looking at radiotherapy and immunomodulatory agents, and of course you need an intact immune system to look at that. So we're looking at synegeneic tumor models.

01:32:18 How do you evaluate these? Well, you can look at growth delay, tumor cure. Do you go for a model that's potentially easier to cure than one which is more difficult with a growth delay? What imaging biomarkers do you use? PET, MRI? We look for blood-borne and tumor biomarkers, and also [inaudible 01:32:37] of normal tissue damage. And the key part to all of this, is the aim is to demonstrate and increase therapeutic ratio, where you're having a greater effect on the tumor than you are on the normal tissue.

01:32:49 So let's look now at specific examples. So let's look at the area of growth factor signal transduction inhibitors. Most of my examples are going to be from the portfolio of AstraZeneca drugs. Why? Because they're the company that are most engaged with the community that is within radiation oncology. And very early on, in Manchester, we set up a Manchester Council Research Center A-Zed alliance. And they were very open to the possibilities of doing radiation drug combinations. Much of the work in this early pioneering work was done in the laboratories of Professor Ian Stratford and Professor Kaye Williams, who's just to my left. So let's look at the MEK pathway. This is an oral inhibitor of the MAP kinase, ERK-MEK pathway. And what you see here from work done in Kaye's laboratory is when we see in vitro, that the drug is hitting the target, and you're getting a decrease in phosphorylated ERK. And you're also seeing that in vivo, and importantly, with the in vitro combination you see that there is increased radiosensitivity. So then when we take it to the tumor models, here you see an improvement in the tumor control, with the inhibitor, with a MEK inhibitor, and you see the, also with the biomarker analysis here, that actually it's inhibiting the HIF pathway, and it enhances the radiation response. And you're beginning to see an idea of what you might use for biomarkers here with the decrease in the [digef 01:34:27], decrease in the HIF-1-alpha, the [GLT-1 01:34:30], and let's have another example.

01:34:34 What about anti-angiogenic agents? So this was the oral [digeth 01:34:40] TKI, which is ... Here what we're looking at is how when you add the drug to the radiotherapy, you see vessel loss and apoptosis, as evidenced with the tunnel that we see here, when you give the drug with the radiotherapy. And then when you take that into the two tumor models here, you see a very good decrease in the tumor volume, a growth delay with the Calu-6 and the colorectal model. And it was on the basis of this data that a clinical trial was performed. This was led by Mark Saunders, and with a really very innovative design, and I think it gives us an

idea, as a community, how we can get on and do these things quite quickly. So here we have two new drugs that we're adding to radiotherapy in the setting of chemoradiotherapy for rectal cancer.

01:35:37 So this is what the trial looked like. Here we have the imaging biomarkers. Here we have the blood-borne biomarkers, and here are the two study drugs. So what Mark did, which was really very innovative, was to do this sort of ping-pong design where, rather than waiting for the toxicity data from the first drug to come about, the second drug is tested immediately afterwards. So that essentially, you go from one drug t-

01:36:00 Immediately afterwards. So essentially, you go from one drug to another and whilst you're waiting for the toxicity data from the first drug, you're recruiting with the second drug and you're able to then proceed with the next dose level of the first drug whilst you're waiting for the toxicity from the second drug, if you follow me. So this innovative ping pong design allows you to study two drugs within the same clinical trial.

01:36:24 And the biomarkers that were looked at were quite extensive. I don't have time to go through all these. But much of this was determined from the preclinical work from Kay's lab that we've already looked at. And then here we have the same with the selumetinib and you can see that these blood bond biomarkers and the imaging biomarkers were looked at in great detail. That trial has been performed. I don't have the time or the opportunity to go through the results of the study.

01:36:51 Here's another drug, AKT inhibitor. This is work again that was done in my own lab in collaboration with Kay, who has supported that the student Emma Surl here in Stratford. And what Emma found was that really, there was no radiosensitization in a very large numbers of tumors with this drug and AKT inhibitor.

01:37:13 However, when she took it into the animal model what she found was that it really matter with the scheduling when you put the drug in with the radio therapy. So if you look at the difference in schedules you see here is the concurrent schedule using the drug before the time of radiation and afterwards. Sequential is essentially when its used, and the [inaudible 01:37:35] is when the drug is used after the radio therapy. And what she found in 2 head and neck models was there really was a very clear signal that this drug was best given after the radio therapy, very good a tumor control with the drug given after radio therapy. And the effect was essentially found to be due to reduced tumor total vascular [inaudible 01:37:59], where you see in these images here the reduction in the blood vessels.

01:38:07 What about DNA damage repair inhibitor, an obvious area that you'd want to use radiation with, you would think. However, isn't it surprising there's such a poor few clinical trials in this area. We know that radiation is the best treatment bar none, at causing both ... DNA damage boasts single strand and double strand break, and we now have a number of drugs which we could use to enhance this, with DNA-PK, homologous recombination inhibitors, pump inhibitors, ATM, ATR, CHK1, Wee1, and ATM. This data was from Ian Stratford's lab, and one of the first studies to look at the use of radio therapies with Olaparib, and you can see with the low doses of 5 by 2 grade, there was a good tumor control in the Calu-6 in the A549 models.

01:39:04 This is from the laboratory of Antony Chalmers, he's particularly interested in glioblastoma, and you see the different varieties of DDRI's. So he's got a pump inhibitor, an ATRI, an ATM,

a CHK1 inhibitor, and the question that comes out of this is, which inhibitor would you take forward into clinical trial, and which patients should receive the drug. So, what Antony did, with his group, was to use Olaparib in radio therapy in glioblastoma, where there was a clear evidence of an enhanced therapeutic ratio. The problem with many of the DDRI's, as some of you will know in the audience, is its very difficult to demonstrate that you're improving the therapeutic ratio because you get an effect on the normal tissue, not so in the brain where you can demonstrate that very clear therapeutic ratio.

01:39:53 So the phase 1 trial has been completed, the optimal dose 200 milligram BD, and the phase 2 trial is ongoing. And there are a lot of important trials which are ongoing across the world. This list is very selected but there's quite a few in the United States and other parts of the world that are ongoing in this area with the pump inhibitors.

01:40:15 An area that we've touched on very briefly is the inability for these preclinical tumor models to pick up normal tissue toxicity. I think this is an area where, its definitely, we can do better. And, there is certainly efforts in the Oxford group, particularly Andy Ryan, to look very closely at this, at the effects of radiation plus the DDRI's to induce lung fibrosis, esophagitis, and skin erythema. And I actually think this can be a very informative area.

01:40:47 Finally to an area that has interested me for some time, which is the combination of radio therapy and immunotherapy. Despite the huge excitement about the use of immune checkpoint inhibitors, the reality is that only the minority of patients with solid tumors respond and the even smaller minority of them respond with durable remissions. So, the question which is being interrogated, I wouldn't say thoroughly, but there's certainly a lot of excitement as we saw in the previous slides with a number of trials is to use radiation as potentially a partner in combination with some of these immune checkpoint inhibitors.

01:41:27 And the hypothesis that we're trying to examine is that radiation can be used to turn a weak endogenous tumor specific immune response to a stronger immune response. And there is some evidence, from my own group and others across the world, that you can actually do that in some tumor types. This was a study we've published a couple of years ago now, but it makes an important point that radio therapy leads to an adaptive up regulation of the tumor cell PDL1 expression. And this is entirely CD8 T cell dependent and interferon gamma dependent. So the target, the PDL1, is enhanced by the radiation. Now what we need to know as a community is how many different tumor types does this occur in and what sort of doses do we have to use.

01:42:14 Now the hypothesis would be that it varies enormously from tumor type to tumor type and also from radiation dose and fractionation approaches. This again is a hypothesis generating piece of data that I think we need to test in clinical trials. Look with me, if you will, at the different schedules that we studied in this colorectal C26 model. So here we're using a small dose of 10 grade, delivered in 5 fractions, in a relatively radiosensitive tumor. We give the anti-PDL1 antibody either on the first day or the fifth day of the fractionated treatment, or we wait a week and we give it 7 days later. And what you'll notice here is that when we give the anti-PLD1 7 days after the radio therapy, we completely lose the therapeutic effect. Now I'm not suggesting for a moment that this is going to be translatable to a wide variety of different tumor types in the clinic, but it generates the hypothesis that we need to examine within the clinic, as to what is the optimal timing.

01:43:17 So what were doing in Manchester, and across the U.K., we've got a large portfolio across the U.K. with radiotherapy and particularly anti-PD1 checkpoint inhibitors. But, these are 2 studies that look at that particularly hypothesis about the timing, so this is a study which is actually being led by my colleague and friend, Professor Corinne Faivre-Finn, who's a leader in lung cancer. And here we're giving the Pembrolizumab with the radiotherapy, you can see, during the treatment. Now that, many would argue, is a very high risk thing to do, because we may see potential toxicity with that, but I think its an important clinical experiment that we need to perform.

01:44:03 Here's another one such study. This is going to be a U.K. NCRI study that will be done at about 10 centers across the U.K. in the rather rarer disease of cutaneous T-cell lymphoma. Where, we're giving the Pembrolizumab and then coming in with the radio therapy, and looking for the Abscopal effects with this combination.

01:44:23 So, just to summarize and bring some conclusions from the preclinical data set, I think everybody in the room agrees that the unmapped potential of radio therapy and drug combination is enormous. The question is how can we best get there quickly. So I believe that preclinical data set can enhance that and can bring us on if we are able to use the drugs very early on. It can inform the decision making about our clinical trials. So I think we have, in terms of demonstrating efficacy in radio therapy in clinically relevant models, I think there are many good examples leading to clinical trials. What about defining effective dose schedule, I think there's some examples of preclinical data. The area of providing normal tissue toxicity and I think is an area where we definitely have to put our hand up and say, "Could do better." It's much less well developed. And then what about identifying particular subpopulations and candidate biomarkers? There are some good examples, but again we need more people working in this area to inform the clinical trial design.

01:45:29 And with that I'd particularly like to thank Kaye, who's sitting next to me, to Ian Stratford, who have been long term collaborators. I'd like to thank Antony Chalmers, who isn't here today, who contributed some of the slides. Ricky, who's already spoken. Mark Saunders, who's one of the clinical investigators, and particularly colleagues at AstraZeneca, who have been really pivotal in gauging this important opportunity. And some of my own lab team, the collaboration with industry was so good, in the case of my own lab that Simon Davide, who did some of the work that I've shown you, jumped from my lab to industry. And I'm quite comfortable with that. Thanks very much for your attention.

Coleman: 01:46:20 So Tim, that was a great talk. So let me address the question of what drug dose do you use in the laboratory and what drug concentrations are really relevant. So many studies have done with drug concentrations that give you results, but aren't clinically relevant. So, how do you choose a concentration of drugs you're using for your combined modality experiments in the laboratory?

Illidge: 01:46:44 So, I think there are 2 parts to that. You're asking about the in vitro or the in vivo, 'cause I think ...

Coleman: 01:46:50 Well, both.

Illidge: 01:46:51 Yeah.

Coleman: 01:46:51 In vitro is usually industrial strength.

Illidge: 01:46:53 Yes, so I think you start off with the lowest doses hitting the target. I think you have to see the, as I showed from Kaye's work, that you are actually getting enough drug to the target. So, the example that I showed was with the MEK inhibition, and I mean Kaye could speak for this, but essentially it is important to demonstrate that you are hitting the target, and you can get some idea of the toxicity with that. I think you're then guided by the activity that you see. As I explained, I think the problem is the toxicity that you may or may not see, in the mouse model, may not actually inform the clinical trial, but the dose, in terms of the efficacy, may.

Coleman: 01:47:54 So do you look at the actually achievable clinical dose, because often the drug that hits the target is far more than is actually achievable clinically, and I think that's ...

Williams: 01:47:54 Yeah, so

Coleman: 01:47:54 And you may address that.

Williams: 01:48:07 Yeah. So for a lot of the studies that we had there, we were lucky enough that the phase 1 data was already available for the clinical studies so it meant that we could ensure that our preclinical data was using doses that were eminently achievable. Obviously it a difficulty if you're developing the preclinical work at the same time as its being developed on its own basically. So that was useful for us.

Illidge: 01:48:26 Yeah.

T. Lawrence: 01:48:29 I'm not usually an argumentative person, but I have another bone to pick today, with you Tim, which is you gave a fantastic talk.

Illidge: 01:48:35 You've had a bad night.

T. Lawrence: 01:48:36 But, yes I guess I did. But there's a reason we fractionate radiation therapy.

Illidge: 01:48:36 Yeah.

T. Lawrence: 01:48:41 And its because we think we effect the tumors more than the normal tissues

Illidge: 01:48:46 Yes.

T. Lawrence: 01:48:46 For each dose of radiation, and particularly, in the context of radiation sensitizers. Let's say you have a 1.41, 1.5 enhancement ratio. If one does that 30 times, one gets a much better enhancement over the normal, than if you do that 4 or 5 times. I think with, for instance, SVRT when the goal is to ablate, its okay to ablate a tumor in the middle of a liver where its okay to damage a thin rim of normal liver, that's no problem. But if you have a tumor budding in an intestine, its not okay to ablate a little bit of the intestine. So fractionation makes sense when you're dealing with radiation sensitizers.

Illidge: 01:49:18 Which I agree with, but the ... And I'm interested in your interpretation of what I said. The ...

T. Lawrence: 01:49:26 You said, "We're gonna bore the tumor to death with fractionation," I didn't do it with your accent but I could.

Illidge: 01:49:32 Yeah, but what you forget is the repopulation. You nipped down too quickly for me to take you on with that one. That's the boring the tumor to death. I think what we now understand, that actually shorter fractionation schedules can be very helpful. So I think we're in agreement about the importance of fractionation, but I hope that you would concede that shorter fractionation may actually lead to a better result.

Speaker 5: 01:50:05 Question over here. So to follow up on the question regarding the drug schedule, the fractionation schedule preclinically for radiation is important as well, and so for most of the study that we've done in mice have been very short fractionation, like 2 grade times 5, its not the same as 2 grade times 30

Illidge: 01:50:05 No.

Speaker 5: 01:50:22 In head, neck, and lung cancer. So the question for you is, what is the optimal fractionation when we test in preclinical animal with immune therapy, because most of us don't do that?

Illidge: 01:50:32 Yeah. I think that's a very difficult question. And I think that it depends on the tumor, the different tumor types, so this is an area that we're actively studying and my hypothesis would be that the dose of radio therapy and the fractionation may vary according to the different types of tumors. So what I would expect that the answer for, lets say, a follicular lymphoma, would be very different from a melanoma or a head and neck cancer. So I think it depends upon the model and I think that actually, the best way of testing that is with 2 different fractionation strategies in the preclinical setting. I don't think that that's going to be the complete answer in terms of informing the clinical trial design. But as I've suggested throughout, I think it is hypothesis generating that we need that information to inform our clinical trial design. And I think we can get things from the preclinical setting with the dose fractionation, that enables us to ask clinical trials in a meaningful way, within the time limited ... The problem that I think we all agree, that we have to get it right quickly. And I think the preclinical data, to summarize, can help us make informed choices. We may still get it wrong, but I think it minimized the risks by doing that.

Buxbaum: 01:52:01 Short question. I really appreciate your talk, and I've been following your ... My names Jeff Buxbaum, I'm from the NCI. I work with Norm. And we've met years ago. When we do preclinical work, we do 2 things that we're stuck with, and I'm curious what you think about. One, dose. We have a hard time mixing dose of drug and dose of radiation, and the 2 camps are on different rulers, and it would be potentially helpful in the preclinical setting to come up with a new rule set. Do you think that's a reasonable thing to strive for as a target of preclinical research, in other words a dose matrix that's somehow able to simplify the complexity? And number 2, we assume we have targets and we assume we have concentrations, but we often don't have preclinical work where we see target availability change with the use of radiation. That being said, the context that I'm coming from is platinum, for example, and its classic DNA binding thoughts. In my ancient history work, we found that it poisoned half the enzymes in cells but that work typically wasn't studies, or even appreciated. So, how can we take preclinical work to potentially inform us outside of the scope that pharma has spent a lot of years optimizing?

Illidge: 01:53:25 Two very difficult questions, and I think the ... What brings them both together is the point that I was trying to make about increasing the therapeutic ratio. I think that is what we strive to demonstrate in the preclinical setting, with the caveat that, having demonstrated it

in a mouse tumor model, it may not be reproducible in the clinical trial. But, nevertheless, I think that enables us to move forward with the clinical trial, at least partially informed.

Speaker 6: 01:53:59 So, in the setting of radiation therapy with DNA repair inhibitors, in the cells that survive, do they have a higher mutational burden, are they more immunogenic?

Illidge: 01:54:10 That's a great question, and one that we're currently looking at with much interest

Speaker 6: 01:54:18 Thank you.

Illidge: 01:54:19 We've got some preliminary data that suggests they might be, but I can talk to you offline about that.

Speaker 7: 01:54:22 Okay. Just before the break its a great honor to invite Kevin Camphausen to give his talk now on preclinical approaches to repurposing.

Camphausen: 01:54:40 This talk will be made so that Dr. Lawrence is happy at the end.

Speaker 9: 01:54:43 You had a smoke today.

Camphausen: 01:54:46 Yeah. Don't you have someplace to go. Holy cow. So, I'm ... Obviously a lot of talks have gone off here, I'm gonna try and fit mine into that. We had talked, spoke to some of the other speakers about this, so hopefully this will fit, fit in well.

01:55:02 The other thing is I stole this slide from George Wilson years ago, and he's never been in the room when I present it, and he's actually sitting there, so I'm glad I actually have his name next to it.

01:55:12 So, these are some of the drugs that we've all talked about already. Some of the target, how do we pick 'em, where do we wanna go. Single target, there was a few discussions about radiation inducible targets, so things that happen after we radiate it, but that could be immunologic, but that's all the DDR stuff, right? We don't need to do serial biopsies of somebody to see if our drug's in there, if the radiation hasn't been given and changed the target yet. So there's really the 2 different classes of when we might want to biopsy somebody, whether the radiation needs to induce that target or not.

01:55:49 Then there's multi-target inhibition. So you've heard single target a couple of times. The immuno's obviously multi-target. But chaperone proteins, like Hsp90 molecules, that hits like every molecule you've ever heard in man, so it's great. HDAC inhibitors, anti-antigenic agents, these things are really multi-target.

01:56:11 For us, so I do brain tumors, that's my thing. We haven't talked about that yet, but getting drug to target is the hardest thing we do. How do you actually get a drug across the blood-brain barrier. So almost all the drugs that you've heard from today, they don't cross the blood-brain barrier. So I can cross all those right off my list to begin with. Antibodies, those have their own problems with interstitial fluid pressure, so would you rather have a small molecule that maybe can get inside the cell. I'm not even gonna argue about hypoxia and hypoxic cell sensitizers, I was gonna jump on my band, my box, but I'm just gonna leave it alone. And the therapeutic ratio is key.

01:56:47 What I wanted to talk today, quickly about, and I was asked to talk about a repurposing molecule, is HDAC inhibitors. So HDAC's are histone deacetylase inhibitors, and their partners are HAT's, histone acetyltransferase inhibitors. So HDAC's are throughout every organism. We use histones to circularize DNA around it, and the thing is, they're incredible dynamic. They open and close so that you can have gene expression, or lack of gene expression. That's how we jam 3 billion base pairs into a human cell.

01:57:21 So this is an incredibly dynamic process between the HAT's and the HDAC's and that'll come up and be really important shortly. We know that almost all tumor cells have aberrant HDAC's. We also know now, when I started there was only 8 HDAC's, now there's about 18 HDAC's. So there's a lot of cross ... Are you hitting this one, are you hitting that one, does that one go up when you hit this one? But, we know that by inhibiting HDAC's, you can sensitize tumor cells. So Dr. [inaudible 01:57:52], who's another person I work with and I have done a lot of work on HDAC inhibitors, and what I wanna show today is the repurposing of valproic acid.

01:58:01 So there are many of my mentors sitting in my room, obviously Dr. Coleman, Dr. Lawrence, Dr. Harari, Dr. Hahn, these guys sat me down and said, "This is your career. You do this preclinical work, you find a molecule that works, you take it to the clinic, you show it works in the clinic, everyone thinks you're wonderful, and you get a really good job, you get tenure, and you make a fortune. Its easy." And look at successful at how they've all been, so that's what I sat down to do, right?

01:58:32 So this is valproic acid. When we started with the HDAC's we actually started with MS275, which is a benzene derivative that CTEP had in their portfolio. And we showed that it was a great radiation sensitizer, and that it crossed the blood-brain barrier. We went back to CTEP and they said, "Company fell apart. MS275's not available." And there was an article, a recent publication that valproic acid, that the side effects of valproic acid might be because it's actually an HDAC. So we said, "Okay, let's use valproic acid, which is an anti-convulsant, we've used it for 30 years in the clinic, so it'd be really easy to figure out how to do this." The question that Dr. Coleman asked earlier about drug dosage is probably why this ended up being successful. There's all these models for, if you give this pill to a patient, this is the amount of valproic acid that's in their CSF serum in mouse models and in vitro cultures. So we took the dose we knew we could give a patient and we just back calculated that all the way down to our in vitro. So it made it way easier than, oh we've got a new molecule off the shelf that's never been in a person, or it might not even be a real drug, it's just a molecule. How do you know where that is?

01:59:43 Well, we were able to go the other direction. I think that's why this ended up working, but ... So, the important thing about HDAC's, and I said that it was that dynamic process. The top figure on the left ... Oh, wait ... This figure here, is when we gave valproic acid before radiation. And what you can see is a modest amount sensitivity. I don't have the figure here, but we show that when you take off the valproic acid, the HAT's pick up really, really fast and get rid of the HDAC inhibition very quickly. What the bottom left graph shows, is that if you give valproic acid before radiation, but then leave it in the media when you do your clonogenic survival, then you get a significant enhancement. So you had to have the drug on before, and after.

02:00:28 We then did an animal model, a simple flank model. Again, we knew the dose that we were gonna be able to get in the mice, so we did a simple flank model here. But we gave drug

before and after the radiation. We actually gave it BID the day before, and BID surrounded the 3 fractions of radiation, and BID after. And the reason we were doing that is the treatment we were gonna give to the patients was BID valproic acid. So, we modeled that and we saw a pretty significant effect. So this was 2005, right? Dr. Hirari, right?, changed the world in 2005. Every radio sensitizers was gonna work. So in vitro models and a sub-cu glioma model, was good enough to get IRB approval, so I took this to the clinic. I think things have changed, but I took this to the clinic.

02:01:20 So, how does an HDAC maybe work? And I think this is what all the biomarkers and all the preclinical work really needs to be, is if we're gonna biopsy patients, let's figure out what we're gonna actually look at when we biopsy 'em. So gamma-H2AX is a marker of DNA double strand breaks. So the H2AX is actually a histone, it's a small histone variant. And when you get a DNA double strand break, it becomes phosphorylated, that's gamma-H2AX. We have antibodies against that, so you can actually count the foci and you can tell how much damage you have at the DNA double strand break level. Gamma-H2AX also then brings other repair molecules, like, p53, the MRN's, and BRCA1.

02:02:01 What we know is that HDAC's in general, with valproic acid here, when you first look, at like 6 hours, when you count these foci. So that would be how much initial DNA damage do you have, there's no difference between valproic acid or other HDAC's and radiation, it's the same. So if things like CldU, or IUdR, you actually get more initial damage because that's actually causing more DNA double strand breaks. In HDAC's you don't get more DNA double strand breaks, what you get is, if you look at a later time point, you actually don't have repair of these breaks. And so, Peggy Olive has shown that you're amount of gamma-H2AX at 24 hours correlates with clonogenic survival. Correlates with eventually tumor cells dying. So this makes sense. But why is it not repairing?

02:02:52 So our first hypothesis was, that something was going on here and we were not recruiting in the molecules to the area of DNA double strand break. So you can actually do foci for p53 BP1 and you can do BRCA1 foci, and what we see is the same thing. They're getting there, the repair molecules are at the DNA double strand break, there just not leaving it, okay?

02:03:21 So the other assay that you can do is a neutral comet assay. So that's actually looking at the nucleic acids of that DNA double strand break instead of the gamma-H2AX, which is more at a protein level. And what we show here by both neutral comet and pull field gel electrophoresis, is that the nucleic acids are actually being put back together. So, this marker, which is our traditional experiment for a DNA double strand break, says there aren't any. That the nucleic acids have been fixed. But the other graphs that I showed you say, "No, we have a DNA double strand break, we have a problem." The gamma-H2AX was more informative to the type of death. So in 72 hours we saw a huge increase in mitotic catastrophe. Cells that have unrepaired DNA double strand breaks undergo mitotic catastrophe. So the gamma-H2AX was more significant there.

02:04:17 So how might that be working? This one blot took 3 years to produce, and a whole post-docs career. He's doing really well no, so that's good. So what we actually had was the hyper acetylation that the valproic acid was causing a hyper acetylation of the molecule gamma-H2AX, because it's a histone. Which was preventing the phosphatase from coming in and taking off the gamma portion. And so the cell, even though that DNA double strand break had been repaired functionally, the molecule wasn't able to be cleared out, and then the cell thought, "Oh, I still have a DNA double strand bread." And underwent mitotic catastrophe.

So that's sort of a whole different ... We had no idea how to find that thing. But this is theoretically something that you could look for.

02:05:13 Alright so this is the study that we ran forward, and we started this in '5. So I study brain tumors, so we wanted to study this in primary GBM's. Right at this point was when the Stupp trial came through and said we have to include temozolomide. So I didn't have any temozolomide data with the valproic acid, but Stupp had patience that it had valproic acid and didn't see any untoward toxicity, so I thought it'd be okay. So we jumped into a phase 2 trial, and we can argue whether that was the best way to go, but I felt like there was a lot of knowledge about the use of valproic acid, there was a lot of knowledge of temozolomide radiation, and that we could just combine those things and move forward.

02:05:56 So this was a 41 patient experiment and down here what we did was, we could do hyper acetylation of the lymphocytes. So you could give patients some valproic acid, you could check their lymphocytes and see if the valproic acid was, at least, circulating through them. And so this was actually the first one. I'm the normal, so that's me in case anyone wonders about my acetylation, it's okay. And then this is the patient lymphocyte. And what you'll immediately notice, right? This is a patient that has a brain tumor, has a GBM. And compared to me, who you can argue whether I'm normal, their acetylation is different already. And that was something that we found almost across everyone of our patients, is their acetylation status was not normal. And so, it was actually somewhat difficult to see changes with the valproic acid because I was starting at such a different level, but that's a side point.

02:06:50 So this was the schema that we did. So most of the patients that get valproic acid as an anti-convulsant are somewhere in the 5 to 10 milligram per kilogram BID range. So that's sort of where they run. Our trial was gonna give 25 milligrams per kilogram, so the PDR says that you can give up to 50. So I magically picked 25 as my number, right? But there's also a black label for pancreatitis for this so we were somewhat anxious. So what we did was we gave a 1 week run in of just the valproic acid. And that gave us time to do our sim, to do all the contouring, to get the treatment plan done and whatnot. So we got the valproic acid in and did 3 dose escalations in that first week and then we treated concurrently with valproic acid, Temodar, and radio therapy for 6 weeks, gave them a month off, and then treated with standard temodar. So we didn't put the valproic acid out back. So every patient had to have whatever anti-convulsant they were having, separate from the valproic acid. They couldn't use this as their anti-convulsant, because we were gonna turn it off the last day of radiation. So it took a while, took 6 years. So I ran into R2G, O525, and then I ran into R2G08.

02:08:00 I ran into RQG0525 and then I ran in to RQG0825 so I had this great number of patients and then everybody disappeared and when 0525 ended then I got another ballast of patients and then they stopped again and went 0825.

02:08:13 But it finally got done. I would argue this is a really good effect. Okay, so overall survivals on the left, we had 29.6 months compared to Stupp which was 14. And on the right is progression free survival which was 10.5 compared to Stupp which was 7.7. So as all my peers said, all my professors said, "do the pre-clinical work, do the trial, get a good result and the glory will come". I'm waiting for the glory. But it will eventually, I'm sure it will come.

02:08:46 I think this is a really good effect. This is a landmark analysis. Some people might know what a landmark analysis is. So basically you set the point in the future and you say, if a patient were to live six months without a failure, how much longer would they live? And so you kind of say to yourself, "well, if you don't fail early, you should fail longer." That's not what that's looking at. What it's looking at, what are your survival curves look like after your first failure?

02:09:14 And what we show here, is with the valproic acid, at every point after that, six months, one year, two years, you do better. Mine argument is, that's showing we have an improvement in local control. And that improvement in local control in this disease acquaints to a improvement in overall survival.

02:09:33 So we put that in. The interesting thing is for those of you who have ever used this drug before, so valproic acid at 25 milligram per kilogram BID is toxic every time you measure it according to the laboratories. On every Monday, I would get calls from the laboratory stat right, because every single value up there but 1 is great than 100. Every single one of these patients was therapeutically toxic on valproic acid according to the labs.

02:10:03 The reason why I show this is we had 16 grade 3 and 4 toxicities, that could be attributable to valproic acid, to the radiation, to other things, and what I show here is, they were not proportionally related to the level of valproic acid. They were independently related to that value. And so I don't know how many of those were related to valproic acid. I believe all the neurologic ones were. In our first 7 patients, most of them had hallucinations.

02:10:37 So some people, one woman smelled rancid meat in the department, which we didn't have, I promise. One person thought everybody was bearded. There was some very interesting things from a clinical trialist point of view, it was only in my first 7 patients. I think I skewed that because I told every patient after that, that they were going to have hallucinations and that was normal and it also proved to me that the drug was getting in through the blood brain barrier into your brain and that was a good thing.

02:11:10 It didn't bother people after that and I had no reported after the first 7 patients. It's just kind of an interesting sort of side bar, sorry. Well interesting to me. So what was wrong with the study, I did no temozolomide work pre. I just kind of through that together, so I'm a pre-clinical trialist. I would argue against ever doing that, but we did it.

02:11:31 We didn't know the MGMT status. So, somebody earlier mentioned that MGMT is this great bio-marker, it's done everywhere. It's not, it's a terrible bio-marker, because it's incredibly unreproducible. So the same tumor sample sent to the 3 different labs, you get MGMT positive MGMT negative and we're not quite sure. Now that's going to change in the future. They're doing these great pyrosequencing and they're going to fix that but we didn't have that so we don't know the MGMT status. That will come up in a second.

02:12:02 The other biggest problem, I think from my study was the accrual took just way too long. I should have gone multi-institutional earlier, got a couple of people who weren't RQG trialist and just loaded up the patients and that would've worked. I had Mitch Anscher collaborated with us and actually got 7 patients from VCU at the time, but it was, I should've done it much faster.

02:12:23 The other problem being an actual clinical trialist, the patients actually get a say in their care, which is terrible if we're trying to control things. But after the fact, if a patient felt 'hoogie', they went on Avastin. And I couldn't stop them. Right, half my patients went on Avastin. Now, those patients actually did worse, we can argue why that is, but it's not mice, and so it's hard to sort of control out the back side in a radiation trial. I heard somebody mention oligometastic disease, wonderful. We're only going to get to treat that patient and keep them from getting chemo for one month. And as soon as they see their med onc they're going to go on another cocktail of chemo. And of course the med oncs are going to say it's the chemo that kept the disease away. Again, that's sort of one of those little problems. Sorry, I'm running out of time.

02:13:23 So, phase II study, really good findings, great. JCO. Nope, get this lovely letter from JCO, we don't publish phase II studies anymore. I send the magazine, here's a phase II study, it's right there, I can see it. The next month, another one. They just didn't want the radiation. Fine, okay, I can do that. Three submissions to the Red Journal, it took me to get this published. And I want to show you some of the comments that they had.

02:13:49 So, this is, there have been six other studies of molecularly targeted agents in the era of temozolomide and radiation and I list those six here. And one of the things, and somebody mentioned this early, but one of the things I think is really important for us to present is not just a cute grade III, IV toxicity. That's sort of a drug thing, right. Yeah, we need to report that, what we really want to know is, the new drugs, did that prevent the radiation from getting in on time.

02:14:21 That's their standard of care. If we say it should take 42 days to get in, how many of those patients couldn't get in, because we were screwing around them up in the ICU with some effect. And that should be reported, and you can see here, it's not, it's not reported. So, the column is not here, right this second, but I can tell you, it looks just like this. The next thing I think we need to do is report late effects. Not a single one of those studies presented late effects, none.

02:14:48 The other problem that I think that we sort of have to write editorials on and decide is, so mine is a phase II study. So I argued that my phase II study should be compared to Doctor Stupp's phase II study of temozolomide and radiation. Apples and apples. And in that he had 62% of his patients had toxicity. Okay. I'm sorry, 62 of 64 had a toxicity. I had 22 of 37.

02:15:22 And what the reviewers kept harping on, time and time again is, well we know a lot more about the drug now, because of Dr. Stupp's phase III study. Which is presented here, and in that only 7% of patients have a grade 3 or 4 toxicity. Not 97. If you look at studies of phase II to phase III studies, that's always the case. The toxicity profile drops dramatically, and that's because we know what the toxicities are and we tell everybody to expect them.

02:15:54 Much like my patients with the hallucinations, it doesn't bother them when they get it and you don't call it a grade 3 toxicity. They don't even tell anybody about it. They're just think everybody has beards. But I tried to reinforce in the reviewers and they just would not let this piece go. It just really bothered them that my, that I was adding so much toxicity to the standard of care temozolomide. That's just something I had to say because it drove me crazy. They let me talk, so.

02:16:22 I want to thank a couple people, Dr. Tofilin obviously and Mary and Tamly did all the valproic acid in my lab, that's two of my technicians, and Uma Shankavaram is the bioinformatics person I work with that gets everything done and I'm a minute 15 over. Sorry. Questions?

Coleman: 02:16:44 Time for one quick question or is people coffee-o-penic.

Camphausen: 02:16:49 Alright, since I'm on my soapbox, I would argue that hypoxic cell sensitizers have not worked because tumors are not hypoxic over the course of six to eight weeks of radiotherapy. That's why they don't work. I thought you were going to say that, Ted, you went in a different direction. All of examples of hypoxia are usually point measurements, so at this time we have this much toxicity. I would argue a week later, those hypoxic cells have flipped flopped with other hypoxic cells. And so we're only drugging a certain amount of cells a certain of time and that's why they haven't worked.

Williams: 02:17:23 I think just on the linkage of that, if you do pre-measurements and look at the relative change within a short time frame of radiation, that's when you will be able to predict when you're getting benefit from hypoxic sensitizers. And pre-clinically we've seen the same as what's been observed clinically with that, so I think that might be the way to go rather than it takes in the reoxygenation.

Camphausen: 02:17:45 Yes.

Speaker 10: 02:17:46 Very interesting talk, my questions related to sort of one point you touching on the slide about sort of the patterns. The problems with repurposing the drug is that you don't have a company that has a invested interest and even though your phase II has a very promising, you know, a progression free odds of survival, how do you resolve that issue, that there's no company, no pharma that's you know investing in your drug?

Camphausen: 02:18:11 Yeah, so I'm sorry, I got delayed, so I skipped over that. His point is excellent. So, I just repurposed valproic acid. So, you know, an immune checkpoint inhibitor just got approved and I saw the patient number, I can't remember what it is, somewhere between 380 and 630,000 dollars, something like that to treat the patient. My valproic acid study, per patient, cost $20, so the entire study was $800. 800, okay. Now, here I am, phase II study, works great, nobody's interested. There is no pharma and our cooperative groups, this is not a trial that interest them. This is an old drug, everybody knows about it, it's not sexy.

Camphausen: 02:18:54 I thought this was going to be the perfect way to do it, I was bringing this inexpensive product forward, and then I realized, I've got to have pharmaceutical support to make this go forward. So I'm asking my AstraZeneca people, to like attach something to valproic acid and make it a real cool booma booma molecule.

Illidge: 02:19:11 Just a comment Kevin really, about drugs not crossing the drug brain barrier. I think that's wrong, and I think, there's a lot of mythology about that. I know I'm not a clinician scientist interested in brain tumors, but I've heard some very compelling data and I have some in the pack that Anthony Chalmers gave me showing that the DDRI's do cross the blood brain barrier. So, I think that's actually a wrong assumption and we're, missing an opportunity for a number of drugs that actually may very well add. Did you have something Kaye, to add there?

Williams: 02:19:49 No, I wasn't going to say, I guess at what point you're looking at the GBM's and how much the brain barrier breakdown there would be anyway might impact on that. But also I don't think we really know what radiation does to the brain barrier, and that's something that's really interesting to start modeling.

Camphausen: 02:20:07 So I didn't mean.

T. Lawrence: 02:20:08 We actually do know a little bit about ...

Camphausen: 02:20:10 Wait, I didn't mean DDR molecules in general, I meant the few that were presented don't cross the blood brain barrier. So I saw Vertex got put up there. Vertex has a DNAPK inhibitor. It's wonderful. Crosses the blood brain barrier, acts as a radiation sensitizer, it's DNAPK inhibitor. Merck has a DNAPK inhibitor, it doesn't cross the blood brain barrier. So, it's drug dependent.

T. Lawrence: 02:20:31 Can I just very quickly say that so we had a study about ten years ago. Looking at doing MRI's during the course of treatment for high grade gliomas. And about one week in to treatment, you see a great increase in gadolinium at least. That now gets in to the tumor that wasn't getting in before and it last for about a month after the radiation's done. So I think radiation does open up, if there is a blood tumor barrier. Radiation can open it up.

Coleman: 02:20:55 Okay, I think we need to go to break. I don't know who scheduled only ten minutes, but, let's try to get back as quickly as we can from the break. Thank you.

Break: 02:20:55 (Music playing)

Coleman: 02:22:53 That doesn't work anymore. Okay. Everybody. Please, please get seated so we can start the next session. And we'll try to get on time and we'll have a panel at the end, so if you don't get to ask your question after the talk, you'll be able to do so, at the panel discussion. So, we'll wait another minute or so for people to come in. The best speech is next. Always be nice to your co-moderator. Things they can do to you.

Coleman: 02:23:34 Okay our next talk is from my co-moderator Kaye Williams, you've already heard some of her great comments already, and she'll talk to us about NCRI CTRad RaDCOM Initiative.

Williams: 02:24:10 Another short person. I want to just thank the organizers for letting us talk about this initiative that set up in the UK. And I hope it just gives an idea of what we can achieve through collaborative networks of labs and that it's something we can then build on.

02:24:27 So, it's the Radiation Drug Combination Consortium or RaDCOM for short, cause that's a little bit of a mouthful. I just want to put it in to context of what was done in the UK, and I guess similar things have happened in the US. It was back in 2003 that the National Cancer Research Institute in the UK identified that radiotherapy was a real area of need. And to increase the amount of research and to increase the number of patients that were going in to clinical trial.

02:24:55 This was on the back of historically very strong research in the UK, so it's almost like we had a little bit of a dip. There was a number of initiatives put in place around this one was the Gray's Street that was set up in Oxford. After moving from London. And there was a review

of the process going forward over a number of years. In 2009, CTRad was launched, and I apologize, there are a lot of acronyms in this presentation. But this is a clinical and translational radiotherapy research working group which Ricky alluded to earlier.

02:25:28 Within this pipeline there's been a number of funding, actually this slide slightly out of date, because we've just achieved round of funding to maintain this initiative. And it really aimed to bring together pre-clinical and clinical researchers across the UK to work together towards getting more patients into trials and improving our radiotherapy outcomes.

02:25:47 CTRad RadCom along this line was set up in 2013. So CTRad's mission statement is quite simple. It's to maximize quantity and quality of life for patients receiving radiotherapy by optimizing tumor control and minimizing toxicity. And you can think from the discussion we've already had, this aligns exactly with at least, in my own head, what we want to do with our pre-clinical data sets, we want to maximizing tumor response and making sure we're not bringing in any unwanted toxicities.

02:26:19 So this is how CTRad is set up. It's a little bit of busy slide, the things I really want to pull out from this, are one, the geographical localization of all of our membership, so it's drawn from all across the UK and we have work streams that are focusing in different areas. And again, from our perspective, this funds the cooperation that you actually do need to be able to bring new drugs in to clinical trials with radiation treatment.

02:26:48 So, when this first set up I was lucky enough to be co-chair of the science base here, and I'm chair the RadCom initiative. But this is really where we're talking about the pre-clinical studies and looking at the radio-biological aspects of drug radiation interactions. The work from workstream 2, which is led by Ricky at the moment, is looking at early phase trials, workstream 3 is interested in phase III trials and methodology. And of course, we're not forgetting new technologies and physics because we absolutely appreciate that we can make as many strides forward in this area as we come from new biologies.

02:27:23 And so working together this grouping can really span all areas where we're likely to make significant impacts to patient treatment. RadCom is set up across workstream 1 and 2. And this is where we've seen the most logical grouping for people around this area because it enables us to bring in the pre-clinical expertise, but also, always with an eye to what is required for that clinical translation. We don't want to be doing fantastic pre-clinical research just for the sake of it. We want to know, what exactly is required for that clinical translation.

02:27:59 So you see in this slide before from Ricky, it's just to highlight that we're critically aware to improve patient benefit it does need the input of these groups of individuals from the academic investigators and clinicians industry and the regulatory bodies. And I think one of the key things for the reason for our work, and is a reason in general, is that because the radiation drug combination interaction is seen quite late in the development of any drug process, often it's really the academic investigators who are really trying to push to be able to take a drug in combination radiation.

02:28:36 And what we really would like to do, is push that in very early consideration for industry, and know there are examples where that is exactly the case going forward. So, RadCom itself, this was the general idea. We hope that if we could set up a collaborative network of labs, in partnership with industry, CIUK and other funding bodies. What we'd be able to do

then is enable a mechanism which would allow the timely delivery of the pre-clinical work package that would give the evidence base for an early phase clinical trial.

02:29:07 So that was our thought process, if we can bring together labs working in this area, we can speed up this whole process. And it was developed by CTRad, also with the CIUK development office and the Experimental Cancer Medicine Center and program office. And one thing to just highlight here that actually with the development of RadCom and how it's managed from the CIUK perspective, is brought much closer alignments with these agencies here. And what that will hopefully do, is enable us to place radiation right on the map where drugs are first discussed early in the pipeline.

02:29:44 Now obviously, there's no point setting up a network if you're not then addressing the problems that people have. So we've spoken to a number of different pharma and companies and looked at what they perceived as being the key challenges for drug radiation interactions. WE mentioned this a few times already in the talks, that the root to the clinic is perceived as long and complex, and obviously the work of Ricky has been very important here.

02:30:07 How to differentiate and prioritize agents within the same class, so example, in DNA damage repair inhibitors, which one, and which sort and target disease? They raise the need for therapeutic index assessment, so effectively can we start expanding it rather just being able to tell them about potential efficacy, but also normal tissue effects. And actually what came up here, was if we could try and find some generalized mouse models for long toxicity, GI and CNS that would be the three things that would be important for pharma.

02:30:39 And actually in labs around the UK, we have two who are working on development of the brain CNS toxicity models as mentioned earlier, there's long work in both Oxford and also some work in Belfast, which I'll show you in a minute. And then from GI aspect, we've been lucky enough to collaborate with Epistem, which is a company spun out of Manchester University. Which has a whole wealth of experience in GI toxicity models with radiotherapy.

02:31:04 We also, we're very much aware that with the moving to immunomodulatory agents that we have to have models where we can look at these, and obviously Tim's mentioned these earlier. So, addressing those points, obviously a key one was Ricky's work in the roots registration working group that led to this consensus statement and some of the foundations for the workshops over the next couple of days. So really bringing people together and seeing what are the hurdles and what we should looking for in terms of getting a drug into the clinic with radiation treatment.

02:31:35 And this has led to thoughts about trial design. And I just wanted to flag this trial up here. And it addressed some of the problems and it links to some comments that Tim made earlier. Out of the CTRad movement, has become this idea of developing multicenter, multi arm platform studies, and so Concord is good example of this. This is a study for nonsmall cell lung cancer. And the idea is that you have continuous recruitment across different agents so this is hopefully to speed up versus having multiple and Phase I trials running simultaneously.

02:32:08 There's also a different trial design tied to a continuous reassessment model. Which effectively gives you real time data with about normal tissue effects within here and any sort of toxicity, so it again accelerating recruitment and dose escalation. And it hopefully

help make decision making within dose escalation process. And also the radiotherapy protocol has been very clearly defined that you get both tumor and normal tissue dose constraints. So that you can accurately map what's happening with the DNA repair inhibitors, specifically to the tumor versus normal tissue effects.

02:32:45 WE also developed a disease site specific reviews and again this was really knowing what molecular targeted agents were available and then mapping those against diseased areas upon that might need an opportunity. And this again has been linked with clinical trial design expertise. So hopefully if there was an area that was identified and a company was interested in that, we'd have the wherewithal to be able to design a trial appropriately for that particular combination.

02:33:10 And of course, within these review articles the considerations of tumor site dependent signaling pathways, so what's the reliance between different tumors, mutations that may favor a specific target therapy, and also the actual radiotherapy requirements to taking on normal tissue constraints for a particular disease site. Moving more to the actual pre-clinical side of this. We developed also radiotherapy capability and facility maps. And what this was about was really finding out what we actually had across the UK as a whole, in terms of both invitro and invivo models, biological systems and also equipments to be able to do radiation research. And so what we can then do is very rapidly identify groups that at least have the capabilities to be able to take forward a drug RT combination very quickly. And then when working together can deliver high quality pre-clinical studies in a very short time frame.

02:34:10 Why has this been useful up until now? Well often labs focus on a particular disease area, so way we had a therapy that might be useful in head and neck long NGI it's unlikely any one individual lab would actually have models of it already established for all those, but if know which labs have, we can bring those together. We were very keen to make sure that we were able to incorporate normal tissue expertise and spilled in on that point that Tim made, this was an area where we were lucky, and so labs have had to go out specifically start developing their programs within this area. But now it's puts us in a much strong position.

02:34:46 I think, really important as well, is just actually promoting that collaboration within any radiotherapy community. I think the big thing that we've learnt from CTRad is once you have a few meetings where people get to know each other and come together regularly at these meetings, it's amazing how quickly you can then start to progress things. And just like the point that was raised before about how important QA is in clinical radiotherapy trials, we're actually trying to do similar things in the pre-clinical space. Looking at RT quality assurance from pre-clinical studies working with the National Physics Lab in the UK.

02:35:20 So this is how it's set up, I apologize it's a very busy slide, we're supported by a project manager from CIUK, Em Auger. We have CTRad representations from both the co-chairs of workstreams 1 and 2, because it focuses on that pre-clinical radio biology and early translation. At the time we set up RadCom we had a series of themes that we thought might be the important places where opportunities were going to arise, so themes are listed here. Of course, we are always involve our patient and consumer reps, we have reps from CIUK, and also from the National Cancer Research Institute.

02:35:56 The current work that we're doing has collaborations with Pharma and across all other groups as seen here as Ricky's mentioned previously. And these are the names at the moment, now you need to take nothing from this other than everybody who's purple, in this

case, is clinical. So either clinical research only or for a vast number of these individuals pre-clinical's clinical. And again I think that strengthens the idea, when we're approach by Pharma, although it's pre-clinical work they want doing, they don't want it doing in isolation from the clinical expertise.

02:36:27 And so having that immediately in place, I haven't detailed it here, but all of these guys have expertises in different and clinical disease sites. It really enables you to put forward a group that can work seamlessly from that pre-clinical to clinical translation. So what does our portfolio look like? Well, so since 2013 there have been 16 pre-clinical projects that have come through RadCom, working with 11 different Pharma companies. We've got our active collaborations at the moment plus ones that we've had previously. They've involved 18 different lead investigators. Across 9 institutions in the UK. And tested so far 13 different agents.

02:37:09 I just wanted to highlight here, also, although a lot of the work focuses on external beam radiotherapy, we've also had projects around molecular radiotherapy, and we don't just focus on the tumor efficacy, but also normal tissue damage and radio protection. So hopefully this is just illustrating that by linking labs together, you can get a very broad portfolio of what you can actually achieve.

02:37:33 I've just got 2 examples here of studies that have been done recently in linking with RadCom. Just to exemplify what can be done. So, this is a study that was in place to actually support the Concord trial I mentioned earlier. So one of the things with the Concord study is that we were well aware of the potential impact of the DNA damage response inhibitors on radiation response and efficacy in the tumor, but there was very little normal tissue data at that point.

02:38:04 And so, both groups in Oxford and Belfast have been working on this, but this is the work from Cal Bottlewich's group where he specifically looked at the impact of radiotherapy plus an ATR inhibitor in both non small cell lung cancer cell models invitro and in vivo but then also looking at the normal tissue toxicity in the lung.

02:38:24 So he can then give a little bit more of an indication of the clear therapeutic index here. And I know there's going to be lots of comments about how well our mouse models are mimicking normal tissue toxicity and hope we can bring those in to the conversation. And when we get to our discussion points, but I think it really does show that there is a bit of step change in that we are having to recognize that normal tissue and damage and being able to analyze it as well as the tumor efficacy.

02:38:49 And I guess from my own perspective, the key thing that comes up in here, with the mouse models that we use, it's very challenging to do experiments under the time scale for the tumor and what's required for normal tissue effect time scale. That's one of the things that has made it difficult for us to bring these things together.

02:39:07 The second study I want to give, it's a sort of repurpose and I'm using that a little bit loosely, however I thought it would fit in with Kevin's talk a little bit and this is from Elora's group down in Sheffield. And she came forward to RadCom having a little bit of understanding in radiation and radiation combinations but what she really wanted was that expertise of being able to take some really promising invitro data that she had about radio protection.

02:39:33 And using cell models in to in vivo models. So she done a little bit of in vivo work but she really need that extra expertise to try and help her refine the in vivo studies. So she looking at a radio protection agent here for the GI tract, so her in vivo study design was supported by Epistem, bringing in their expertise at being able to do this as a commercial venture, so obviously very stringent and studies there. And also she was interested to see if we could, if there was option for us to be able to look at coincidental

02:40:00 If there was any option for us being able to look at coincidental tumor and normal tissue effects in the GI tract, and we were able to help there, and because we have complex in vivo models, where we can actually do abdominal radiation for normal tissue and tumor within the same animals, and then track what was happening from the tissue pathology. So, I think what's nice is here is this is just illustrating it isn't all about pharma. This is an academic coming forward, and often we get proposals from academics who haven't got any great background in radiation, but they just think that there's a real potential for their particular protocol, and we help with that in design. So, the current status of this is that a clinical trial outline is being developed. And obviously what we want to do is publish the research, as well.

02:40:47 So, I just want to point on about the funding opportunities for preclinical studies, and that there are issues here. One of the issues I think is that, obviously, if we can engage with pharma very early in the process and they can see a really exciting opportunity in radiotherapy combinations, then there's a chance they may fund preclinical work to support that, and that is often the case. However, because of the fact that a lot of the research comes from academic-lead, and clinical academics leading research to say that this would be a great idea to do that, that doesn't always come with the pharma backing, or the pharma will back by enabling them access to the drugs. And in that situation, we're often being reliant on a preclinical combination from these stream that say are you [inaudible 02:41:32]. And this was for very small, discreet pieces of work because the other thing is we're often not doing the really sexy science.

02:41:39 You just want that last piece of data. It might be that a drug's being used in combination with single-fraction radiotherapy and you want to do the fractionated schedule. Something like that, that helps you ... Or you might want to do a biomarker analysis, and that's often what we get is, "What could we use as a biomarker for this particular interaction?" So, short pieces of work and it has to be developed with an idea of what a clinical trial will look like. So, this has been very successful and underpin a lot of our work. And we also help people when they're applying for these so we can improve their funding potential.

02:42:09 MRC also have a funding streams in radiobiology highlights, but here you really are talking about bigger studies with a lot of biology input. So, I think the type of work that we want to do often falls between what funders wants, and that can be quite challenging for us. And there's a review at the moment of this funding initiative, and hopefully that will be taken forward positively to enable us still to be able to access small pots of funding that are simply for very small studies required for this translation.

02:42:38 We've also been able to successfully exploit CRUK working in partnership with specific disease site charities, so be that brain cancer or whatever, to help us develop programs of work specifically in that area. And of course we're supported through all of this through Cancer Research Combinations Alliance and the CT WRAP Network. So, [inaudible 02:42:58] the support for all of this from the RadCom perspective, CRUK Combinations Alliance, so

that they've helped with the initiation of all of these studies. If anybody's interested, obviously, you can chat me over the course of this meeting, but also contact via [Agath 02:43:15] and our RadCom project manager, and she will be able to help you figure out how to develop it ... an idea further through RadCom. So, I just want to thank you for your attention and I'm happy to take any quick questions.

Coleman: 02:43:32 Let's see if we have time for one or two questions, perhaps, or we can save it for the break. But to bring something to your attention ... So, the NCI has been working to get combined modality preclinical work done, and we have a cooperative agreement that we hope will get four programs funded.

Williams: 02:43:49 Excellent.

Coleman: 02:43:50 And I think this would be a perfect way to liaise across the ocean to work with you folks.

Williams: 02:43:55 Yeah, fabulous.

Coleman: 02:43:55 And your organization is really spectacular. And so [crosstalk 02:44:00] to-

Speaker 11: 02:44:00 Kaye, a very quick question along those lines. Would you welcome people from the US participating in some of the conversations that you're having on how to organize these?

Williams: 02:44:00 Absolutely, absolutely.

Speaker 11: 02:44:00 How do we do that?

Williams: 02:44:12 Just talk to me. Talk to us.

Coleman: 02:44:12 I think you need a better accent.

Williams: 02:44:18 Thank you very much.

Coleman: 02:44:21 Okay, thank you. So, these discussions will come up more, and it's really terrific. So, we have FDA next, and the FDA's always great because if you need to blame somebody, you can always blame the FDA. No, the FDA's been terrific, and I'd like put a special nod on to Amanda Walker for the incredible job she's done in helping get the FDA going to the level that it has in combined modality and to the collaboration you've developed across government agencies. So, my kudos to you, thank you. So, Todd, thank you very much for coming here and-

Palmby: 02:44:49 Yes. So I'm Todd Palmby. I'm one of the pharmacology, toxicology supervisors in the oncology office at FDA in CDER. So, the team that I work with, and there's three of us, we review all of the nonclinical studies and data that are submitted with regulatory submissions to support the cancer indications at all stages of development. So, I'm gonna talk a little bit, briefly, about some FDA considerations for development of pharmaceuticals in combination with radiation. So, there's a list of abbreviations for your reference. So, I'm gonna focus a little bit, because of the audience here, I'm gonna start with a little background on nonclinical IND-enabling studies for pharmaceuticals, talk a little bit about how we approach combinations of pharmaceuticals, and how we can apply that similar thinking to

combinations of pharmaceuticals with radiation, some specific considers to moving to earlier line therapies, and then finally, I'll just give a couple of case examples to illustrate some points.

02:45:57 So, we follow the International Council on Harmonisation S9 guidance, Nonclinical Evaluation of Anticancer Pharmaceuticals. So, you'll notice the S9, the S stands for safety. So, I wanted to point out just based on some of the discussions that have gone on previously in this session, at FDA our nonclinical review is primarily focused on safety. We do expect that there is a biological and scientific rationale supplied in an initial IND submission, as well as for a new protocol of a combination, etc. And I'll get into a little bit about that, but our primary concern really is safety and safety of the patients enrolled in the trials. So, this guidance aims to facilitate and accelerate development of anticancer pharmaceuticals, and protect patients from unnecessary adverse effects. It provides recommendations on the type and timing of nonclinical studies for anticancer pharmaceuticals, specifically focuses on patients with serious and life-threatening malignancies, and it does include both small molecule and large molecule, or biologic, products for which the ICH S6 guidance is generally referenced.

02:47:07 So, what is needed to support a first in-human clinical trial for a pharmaceutical in patients with advanced cancer? The data should provide a proof of principle of what your molecule is expected to do, the projected, at least preliminary, mechanism of actions studies. It should define a safe clinical starting dose to initiate dosing in patients, and it should assess the toxicity and the safety of the drug, specifically that target organs affected in the animals, which can inform on the patient monitoring in the initial clinical trials.

02:47:40 So, specifically the pharmacology studies, these provide the proof of principle. They provide the biological rationale of why you think this particular product is going to have activity in a given disease setting. These include preliminary mechanism of action studies, and they also include preliminary activity studies in vivo, characterizing the activity in vivo models. These studies may also guide the clinical development, they can aid in selection of start dose and dose escalation scheme, the administration's schedule, the safety biomarkers, and any diagnostics that you may want to develop to select patients who enroll in the clinical trials.

02:48:24 So, the IND-enabling toxicology studies are primarily focused on safety. These are aimed at determining whether the risks are acceptable and manageable in the given patient population. They also can guide clinical trial design by selection of a safe start dose in patients. They assess the target organs of toxicity and enable monitoring. And they can assess potential reversibility of serious toxicities, and they can be used to optimize the route schedule and dose escalation, as well.

02:48:57 So, in general I just wanted to highlight what a toxicology study looks like, because many of you may not be aware but the expectation is that one study in rodents and non-rodents are conducted to support an initial first in-human trial for a small molecule. Single spaces may be justified, for example, for monoclonal bodies. Many of them don't cross react with the murine or the rodent target. So, the route and schedule used in a toxicology study should simulate the proposed clinical protocol, and in patients with advanced cancer, toxicology studies of one month duration are generally sufficient to support continuous dosing in clinical trials. The product that's used in these studies should represent the active substance that's used in the clinical trials.

02:49:47 So, I put this up here not so that ... I have a few slides to follow here on how we go about selecting a starting dose for various types of products for patients with advanced cancer. And the intent of this isn't so much that you all know how to do that specifically, but it's basically to just you a feeling that, depending on that activity, the characteristics, the type of molecule, etc. that's being developed, the approach that we use for determining a start dose can differ. And that regardless of whether you're using that pharmaceutical by itself, or in combination with radiation, which I'll get into in the future, you should still follow that similar approach for that particular pharmaceutical. So, it doesn't necessarily change what we would expect for how you're selecting the start dose for the actual drug.

02:50:39 So, in the case of a small molecule, we use something called a severely toxic dose to 10% of the rodents, or a highest non-severely toxic dose in the non-rodents species. We convert to make per meters squared or body surface area to scale between species. And then we use a various, sort of, decision tree to determine whether we would use one-tenth of the rodent dose, or one-sixth of the non-rodent dose to select the start dose. So, for large molecules, or biologics, we use different approaches, such as a no observed adverse effect level, and a fraction of that on a milligram per kilogram basis, and this is because those molecules are not expected to leave the vascular space. Start dose can also be informed by pharmacokinetics, pharmacodynamics, and other approaches for large molecules.

02:51:26 For antibody drug conjugates, we use a similar approach to a small molecule, actually, even though they include an antibody. The approach of one-tenth an SDT10 or one-sixth an HNSTD based on body surface area was found to be generally safe in a retrospective analysis done by some colleagues at FDA. This was done for first generation ADCs with microtubule inhibitors such as MMAE. Alternative approaches should be considered and have been acceptable, and for second and third generation ADCs with other payloads, a different approach may be warranted. Toxicities with ADCs are generally related to the small molecule and independent of the target of the antibody.

02:52:10 So, immuno-oncology agents obviously are a huge class of products that have emerged in the last few years, and have been discussed already today extensively. The greatest concern for safety for a first in-human trial is often the potential for cytokine release with these products, and therefore the start dose selection is typically based on what we call a minimally anticipated biologic effect level, or a MABEL. There's no universal approach at this time for determining a first in-human dose based on a MABEL, but it's often based on a compilation on in vitro pharmacology data from target cells and concentration effect data from in vitro in vivo studies. This does result, many times, in a starting dose, which can be well below and efficacious dose in patients with advanced cancer, and many of whom, or most of whom, have exhausted available therapies by that time.

02:53:02 So, I thought now I'll talk a little about how we approach combinations of pharmaceuticals for oncology. So, at this time there is no regulatory guidance, as has been stated, for nonclinical studies to support development of combinations of a pharmaceutical with radiation. However, we can apply similar thinking that we applied to pharmaceutical combination development. So, there is an FDA guidance for industry co-development of two or more investigational drugs for use in combination. And specifically within this guidance, it references the reader to the ICH S9 for development of the anticancer combinations for the nonclinical studies. So, if we go back to the ICH S9 guidance, this recommends that toxicology studies with each pharmaceutical should be conducted with that particular drug alone, and that data to support the rationale for the combination should be provided to

support the combination study. This data can include in vitro and, or in vivo data, or even a literature assessment if there are adequate justifications available through literature.

02:54:12 So in general, combination toxicology studies are not warranted for patients with advanced cancer. So we do not expect a combination toxicology package for pharmaceutical development for oncology. And there a couple of different scenarios that we get quite frequently. So, if the human toxicity profile has been characterized for each pharmaceutical, for example, there's been a completed phase one, or a monotherapy phase within a phase one for each drug alone, then generally no combination studies are needed to support that trial. If there is one of the drugs in the combination is in early stage development, such that the human toxicity profile has not been characterized, then a pharmacology study to support the rationale should be submitted for the combination, which should provide evidence of increased activity in the absence of substantial increase of toxicity, on the basis of limited safety endpoints, such as mortality, clinical signs, body weight, etc.

02:55:12 So, why do we not expect combination toxicology studies in oncology? For one, patients have advanced disease with limited therapeutic options. Two, large numbers of industry and investigator-sponsored INDs are submitted to FDA for clinical trial with combinations of investigational products, and it's not practical and may actually impede discovery or development of efficacious combinations if we require these studies for every such IND. Treatment of patients with cancer involves more drugs than those treating the cancer itself, such as antiemetics, antifungals, steroids, supportive care, etc., and it's not practical to include all of these in combination toxicology studies.

02:55:54 In addition, we generally have some clinical safety data with monotherapy before doing combination trial. So, first in-human administration of an investigational anticancer drug is typically as monotherapy, and it's actually pretty rare for us to receive protocol for a trial as a first in-human dose as a combination. Clinical data as monotherapy can be limited, as well, such as even lead-in phase, a monotherapy phase, or concurrent trial with monotherapy. In fact, clinical data with monotherapies has generally been more useful to determine appropriate combination starting doses, when it's available.

02:56:34 So, what are our nine clinical recommendations at this time for combination of a pharmaceutical with external beam radiation therapy? So, first, as was stated many times, you need to provide a rationale or proof of concept for combining it with radiation. We don't get so much into the efficacy studies as has been focus of many of the talks prior to mine. We need a sound scientific plausibility, a rationale, but we don't specify what that should be at this time, generally. That goes for all pharmaceutical development in oncology, at this point. So, our recommendation is to follow the appropriate guidances for the development of the pharmaceutical, and that safety evaluation of the pharmaceutical alone, in relevant animal species prior to the first in-human radiation combination study, should be provided if there's no previous clinical experience with the products. So, if your first in-human study is expected to be in combination with radiation, you provide the safety evaluation with the pharmaceutical alone, as we expect for combinations of pharmaceutical, and you provide your proof of principle rationale. You may rely on previous clinical experience, if it's available, with the pharmaceutical alone, as was stated for combinations of pharmaceuticals, and any nonclinical evaluation with the drug by itself, to support dose selection of the actual drug in combination with radiation.

02:58:06 Examples have been given already of development programs that were initially done as monotherapy and then subsequently done in combination with radiation, such as temozolemide or Mident, and then [sutuxemen 02:58:19]. So, again combination toxicology studies with pharmaceutical and radiation are generally not warranted with advanced cancer. Specific case when a pharmaceutical is being developed as radiosensitizer, especially in cases where it's expected not to have any antitumor activity by itself. In addition to the safety assessment of the pharmaceutical alone that's expected, a study in animals comparing the toxicity or the pharmacodynamics in the presence and absence of radiation, maybe provide additional useful information in assistance to selection of radiation dose in patients on the basis of the extent radiosensitization. So, just a few brief words on moving to an earlier line setting. So, often times these populations, if you move to an earlier line setting are smaller subsets of patients based on genetic or expression markers. The clinical history of such smaller subsets can be less characterized. It's often more difficult for us to work with our clinical colleagues to figure out what is the actual prognosis of patients in this setting, what alternative therapies would they get, that sort of thing. Treatment in the neoadjuvant or first-line setting, or treatment of indolent cancers often results in longer expected survival times. There's often more available therapies with clinical benefit that have a more toxicity profiles, and the standard of care many times may not include any treatment at all.

02:59:50 And so this raises the question, are additional nonclinical studies needed to support trials of combinations of a pharmaceutical with radiation in such settings? And it really depends on multiple factors. It depends on the particular mechanism of action and the safety profile of the drug that's involved. What are the safety concerns that have been identified to that point in development? What is the extent of the clinical experience in patients with more advanced disease, such as the metastatic setting, or relapse and refractory disease? What's the prognosis? What are the alternative therapies for the standard of care? And then finally, the route, frequency, and duration, and administration. So, unfortunately, the best advice is that this is gonna be taken case by case, and we would recommend that you talk to your division, have a clear definition of what your expected patient population is gonna be, inclusion, exclusion criteria, etc., so that we can work with our clinical colleagues to really figure out if there's really a data gap in the assessment of safety that can be addressed by a nonclinical study.

03:00:52 So, finally, just some case examples. So, the first example is a more rare example that we see. So, this is an example where someone is submitting a protocol for a first in-human study with a small molecule drug, where it's gonna be given with combination in that first in-human study. I have not seen such a case very frequently at all in my time at FDA. However, if such a case occurs ... So this is kind of a made-up example, but based on some examples that I had. So, there's a proposed phase one first in-human trial with [combinatanib 03:01:27] and radiation in patients with GBM. [Combintanib 03:01:32] is a kinase inhibitor that crosses the blood-brain barrier when administered orally to animals, and is proposed to have multiple mechanisms of action, that may lead to enhanced antitumor activity when combined with radiation.

03:01:44 So, the nonclinical studies that are submitted to support a first in-human trial to the FDA package are in vitro and in vivo pharmacology studies of [combinatib 03:01:56] to demonstrate that it does have some monotherapy antitumor activity. However, in an in vivo mouse tumor model with [combinatib 03:02:02] and radiation, there was an enhanced antitumor activity over each treatment alone. The one month repeat dose toxicology studies

in rats and dogs were submitted with the oral [combitanib 03:02:14] to assess safety. The human starting dose of the [combitanib 03:02:19] that the actual drug is based on the animal toxicology studies as was described in some of the earlier slides that I presented. The clinical trial design included combination of the oral [combitanib 03:02:32] administration with radiation and included a lead-in phase of the [combitanib 03:02:37] alone prior to the radiation. So, in this case, we would not require any additional nonclinical studies to support this trial.

03:02:48 Example two is a more common example, so this would be many of the investigator-sponsored INDs that we receive for combination of an investigational agent, or approved agent, with radiation in various disease settings. So, in this case, you already have some clinical monotherapy safety data, in addition to all the nonclinical safety studies and pharmacology studies that were submitted to support that initial first in-human monotherapy study.

03:03:16 So, in this example, you have a proposed phase one trial to assess the efficacy and safety of [rediliamab 03:03:22] plus radiation in patients with metastatic triple-negative breast cancer. [Rediliamab 03:03:26] is a checkpoint inhibitor monoclonal antibody that's been tested in a completed phase one trial as monotherapy. The nonclinical study submitted with [rediliamab 03:03:37] to support the first in-human monotherapy trial included in vitro pharmacology studies, assessing its mechanism of action, as well as an in vivo pharmacology study, including syngeneic mouse tumor model with murine surrogate antibody. They also submitted a one month repeat dose toxicology study in monkeys. So, the proposed dose in the combination study with radiation is based on the monotherapy clinical experience. The rationale was provided for the combination by submitting results of an in vivo mouse breast cancer model study with a surrogate antibody and radiation, and it was based on the literature assessment. So, again, in this example, to support this combination trial, no additional nonclinical studies are needed to support the proposed trial from a nonclinical standpoint from FDA.

03:04:31 Now, based on some of the discussions ... I have 20 seconds. Based on some of the discussions previously, I just wanted to bring up a scenario. What if we didn't even have the in vivo mouse breast cancer model data in this example? What if we were just relying on literature? So, for example, what if this particular product was a PD-1 or a PD-L1 inhibitor, of which we have many in development, we have many approved, etc. There is a breath of published data now to support the biological plausibility of combination of a PD-1 or PD-L1 with radiation. In this particular case, if this was a PD-L1 from our standpoint, we would accept the literature assessment as sufficient. We wouldn't even require an individual mouse study to be submitted. So, for example, for many investigator-sponsored INDs, we don't expect even pharmacology studies, often times, to be submitted, other than what's available in the published literature. So, there are cases where that would be sufficient for us, and often have been in the past.

03:05:34 So, just to summarize, very quickly, follow ... Excuse me. Follow appropriate regulatory guidance for development of the pharmaceutical, including pharmacology and toxicology studies. You have to provide the rationale, the proof of concept for the combination with radiation. Combination toxicology studies, the actual big safety studies, with the pharmaceutical and radiation, are generally not warranted. And for radiosensitizers, an additional study in animals comparing toxicity and, or PD with or without radiation, made in

selection of a radiation dose in patients. And there's some references at the end. Okay? So, any questions?

Coleman: 03:06:14 Okay, so what I think we'll do now ... We can have the other speakers come up. We can have some questions for Todd. That was just such an incredibly useful talk, by the way, and very illuminating. So, the other speakers come up. We have two additional panelists, [Ozlem Ataman 03:06:29] and Melinda Merchant from Sojo and AstraZeneca. So, we'll start with questions to Todd, if you want some. We'll have the two industry folks say a few words, and then we'll have an open session.

03:06:43 We have a slide with three questions that we wanted to raise during the session. They promised it would be here, you can't trust anybody anymore. Okay, so the questions we were gonna have if you guys have them, and this last talk really just opened it, is what is the minimum needed for preclinical data, so that a committee will pass it along to a study, and FDA will accept that as sufficiency? What's the lowest buy you have to cross? The second is, if you like that or not, what good are the models for prediction? And need they be efficacy and toxicity? And we had some discussions on those. And the third, which I think for what we clinicians really wrestle with, is what data would you want to see before you would ask a person to actually join a clinical trial? What could you sit down face to face with somebody and say, "This is a study that I would put my family member on, and I think it's one for you to go on."

03:07:42 So, do we have any questions for Todd first, specifically on the just incredibly informative talk? If not, just leave your number, or you're gonna get a lot of phones calls. That was really just so useful.

Speaker 12: 03:07:55 I had a [inaudible 03:07:58].

Coleman: 03:07:57 Sure. Please.

Speaker 12: 03:08:02 So, Todd, in the immunotherapy space, some of the drugs are now meant to be put into tumor, say STING agonists and whatnot. So, could you comment on that relative to combinations with radiation? I think Mark has data on STING and radiation, and some others in the room, too. Or even repurposing. There are some folks using CTLA-4 inhibitors, putting them into tumor, etc.

Palmby: 03:08:33 Yeah, so for intratumoral injections we have see many INDs, especially lately, so the STINGs are one class that we've seen that with. In that example, we would generally recommend that the actual toxicology studies be conducted with a similar route of administration. So, those are done in healthy animals, so we can't do intratumoral, but we generally recommend stuff like subcutaneous injections because that will give us a more appropriate pharmacokinetic profile, as well as the effects on local tissues that you'd expect from an intratumoral injection. So, for something like that as well, generally the efficacy models that we get for nonclinical models, so the xenografts, which is generally what we have, are done with an intratumoral injection of the STING. So, I would just recommend that you follow the proposed clinical route of administration like we would for the safety assessment for the tumor models, as well. I think that's about all I have to ... Did I address the question fully [crosstalk 03:09:47]-

Speaker 12: 03:09:46 Yeah, I mean, I think relative to what Kevin Camphausen talked about in terms of repurposing drugs, different routes of administration, right? So-

Palmby: 03:09:54 Right. So, we ... If you want to change the route of administration from what has been studied previously in the clinic, sometimes you need additional nonclinical studies, sometimes you don't. It really depends on what you're going to. If you're going from, for instance, IV to subcutaneous, you may not ... Depends on what the product is. We may want just an initial study with some subcutaneous just to make sure there's no real local tissue effects. It depends on what the product is, too. It depends on what the difference in the total systemic dose would be. If you're going the other way around, where you start with subcutaneous and then you wanna go to IV, you'd probably need a toxicology study to support that. Now, what studies would you need in combination with radiation? Again, it would probably just be a proof of concept, so I don't know that there would be any requirement for a new proof of concept study if you can sort of bridge to the PK and toxicity profile itself.

Speaker 12: 03:10:55 Thank you.

Palmby: 03:10:55 Okay.

Goldberg: 03:10:55 Thank you. Two questions, actually, Todd. The first is, is there a plan to develop radiation drug guidelines in the near future? So, that's number one. Pause there.

Palmby: 03:11:09 I would maybe give that question to Amanda. I'm not aware of any from my perspective, that doesn't mean there isn't talk about it, and in what stage, I have no idea. But I'm not aware of any.

Goldberg: 03:11:22 Okay. And the second is as alluded to through a number of speakers, there's a very well-worn path to get drugs into people. We have a clear path to the IND. We have a clear phase one with patients, and just speaking about oncology, with very advanced disease with no other treatment. That doesn't work for combinations with radiation unless we allow the model of simply giving the drug with a bone met, for example, some kind of short course palliative radiation, as a safety phase one type experience that would then allow us to leapfrog into a phrase three in a different indication with a different drug schedule, a different radiation.

03:12:00 In a different indication with a different drug schedule, a different radiation schedule, a different body part. How open is the FDA to accepting that kind of a paradigm? And maybe that really is to imagine as well, but I ...

Palmby: 03:12:00 Yeah, that's probably more ...

Walker: 03:12:19 I've spent a lot of time thinking about this because really the goal is to develop better drugs with radiation in the more earlier stage curative setting and how to best really develop that from a pharmaceutical company's perspective. That is not often suggested, but I think that, again, we would have to take it on a case by case basis but the agency would be open to considering that sort of platform for moving those concepts forward. But I think about is a phase one clinic appropriate where you just start a bunch of drugs in combination with radiation and you have, you know, local controls and end point. You expect the tumor to have local control with palliative radiation but perhaps that's some sort of mechanism to

obtain a better signal and then move the most promising drugs forward in clinical trials. I mean, I just think these are concepts and ideas and the agency would be willing to take the clinical data that is collected and then use it to decide, from a safety standpoint, if clinical trials could move forward in the earlier stage setting. Yeah.

Williams: 03:13:20 Just a comment though, I think Tim will remember this. There was a trial from Takeda & Harrington, which I think it was going exactly down that route. That it was done a bone match study first and then going into using that as a foundation to then hopefully bridge the gap into a curative intense study. So I think that has been taken forward in the UK.

Coleman: 03:13:37 We need to have other people speak.

Speaker 13: 03:13:40 My question is that regarding that case to where the drug went through the phase one, you know the phase two that was not even putting it into radiation combination. Does FDA prefer that you go for the second phase one? Do you go back to the original one tenth of a dose or can you do like a safety round and use a phase two dose from a previously phase one and combine a clinical dose of radiation to Rb? I just don't want to do a safety wrong, I mean. When do you make that choice between those two scenarios?

Palmby: 03:14:06 Uh, so generally my experience has been that the dose of the drug, whether it's biologic or small molecule, but the dose of the pharmaceutical is gonna be based on the myotherapy clinical experience that you have already. Now whether you'd want to back off on that dose a little bit is usually a discussion that we have with our clinical colleagues at the time when we're reviewing the protocol. It depends on what the drug is, what the toxicities are. But it's generally not gonna be based on the animal studies at that point.

Speaker 14: 03:14:39 I noticed twice in your slides that you had commented sort of on a combination therapy. That the combination, the radiation sensitizers would dictate the dose of radiation. No, the dose of radiation is fixed on sort of historical controls. So, I would think the question that answers is we would back off one level of drug because we can't drop the radiation dose.

Palmby: 03:15:03 Right. So, I did want to comment specifically on that comment within my slides. Is it right? In the majority of these cases that we're discussing, you've already got sort of a definitive dose of radiation that you know has a certain level of outcome associated with the particular disease. The expectation from our standpoint is not to back off on that. If you have something that has known benefit, we're not suggesting that. It was more in a case where you're really developing something sort of in a novel space where you don't really know what the dose is going to be and you have a sensitizer there that's expected to modulate the actual dose of the radiation that you don't have a good clinical feel for yet.

Coleman: 03:15:46 Last question and then we'll have the ...

Speaker 15: 03:15:47 Yeah, so toxicology evaluations particularly for large biological therapeutics can be completely altered by immune responses of the animals. And this is a persistent problem. So what are the recommendations regarding immunogenicity evaluations in the animals or developing murine versions or whatever and animal versions of the same therapeutic?

Palmby: 03:16:15 So generally we never require a sponsor to develop a surrogate version of a product to cross-react with a species that their clinical candidate does not cross-react with. It can be helpful especially if there is just a lack of data that we have. It can be very informative. But

we don't require it from our standpoint. So if your particular product is not ... and this is the case as you said. The majority of the immune modulating agents that we've seen so far, that we have good clinical experience with, the animal models are not great predictors for the types or sensitivity of the immune response that we see in patients. And so the models have limitations.

Speaker 15: 03:17:04 Right, but do you ask for immunogenicity evaluations so that you understand that the toxicology profile you see may be altered by an immune response the animal has made to the therapeutic?

Palmby: 03:17:16 Oh, I see what you're saying. I'm sorry. So that's kind of a different question, but yes. We do recommend for biologics that toxicology studies include an assessment of immunogenicity. It isn't a de facto expectation but if we recommend that those samples are taken, and that if there are reasons to assess them, that they be assessed to explain the results of the toxicology study. So for instance, if you have some immune type reactions, then you can go back to your samples and see did we have immunogenicity in those animals? Could that explain those reactions? As well as the toxicokinetics, so is it...

Speaker 15: 03:17:56 Right, but if you see no toxicology and you assume it's safe up to a given dose, that could be because the animal has made immune responses that nullify the activity of the product.

Palmby: 03:18:06 Right, so in that case where you have no toxicity and the toxicokinetics are not modulated at all, we would probably ask them to evaluate was there ADA's present that could be neutralizing the effect. Yes.

Coleman: 03:18:21 Okay, so Ozlem you have the microphone. Would you like to say just any comments or general comments? Because we welcome you to the panel so we want to make sure you have a chance to comment and Melinda will be next.

Ataman: 03:18:34 I apologize for my voice because I' having some difficulty. Hopefully I'll complete it. I was involved in a study where we knew the single agent dose of the drug which is a new modulator. The drug didn't have any efficacy on its own. It was meant to be combined with radiotherapy with some good regulator. In that sense we weren't sure like if this possible to register a drug that has no activity on its own and not registered as a single agent. But so that the first call of registration will be with radiotherapy. In this sense, I don't know if there is any guidance or is there anything that companies should be aware of? Because I think there are more and more compounds might fall in this space.

Coleman: 03:19:28 You've done a lot of work in combined modality. Do you have just any general comments about this topic of this meeting and your experience in getting radiation drugs together?

Ataman: 03:19:38 I think in general I ... you know, all the important comments have been highlighted. I agree with them and probably it requires a lot of interaction at the early stage. And you know that the companies are aware of radiotherapy before the life cycle management point. And that is the most important thing to have the early combination. And I think with the UK group we managed the highlight some of these issues. But I think it's still a common problem probably in the industry.

Coleman: 03:20:14 And then Melinda, you'll be next.

Speaker 16: 03:20:15 That topic of the early uptake that came up here on the timeline and radiation drug studies coming early enough in the timeline. That's a big problem. And I think it would be great to have some feedback from the panel about that. Think of the power of the pharmaceuticals in North America and that they know what they ... With the bankroll that they can apply what they're gonna apply to advertising, what they're gonna apply to pre-clinical. And they can move drugs through a pipeline rapidly and decide go or no go and which to develop for clinical trials. And in-house they can do the animal studies, the in vitro studies rapidly. Now, most pharmaceuticals don't have experience with radiation. Most of them don't have radiation equipment in their scientific domain. That, for the select few radiation oncologists that have interfaced a lot with pharma, that's kinda been an opportunity for us. And yet, we are so behind because they don't come rapidly to the radiation question.

03:21:26 Imagine if every pharma knew that they had to have radiation equipment and they were studying right at the beginning their drugs with radiation. This process would go much faster. So that waiting for academia to selectively weight in, occasionally do a study on a new drug with radiation, is part of the problem and the bottleneck. We need to look at ways to obviate that.

Coleman: 03:21:51 Okay, so Melinda from AstraZeneca, if you'll go next and then it will be open mics.

Merchant: 03:21:55 So probably is a good segue. I'm here representing early clinical development with AstraZeneca. Tomorrow you'll have panelists and Dr. Kim and Dr. Iannone from the leaders stage group. But really some of the questions that have been asked here are some of the things that we have struggled in house, specifically with our DDR pipeline. IO pipeline you'll hear as well. But there are other things in combining and if you look up AZ values on google, you will see the first two things are, we follow the science and we put patients first. And so really, I come from a pediatric oncology background. I've been at AZ for a year and a half and I'm leading the medical development of the ATMBBB. So an ATM inhibitor that crosses the blood brain barrier, the clinical trials.gov is up and we hope to actually be dosing in patients. So, it was very similar to the example raised in getting IND and NHRA approval to safe to proceed to start the first in-patient clinical trials with the drug. It did not necessarily design for single agent activity, but good pre-clinical evidence of combination activity that has been presented.

03:23:12 So in looking through those strategies in dealing with groups like Rad Com, Anthony Chalmers, with the LapRib, and other non-approved drugs in our portfolio that are good combination agents with radiation therapy, we have learned a couple of lessons and I wanted to just highlight two as we kick off the panel and then I'm willing to answer some of the questions as well.

03:23:39 One is that the type of platform studies that you heard, the Concord platform in non-small cell but certainly many of you in your own expertise can think of places where it would apply, that that ability to use one clinical trial platform and the radiation specialist that ... it really takes a village to do these trials. It's not a cookie cutter thing. It has been a long year putting together the soon to come to fruition trial. That getting all that expertise in one place and then having multiple drugs that can go through that platform can actually benefit both pre-clinical and clinical development of combination agents.

03:24:22 The second thing gets back to the questions and I'll sort of leave it at there to segue so I don't take too much time. But that is really the questions of what did we need to go into the

clinic and what did we need based on our modeling to go into the clinic would the safe doses that Todd has nicely talked about were required to hit to propose what we're starting with. What do we really need to know about those PK's and the mechanism in the early clinical development that helps us be safely moving forward with the standard doses of radiation. So, in our trial we picked different settings of radiation because it was clear whenever I talked to a radiation oncologist we were not going to move your dose of radiation. I got that loud and clear, Kevin. Early on in the process. And so how can we in lower toxicity, lower risk settings, apply that? But then you get to some of the questions that you've also raised, which is well is the safety and toxicity of a palliative radiation going to apply to the upfront situation where we're really aiming to develop this in our line of sight.

03:25:31 So lots of good questions but I do think there are some lessons learned and some bright spots on the horizon for us to get to.

Speaker 16: 03:25:40 Kaye, thanks. So, Tim you had your hand up and anybody from the audience now who would like to ask questions. Panelists, please just yell out.

Speaker 17: 03:25:49 I think that that leads into beginning to approach the last question on the discussion questions. Which data do you want to see before you would ask a person to join a clinical trial? I think that hugely depends upon the clinical situation. So a patient who is potentially having curative treatment with a protracted course of radiation therapy. It's a very different set of data that you need in the conversation to the palliative situation. So I think that is hugely different actually, the way that we approach that. I mean, what we don't want, and unfortunately we have more examples than we have successes, is where the drug has added various [inaudible 03:26:37]. Or even worse, could actually be detrimental to the delivery of potentially curative treatment. So I think my approach to that last question is, in that curative setting, you're not going to change the radiation dose. You don't want to compromise the delivery of a potentially effective curative treatment so you'd need to have very robust data. Or a different situation where you practice using the treatment after the completion of radiation therapy.

03:27:09 So that situation is very very different where you might play around, for example, in the metastatic setting where you are using a saber approach. We're still, I think, finding our way with the dose in fractionation in combination with an immuno regulator agent. There, I think there really is an opportunity to simply alter the dose, alter the fractionation and that's a very different conversation than the first one.

Coleman: 03:27:40 We'll start with three first this time.

Speaker 18: 03:27:42 Okay. I had a question about for companies choosing to develop things with radiation. And you gave a very nice example of a drug that you have that didn't work as a single agent, which gives you an impetus to develop it with radiation. But if you have a drug that has 15% single agent efficacy, and I come to you and say, "I can double that with radiation." You get approval whether you combine it with radiation or not if you can show efficacy. And it doesn't matter for you if it's 30% efficacious or 15% efficacious. So what's your motivation to take the risk and the extra cost in testing the combined therapy in that setting when you know single agent may get you approval?

Merchant: 03:28:34 So I'll start to tackle that. I do think it does make a difference whether you're at 15 or 30%. It is very clinically specific what targets you're aiming for, your differentiation from what's out there and what bar you're going to have to reach to get different statuses of approval. And so I think that in a setting where you have very poor responses and you think that you can increase it with radiation, that using something like a platform study. Or honestly most of our studies with radiation have been in more investigator initiated settings, where you say, "I'm gonna start out with showing a proof of principle that I can increase this." And then that data, that science drives the next step. So success begets success. And yes, that degree of success I think is important for making the large monetary decisions and risk decision for how to move forwards with a given line of sight for a drug.

03:29:39 It also depends on where it is and how it's hitting with its primary line of sight. Then honestly, as has been said, is looked at very early. I mean, we have to map that out from an early standpoint.

Speaker 19: 03:29:52 It's really a comment and you might be the right person to answer my secondary question. I'm a pediatric radiation oncologist by training, and the radiation PI for the current medullar study in the United States which has decreased the dose of radiation therapy to 18 gray from 23.4, which was decreased from 36 gray in a combination setting. So I think it's important for the group to not stick to a point where we have a dose that works and we're not changing from that. I think that's a mistake. I think it's important in this context to look at the pediatric community as an example. I don't, and I have not experienced the problems that have been experienced in the adult world, mixing chemotherapy and radiation. For number of reasons, some of which don't know. It's different culture maybe. There's a cultural issue associated with all of this, not just a logistic or scientific one.

03:30:48 But the question is this. Given that you're a pediatric medical oncologist, and I have to tell you if I had an ATM inhibitor I would be very much motivated to decrease my standard dose of radiation up front. Just in the beginning. But how do you see the combination vulture in the adult space from the corporate point of view differing from possibly the pediatric space. Is there any wisdom that the pediatric space can give the adult space?

Merchant: 03:31:15 So, I fully agree with you. My giving into not moving at the very beginning is not changing my goal of ultimately decreasing the radiation and doing exactly what the baby brain studies have done, essentially in decreasing that overall. And especially as this is gonna be important in the tumor vs normal treatment window. And if we can have a drug that really helps us take advantage of that, and that's where also understanding where the science is gonna drive us. That might be a different drug when you're going into the brain than it is a drug when you're going into the lung. And so those sort of things that help us to increase the therapeutic window to basically make a same dose of radiation more effective, that absolute next step is can we start decreasing that? To decrease the intermediate--the acute even--intermediate and late term effects of radiation.

03:32:10 So I agree, it does need to be a goal. The layer of pediatrics obviously it's a little tough to think about going there first, but just like leukemia, you brought up medullar blastoma. There are a ton of things to be learned from drug development and pediatrics that have impacted the cancer world that we necessarily don't get to very quickly because, like the radiation, the ped studies often come much later too. And so what I would encourage, and what I do encourage on both of those accounts, is we really need to have the earlier

interaction that starts at the pre-clinic and early clinical stages to lay the foundation to get there earlier.

T. Lawrence: 03:32:50 I'd like to get us refocused on the topic of the session, which is one of the question on animal models. I would love to hear from the industry folks as opposed ... maybe I shouldn't say as opposed to. In addition to the academic folks about what are the model systems that, when you look at those data you say, "I'm convinced that we should move ahead." Versus ... we have gens, we have pediatrics, we have xenographs, we have some of the in vitro systems which set those up. Are there data that are more compelling to people to move something into the clinic? That's a question for everybody.

Ataman: 03:33:31 My take on is that it's not very different from the any other new agent. And I think if you see that among the pediatric activity is much less and combination really is much preventive in the given system of it, so it depends on the drug and which combination you are looking at. I think pharma companies will be inclined to take it to the combination rather than going to the monetary root. We know the future is combinations. So and that brings back to the point because there are not clear I think pharma companies that can you actually reach a street drug with combination, with radiotherapy as the first port of registration. I think this is very important. You can see the efficacy but they are very, I mean in general, not sure about the registration pathway. You know, what is the line of sight of just going with combination. I think that's key.

03:34:29 I also agree that we need more platform studies to know how to have more of them. Like you were mentioning before.

Lacha: 03:34:41 Hi, Benjamin Lacha, Princess Margaret, Toronto Canada. So I'm a new clinician scientist there. One thing that I've found quite enlightening is when I did my post-doctoral training in a medical oncologist physician scientist laboratory. And i guess ... participating in this has been a fantastic experience and just hearing all the discussion for me. I guess one question for me in terms of the Rad Com model is to Dr. Williams and then I guess to the panelists at broad, is I see it as a way that we would need to also really collaborate strongly with the medical oncologist's colleagues as they are sort of ... That is their primary focus in terms of delivering drugs. I know the UK training model is a little different than in North America where we sort of specialize sooner, but I guess the question is how ... Within Rad Com how many are more predominantly medical oncology focus or trained, and then also how is that engaging them as stake holders into this combination space. Because I'm quite interested in how that could also be replicated outside of your program.

Williams: 03:35:46 Within the Rad Com steering group, Ruth Plumber is the medical oncologist. I don't know the background of all of the other guys in there but I know she comes from the medical oncology side and has always been a very major advocate for being able to do drug-radiation studies. So, I guess it's again just recognizing where the winds are in that sort of situation. So, we do have at least a partial balance within there to make sure we kept to that community as well.

Lacha: 03:36:08 Who approached who in that context? Was she interested in joining the group, or ...

Williams: 03:36:15 It was probably a two-way thing. Because I'm just thinking a long time ago we did some of the first work with path inhibitors in radiotherapy back in early ... I think it was published

back in 2004. Ruth was involved in the research groups there so I think she's always had an interest there but I think it's been mutually beneficial.

Speaker 20: 03:36:34 Yeah, I'll just comment on that. So within work streams two we actively encourage medical oncology radiology and some other allied specialties to join. And if one of our medical oncologists from work stream two is here today, Rich I don't know if you want to say anything, but that has been very fruitful, actually. Having medical oncologists within that work stream.

Merchant: 03:36:53 And I would say too from the standpoint of AZ, Anthony Chalmer's original LapRib trials, the operatic, the paradigm were nice foundations to sort of build on and go to bigger platforms. There was the question I just wanted to answer. I do think orthotopic pre-clinical models that do show efficacy, we have partnered nicely with researchers outside AZD 90, the ATM inhibitor with Chris Valerie at VCU, doing stereotactic radiation which we don't have the ability to do in house. But through the stereotactics start to understand that efficacy that you can get with combination. Those are very helpful and useful pre-clinical things to get.

Coleman: 03:37:41 Okay, I think our time is up. So, let me give one call out to AACR. First of all, thank you very much for having this meeting. It's an addition of a molecular cancer therapeutics on the table out there which focuses on radiation. Some of the people in this room were in a workshop a few months ago sponsored by NCI called the Shades of Gray, or Shades of GY. But the whole idea of beginning to change the concept of radiation, of getting away from just using those in gray, but using those into what the molecular perturbations that are created, essentially bringing radiation into the mechanistic field and I think this is gonna be a fantastic marriage for combined modality therapy.

03:38:25 So I'll give Kaye the final word. Thank you very much as I run out to my airplane.

Williams: 03:38:31 Okay, so I don't really have anything particular to add to that but thank you all for your questions and discussion and I look forward to more of that over the next couple of days. And thank you to all of our panel. Thank you.

Sharma: 00:00:27 Good afternoon, everyone. If you could take your seats, please.

00:00:31 It's okay, there's no need to run.

00:00:42 Thanks very much. We do have to start on time because of the live webcast that's been mentioned already. So I think you'll agree that the morning session was very stimulating. It's gone very well. And we're gonna build up even more momentum now with the afternoon session on clinical considerations, and our first speaker is Andrew Sharabi from UCSD Moores Cancer Center. Andrew.

Sharabi: 00:01:09 Thanks very much. I want to thank the organizers for the opportunity to speak today. I specifically thank Amanda. Just putting together such a wonderful group of leaders in the field for this critical topic. So she asked me recently to present on clinical trials, and I'm happy to do so. I'm a radiation oncologist. I'm also an immunologist, a physician scientist, and I run a research lab looking at combinations of radiation and immunotherapy.

00:01:34 These are my disclosures. I will discuss a non-FDA approved or off label use of a number of checkpoint blockade agents. So objectives for today's talk. Understand some of the unique challenges to oncology clinical trials. Certainly learn about some novel radiation therapy trials and design. Really want to highlight the importance of biomarkers for personalized medicine and hopefully for personalized radiation.

00:01:58 Why do we need a specific lecture for radiation oncology clinical trials compared to medical oncology or other disease sites? Well, we certainly have different endpoints. Local-regional control, safety, toxicity. Different patient populations that are involved. Palliative, definitive, oligometastatic. Steve Chmura is here, so I certainly look forward to his talk as a leader in that field. As well as a different risk benefit ratio.

00:02:23 I think, from my point, I think, as radiation oncologists, we are quite risk averse. I think that may have been due historically to the toxicities of older technologies and treatments. But looking forward, if you look at systemic chemotherapies, if a patient is hospitalized and dies, or has a grade five toxicity due to a systemic therapy, that may have some incremental benefit. I think that's just seen as part and parcel of trying to push the boundaries in that setting. Or a surgeon may go in and say up front you're gonna have this deficit, you may lose this nerve and have a palsy. But as radiation oncologists, if a patient dies during treatment or has a significant toxicity, sometimes that's seen as the fault of the issue with the radiation oncologist, or a specific sentinel event.

00:03:12 So, I think, looking at that as important as we look at risk benefit ratios, as well as in personalized radiation medicine. So I think this is kind of a future. Are we there yet? Personalized medicine is certainly moving forward, and medical oncology with a number of specific disease sites, but I think this is something that we can hope for with markers as well.

00:03:29 What can we learn from? I think truly looking at the genomic linkages, genomic markers, can that improve your success rates of trials? It certainly can, as well as biomarker guided. And I think focusing for us as we design additional trials to truly select the right population that's going to benefit from our treatment or a combination. So EGFR, HER2, ALK rearrangements.

Looking at those success rates, those trials are significantly much higher success rate. So I think this is general, and I think we all know that the these phases, of course pre-clinical, Phase I, safety, toxicity. Phase II, continued safety, some efficacy signals. And Phase III, primarily comparing to standard of care efficacy. And importantly, Phase IV as well, post approval, post FDA approval, looking at continued safety signals, long-term and opportunities to combine with radiation therapy after a drug is approved. That's certainly an important space that we can be in as well.

00:04:29 And I think I will touch on, at the end of this talk, on immunotherapy combinations. I think this classical paradigm is still critical, and still very viable in understanding first the safety in toxicity, efficacy, and then in comparing the standard of care. And those are moving forward.

00:04:46 So really, radiosensitisers. Systemic cytotoxic therapies are increasingly combined with radiation to improve tumor controls, targeting micrometastatic disease. But there's actually little evidence that the systemic therapies given at those doses really do much to control distant or systemic disease. This is certainly not a comprehensive view, just some common agents that come to mind and had significant success with cytotoxic agents. So, cisplatin, etoposide, carboplatin, [taxins 00:05:13], 5-FU, vincristine, temozolomide, and so forth.

00:05:17 But I think it was alluded to, briefly before, that there may be additional synergies that are not just these agents helping the radiation work. The radiation may be synergistic ways, specifically with the blood brain barriers. So these agents, radiation can disrupt the blood brain barrier and can help the chemotherapeutics get into the right areas and reach the target cells. So, I think it's important to understand the synergy that can go both ways.

00:05:41 Biologics, I think as discussed earlier this morning, not as much success, but we hope to have some additional successes. So cetuximab, nimorazole, don't forget hormonal therapies. Which have shown significant benefit when combined with radiation therapies. And of course, this is not an exhaustive view, but a number of drugs in trial that are moving forward. But one question that I have with radiosensitisers. Are we already at or close to tissue tolerances for chemoradiation? For just an additional drug that just radiosensitises, is that increase in tumor control just going to be associated with an increase in acute and late tissues toxicity? So, I really believe that for additional radiosensitisers to be successful, they do need to be selectively targeted and have some molecular mechanism which they can directly bind or interact with just the target cells of interest in order to be effective. Because when you look at chemoradiation adding additional drugs, we do see additional toxicities and we're at that kind of barrier of dose tolerances.

00:06:46 So, this is a wonderful paper, really a review by Harrington and Tim Illidge, outlining some of the guidelines for how we can design radiosensitisers for pre-clinical development. And it's kind of a large overview. This is very early on, starting with target identification, validation, and identification of hit and lead compounds. Can use in silico modeling, in vitro for chemistry effects as well, and then in vitro cell line studies. You know, validating these with siRNA and shRNA screens classical cell death to look at synergy. Different mechanisms of cell death can be in play depending on which cell type your looking to radiosensitise. We can model effects of hypoxia, isobolograms to truly look at the synergistic effect. Is this just adding to the radiation effect or is there some true synergistic toxicity? And of course in vivo studies have mouse models which we know about.

00:07:45 So this is a window of opportunity, phase zero. And, I think a interesting model that can move forward and help get additional data early on. Potentially in therapy naïve patients. Can be randomized to investigational medicinal product versus placebo. Get baseline imaging or baseline tissue. And then in this quick window of opportunity prior to a definitive course. And as a way we can move into locally advanced settings as well. It doesn't just have to be definitive radiation, it can be a tri-modality approach, so neoadjuvant chemo rads followed by surgery. For example in colo-rectal or lung cancer, and which can give you a large amount of tissue to analyze the effects of a drug on this population. So this is a classic model for radiosensitisers and I should ... in putting this talk together it does focus a little bit on head and neck cancer. This is the design that was used to use lapatinib in combination with chemo-radiation for head and neck cancer. A kind of traditional, classical design of using cohorts and a dose escalation of the drug using a classical three by three design to allow for dose escalation. Which, only permitted, if none of the additional three patients suffered a dose limiting toxicity. For drug duration, you know this is I think this is an interesting question too. How can we use a drug duration study to try to understand the importance to limit toxicity or also specifically in an immuno-therapy setting. How long do we need to give immunotherapies? If we can modulate the immune system, can that take off on its own and have effects after the discontinuation of immunotherapy? We've certainly seen that. So I think this is an interesting model, of which can be used to limit toxicity and cost as well.

00:09:33 And this is kind of a more advanced model, which is actually discussed previously. The ping-pong or also there's flip-flop. I think I like ping-pong better. But, were you can test multiple different drugs using a different dose levels and have one slots available on either arm or either a drug of the study so that you always have slot available for the study while additional data is being captured from the other drug levels. Certainly interesting as well.

00:10:04 But you know, what I think is interesting from these studies is we focused a lot on the drug dosing, but I think what struck me from one a critical lecture was how classic Phase I trials are meant to look at safety and dose limiting toxicity, but what about the dose of radiation? And I think the identification of maximally tolerated dose, we still do not know the true dose and tissue tolerances for many structures. I think a lot of them are classically still done from [inaudible 00:10:38] radiation before heterogeneity corrections and advancing on. So I think this is a critical situation to study as well.

00:10:46 This is an example in GI, which is a classic Phase I dose escalation study. Getting to pretty high doses to treat pancreas cancer. You know looking at twelve times five in the GI, and we will likely see some toxicities with this, but this will help establish that. And so, we can identify and truly treat to the highest dose possible, dependent upon surrounding tissue constraints. And I think that's critical to do. Potentially in the palliative setting, but also SBRTs in new technologies.

00:11:20 And this leads to dose escalation versus dose de-escalation. Can we use a biological markers to drive dose selection? So we traditionally use classical staging or pathologic features, but are there other biomarkers or molecular profiling that we can use to choose dose? Do all patients have the same sensitivity to radiation? Likely not. There can be additional assays which could potentially be used to test whether a patient is more radio resistant or radio sensitive to radiation. As well as dose-driven field selection. So classical staging and pathologic features are usually used, but can we use biomarkers or molecular profiling to understand field selection? I like this trial, highlight this trial, because I think it incorporates

a number of features, which have a rational design. Really studying this ECOG 3311, a transoral resection surgery and then assignment based upon expected risk, but then also asks critical radiation question. A potential dose de-escalation based upon this intermediate risk criterion. But can we use additional, can we move that into a more personalized setting? Could we use molecular profiling to help identify patients truly at risk or ctDNA, circulating tumor DNA, which is shown to be predictive in the locally advanced setting for response rates. And could that be used to help guide adjuvant therapy in these trials, or help guide a combination?

00:12:47 So for the remainder of the talk I will go over a number of trials combining with immunotherapy. This is one area that my lab is certainly interested in. We helped, as many of the others in this room, generate some of the critical pre-clinical data to support this combination at Johns Hopkins.

00:13:03 I think an important point is that there's two sides of this coin. The abscopal effect. Trying to, in the metastatic setting, using radiation as an in-situ vaccine, treating one or more legions to try to induce an immune response. And here, the radiation is trying to help the immunotherapy work. Okay, so giving radiation and try to induce a more systemic response.

00:13:24 The alternative and the converse and flip side of that coin is radiosensitising in the classical sense. Just like chemoradiation, low dose chemotherapy's a radiosensitizer. Can immunotherapy be a classical radiosensitizer and improve our local-regional control? I think this gets at a key indication for these studies and for pharma as well, because if you could identify that immunotherapy is classical radiosensitizer, you could easily move that forward. And that is being done. Move forward into locally advanced settings, and have an indication in the upfront treatment of disease instead of just after in the development of metastatic disease.

00:14:01 But in this setting, you're gonna need to have radiation plus or minus the drug. In this case, focus on this abscopal effect, and this is immunotherapy with targeted therapy, we see a shift in this curve. An improvement in potentially median survival with immunotherapy, as we all know now, we see this improvement in overall survival, long-term tail of the curve, but can the radiation combination improve this? And in this metastatic setting, it's important to remember that radiation is the drug that we're trying to add here. And so, this opens up a lot of opportunities. We had some discussions on dose and dose constraints. Well, if radiation is the drug, there's a lot of very nice mechanistic data showing that dose can have a critical effect on this response. And so we need to modify that dose in the metastatic and palliative setting to see what's best. And I think clinical trials can do that.

00:14:51 The one question that comes up is, what is the data. There's so much pre-clinical data, what's the true clinical? I mean, the proof is in the pudding now. And I think this is some of the better data that I've seen. This is a large, clinical retrospective review of patients in Europe that all had ipilimumab. All the patients had CTLA-4, and some got combined with radiation therapy. And they looked back and they saw a significant doubling of the overall survival in the group that received radiation therapy. So it's a retrospective review, but this is quite a remarkable increase. Certain to be some bias, but this clear data that radiation added ... I mean this curve looks almost similar to the combined nivo+ipi arm in some respects. So I think this is some important clinical data to move forward with this combination.

00:15:36 There are number of studies doing this. This is certainly not an exhaustive list. I apologize for not listing any study. This is actually just limited to head and neck cancer as well, but Jon Schoenfeld who'll be talking has a very nice study looking at focused higher low-dose radiation at Dana-Farber. Of course at Thomas Jefferson with Adam Dicker looking at different doses of radiation combined with pembro. We have a study at UCSD, I'm the PI of a Phase II randomized study looking at different checkpoint block agents combined with SBRT and there's some similar studies going throughout many different disease sites. So I think this is certainly very active area of investigation.

00:16:12 One slide on umbrella and basket trials. So certainly umbrella trial we have single disease and then looking at multiple biomarkers that can be within that disease. Or a basket trial, where you have multiple different diseases, but then all testing for one postie single rearrangement. Can we combine these? Or could radiation be used in this setting? It's not traditionally done, but this is an example. Something we proposed. Patients with current metastatic disease, and can you use, again radiation as a drug? Radiation as one of these drugs in combination drug extra [inaudible 00:16:44] plus SBRT or palliative radiation? Could that be a novel trial design?

00:16:51 Focusing on the definitive setting. And just highlighting one study. This is actually, I'm the PI of this study. This is focused on lung SBRT. This is early Stage 1 disease. It's curable. We're treating with definitive SBRT. And here, of course we don't modify the dose of radiation, but we're adding in a avelumab, a concurrent and adjuvantly. And so this is an approved study, which is ongoing and we've enrolled some patients on that.

00:17:18 This is, I think, a great example on head and neck cancer by Bob Ferris' group at University of Pittsburgh. Just a very simple and rational design. And it's bound to answer just very simple and important questions and incrementally add to this literature. I think of the worst situations is to have a clinical trial which raises more questions than answers. But here it's a simple question of sequencing. You have concurrent chemoradiation giving the pembro adjuvantly or concurrent chemoradiation, giving it concomitantly and adjuvantly and will this lead to differential in toxicity or effect efficacy? That remains to be seen, but I think a very nice design.

00:17:57 This is a Javelin study. So of course, [Zelanna Goldberg 00:18:01] here. But so this is a very nice eschema which moved forward a number of locally advanced settings with avelumab. And this is a large, randomized, double-blind Phase III placebo controlled study that to try to identify the benefit of adding avelumab anti-PDL1 with the standard course of concurrent chemoradiation for head and neck cancer. A large enrollment and really designed to look at this potential benefit of this combination. This is Keynote 412. So you can see a very similar design. A large randomized, Phase III, double-blind, placebo controlled with pembrolizumab in a similar population. So these are excellent studies, which need to be done and are moving forward, and we're participating in them, but you know it does raise an interesting questions of use of resources and patients. And certainly something for discussion later one, but if you look at nivolumab versus pembro, very similar activities. Is it possible to have some sort of class approval? Certainly that would require significant discussions with regulatory agencies and so forth, but could we help design trials to maximize the use of an agent given a cross approval. But certainly not between disease types. A between antibody specificities. There can be differences in FC receptors, that can can have differential activities and some differences, so we certainly need to test them, but. Specifically between nivo and pembro I think a lot of similarities. This is HN004. This is a large Phase III. In just

highlighting this trial, I think 'cause it has a number of endpoints. There's a Phase I lead-in of looking at safety. Then there's Phase II, which is PFS. Then it goes on to Phase III for overall survival. And I think this is testing a very interesting combination. Comparing to the standard of care, otherwise a standard otherwise in this setting, which would be cetuximab add with radiation. This is in cisplatin unfit or ineligible patients. And looking at durvalumab concurrently and adjuvantly. And I think this also raises an important point about safety and toxicities as an endpoint. In the elderly population with concurrent chemoradiation. Let's say that these two arms have similar efficacy, but one may have an improved safety or toxicity. Could that be a route to a regulatory approval? I don't know, but that's something that could be discussed. And so I think that's an important point as well.

00:20:27 So my summary, really for IO and RT in the locally advanced is that multiple trials are ongoing. I think it's great to see the tremendous activity in this space and combinations with immunotherapy. The preclinical rationale is extremely strong. The clinical data is emerging. There is now emerging feasibility and safety data from these ongoing large trials. And for the most part, and from what I've reviewed, the combination of radiation and PD1 appear to be very safe outside of the CNS, but a potential impact for patient selection, local-regional control overall survival. And we talked about differential toxicity profile.

00:21:05 So my conclusions on novel radiation trials are, you know my experience I would recommend just a straight forward, rational design. Try to answer one question. Two questions. And incrementally add to the field because many times at the end of the trial there can be additional changes in the field even. And that trial could have an impact based on some other biomarker or some other selection of population that wasn't potentially initially anticipated.

00:21:35 Need to continue to address tissue tolerances. I think this is key with SBRT. With protons, classic Phase I dose escalation studies in combination with radiation. And biomarker-driven patient selection. You see a lot of these trials that I listed were not selected based upon any biomarker. If they were, if you had even simple biomarkers like PDL-1. It's not perfect, but it is effective. And it's widely available and would that increase your potential to have a positive outcome in that selected patient population and the ones that are most likely to be benefited from immunotherapy? Potentially.

00:22:14 Continue to address dose and field size issues. I didn't get much into that, but certainly this raises a lot of really interesting questions, especially with field size in different malignancies. Elective nodal radiation. How does that impact combinations? And then, safety and toxicity as an endpoint. With new techniques and with combinations. Thanks.

Sharma: 00:22:34 Thank you. That was a very comprehensive talk. So, Ted's got the first question.

T. Lawrence: 00:22:48 Just a quick comment. I think that three plus three designs are antiquated. We had, I guess, I'm trying to think about who was speaking this morning who talked about time to event continual reassessment models. That is there are models ... We can talk more about this offline ... In which you don't have to close a trial, you can continue to accrue patients. It's a [Bayesian 00:23:07] approach that picks the dose for the current patient, based not just on the prior level, but all of the prior patients. It's a much more comprehensive way of assigning doses. That's just my soapbox comment. You can do with that as you like.

00:23:21 My real question that I wanted to ask is, does synergy really matter? This has been discussed already this morning. Or if you just have additive efficacy, but not additive toxicity. Is that good enough? Does synergy really matter?

Sharabi: 00:23:40 Synergy does matter. I think one of the important ... With these specific drugs, I guess focusing on immunotherapy, is that you have potential for significant improvement outside of the radiation field independent of the local-regional control. So for example, would be in head and neck cancer. Because these aren't low doses of the drug, this would be your standard dose of immunotherapy, you can potentially control in-situ disease or help to prevent the development of a second primary outside of the high dose radiation field. So, that would actually just be effect of those both. The synergy in local-regional control, I think is critical.

00:24:28 Yeah, as far as the three by three design, I agree completely. And one of the best methods, mathematically to get to an endpoint is actually a bi-section model where you don't go [inaudible 00:24:38] you go low, go high, and then come back down. And so that's, I agree with that.

Sharma: 00:24:44 Okay, microphone one.

Speaker 1: 00:24:45 So how do you define synergy? Is synergy one plus one is one point five, or one plus one is three? I mean, I concur, not often, but with Ted this time because I think we're sending the wrong message about what does ... First of all, no one's defined it and Chou-Talalay models are not really helpful. Two, there's no clinical example you can show me where the pre-clinical level of synergy really was demonstrated what the true clinical benefit was. I think we just want to see that as long as it doesn't have overlapping toxicities, and there's a ... At least an additive potential, I think that's good enough to go ahead for a clinical trial, but if there's data that's out there that can argue otherwise, I'm interested.

Sharabi: 00:25:39 I agree. I think synergy is a difficult term to describe even mathematically, you'd have to do very specific studies to describe it, which are probably not done in the clinical trials. So I think from a clinical trials standpoint, I agree. An additive effect, an improvement in toxicity, or differential toxicity profile would be significant, but I think both could be an effect. I think.

Sharma: 00:26:09 Okay, we've only got a little bit of time. One very quick questions please.

Speaker 2: 00:26:13 So I'm curious to your thoughts. There's been a lot of examples. Two just off the top of my head about the late wave of side effects with radiation, which we often when we design these Phase I trials, they're looking similar to drug trials, the acute side effects. But a recent combination trial run through U of M adding a [parp 00:26:29] to radiation it was really at three years. A surge of late side effects of fibrosis occurred or even radiation-only trials at UT Southwestern that are SBRT for prostate cancer. Their Phase I was deemed safe essentially, they published it, and their follow-up paper had all the, basically colectomies because of the perforations and ulcerations and the radiation, so when you design Phase Is, I agree with Ted, the [inaudible 00:26:57] model, but it's still is this challenge the delay when a may even be beyond six months we need, or even years to be waiting. Just your thoughts on this.

Sharabi: 00:27:06 No, I think that's a very important point. Late toxicities can arise months to years down the line. And so I think that this needs to be incorporated into the clinical trial design before moving forward. To truly demonstrate that safety toxicity signal.

Sharma: 00:27:24 Alright, thank you. That was very helpful. Thank you very much.

00:27:31 So, I'd like to welcome to the podium then our second speaker. Dr. Jessica Lowenstein, who's going telling us about radiation therapy quality assurance in clinical trials, why and how.

Lowenstein: 00:27:43 Good afternoon. I am actually a medical physicist at MD Anderson. I work for IROC, which is the Imaging Radiation Oncology Core Group and we perform the QA for the NCI Clinical Trials.

00:27:56 So, I'm gonna explain to you why quality assurance is very important when dealing with radiation. Whether or not the question is a radiation question.

00:28:08 So we know the more accurate the data is, then the clearer the true outcomes of trial can be determined. It is not acceptable to allow mediocre patient care. And we also know that radiation oncology is based on the physical sciences and therefore is very quantifiable.

00:28:29 We have looked at single institutional trials versus multi-institutional trials and have seen an increase in variability in the delivery of radiation dose for multi-institutional trials. And this is due in part to the difference in contouring of targets in normal tissue between different radiation oncologists and institutions, the difference in the calculation algorithms in all the treatment planning systems that are out there. Also, the difference in the delivery machines that are out there. And as always when it comes to trials, the interpretation of that trial.

00:29:06 So a good example of this is RTOG-0617. It was a randomized lung trial, which had a standard dose arm, and a high dose arm. And it was found when we looked retrospectively at the single institutions, that the higher dose arm did had better survival. Whereas, when we looked overall at multi-institutions, it was the lower dose arm that had better survival. And so there's a need for consistency that QA can bring.

00:29:38 Radiation is versatile, complicated, and is important to many patients. We need to make sure that correct dose is delivered to the correct place. As trials become more complex, and treatment techniques and technology become more complex, achieving optimal quality can be challenging. And [inaudible 00:30:00] said, "advantage in radiation oncology is that we are able to quantify the delivery and its quality".

00:30:09 So quality assurance is required at each step in a patients treatment process. Starting when the patient is placed on CT or MRI table for simulation to the treatment planning through treatment delivery. But at times the process can be a black box, as every part has some vendor- specific aspect to it; and, therefore proprietary information that they will not release to your physicist to understand what's really going on.

00:30:41 So, this is an example of a fault tree for our intensely modulated radiation therapy, or IMRT. Starting from the moment a patient simulated through treatment delivery. It's not meant for you to be able to read, it's just there to show you that there are many potential causes

for failure in radiation. But we create these fault trees to attempt to minimize the potential for failure.

00:31:06 So what accuracy is necessary? First, what is the right dose? If you look at ICRU Report 24, what we're trying to do for accuracy is to be within plus or minus 5 percent in the delivery of the dose to the target.

00:31:24 In regards to tumor control, in a randomized trial between photons and electrons, the same nominal dose was given, but it wound up that the treatment with electrons had a poor tumor control. Retrospectively, it was determined there was a seven percent low calibration error in the electrons, resulting in a lower dose being given to the tumor.

00:31:46 In regards to normal [inaudible 00:31:48] complications, a gynecological trial showed a high rate in GI in skin reactions in some of the patients. And again retrospectively, it was discovered there was a seven to ten percent high output calibration error.

00:32:00 -an output calibration error. So this is a dose-response curve. Sensitivity depends on where you are on this curve. If we're on the shoulder, it's not as sensitive but usually we're somewhere in the steep slope and therefore sensitivity to the dose variations. So because of the steepness of the dose-response curve, we need to be within 5% of the intended dose delivered. As shown previously, dose variations show observable effect in tumor control and tissue toxicities.

00:32:36 Our next question is how does quality affect the radiation therapy outcomes in contemporary radiation therapy. So, this trial was talked about earlier in a previous talk. It was published in 2010 and this looked at the impact of radiation therapy protocol compliance and quality and the treatment of advanced head and neck cancer. Now the question for the trial was asking a drug question, not a radiation question. And all patients on this trial received the same radiation fractionation. The hypothesis was a 10% improvement in 2-year overall survival. Now, if you look at the yellow line here, these we went back and looked retrospectively at how the radiation [inaudible 00:33:30] per protocol or not. The yellow line are those treatment plans that we're considered per protocol. The blue were retrospectively reviewed and were considered compliant. This gray line is minor deviations which they still get lumped in the protocol when doing evaluation. And the red are what's major, not per protocol. So, if you look at this yellow and the red line, at the 2-year survival, you'll see a difference of 50% survival versus 70% overall survival.

00:34:07 So remember they were expecting a 10% improvement in 2-year overall survivor and what they learned retrospectively was there was a 20% difference in survival depending on the quality of the radiation given. So, quality of radiation is critical when doing patient survival.

00:34:28 It's essential that the quality of the delivered radiation be good whether or not the trial is a dose question. Variability in radiation therapy delivery will create uncertainty which can result in poor survival and complicate trial outcomes.

00:34:46 Through quality assurance and peer review, we hope to improve the accuracy of dose delivery to the intended location, provide the best treatment to our patient, making sure that everyone is protocol- compliant, improve the outcomes for the clinical trials, enhance patient safety for all patients treated at that institution. And the key item is to learn from any of our mistakes.

00:35:12 IROC's mission is to provide quality control programs assuring high quality data for clinical trials designed to improve the clinical outcomes for cancer patients worldwide. Part of our group, what we do, is there's a Global Harmonisation QA Group and so we work with them in trying to standardize QA globally for trials.

00:35:39 We can look at all the pieces that go into calculating and determining the tumor dose. And this is what we do in our office in Houston. We can evaluate using dosimeters, we do site visits, we review patient charts, and we have phantoms so that we can actually make sure that the dose that you think is being given was actually given. On an annual basis, any institution that participates in the NCI clinical trials, they receive output checks on their machines. A dosimeter is sent to them, they provide a known dose, it comes back to us. We review it and say, yup, that does is within plus or minus 5% of what you've stated. We do this for all types of machines, your standard LINACs, TOMOs, proton machines.

00:36:27 So this is an example of what we would call a good machine. What you can see here is the data is fairly consistent. It is within 5% and it stays normally within 1-2%. Now this is an example of a poor machine, they're very erratic, they're data is not consistent, and they range anywhere from 8% to 5.5%.

00:36:57 We will also do an onsite dosimetry visit where myself or another physicist shows up at your institution and we make lots of measurements on your machines late at night after patients are treated. It is a comprehensive audit tool. We go in and we verify if there are any errors. We provide comments and feedback to the institution. Our aspect is to improve the quality of the patient care at the institution. Not just those on clinical trials but every patient that is treated on that machine.

00:37:36 Here are some of the recommendations that we have made. Roughly 75% of all the institutions we visit, they get a recommendation about their QA program they're missing something that they need to do that they should be doing to follow guidelines. We still get 16% recommendations on somebody not modeling their beam correct [inaudible 00:38:01] that dose if off. And surprisingly, 8% of our institutions still get that their photon calibration is off. They've done some error and we hope that we have fixed it by the time we walk out the door.

00:38:17 We also look at patient charts put on clinical trials and we find systematic errors, individual errors, as well as reporting errors. A systematic error is one that's going to affect every patient at that institution. Individual errors and reporting errors only affect that given patient, plus the trial group's data. But what we have found is that if we hadn't looked at this data, 39% of the doses used by the NCTN groups would have been incorrect.

00:38:49 What is credentialing? Credentialing is there to verify the appropriate level of competency and to make sure that an institution can perform what they say they can perform. It is basically a peer review and it can apply to an institution, a specific protocol, it could be the radiation oncologist, physicist and dosimetrist team, the treatment planning system algorithm, treatment machine and modalities.

00:39:16 The purpose of credentialing is to reduce the number of protocol deviation. We do it through educating the players at the institution. We wanna make sure that they can calculate the dose correctly and actually report the dose correctly also.

00:39:35 So this is a cohort of trials that never had credentialing on them. This is before credentialing became what it is now. As you can see here, we go from 7% to 44% of major deviations. To understand the clinical trial world, if you receive a minor deviation per protocol, those are lumped together and evaluated. A major deviation is something that is held against the institution. And so, there is a very large rate of major deviations. In the early 2000s, there was a GOG trial that came out that you had the choice of using HDR or LDR brachytherapy to treat on this trial. The external beam was given the same way no matter what you chose. But if you were choosing to use HDR, you have to go through a credentialing process. So as you can see here, those institutions that actually did the credentialing process for HDR received no major deviations on the whole trial, whether or not they used HDR. They could have treated with LDR. But those institutions that did not go through credentialing, 21% of those patients received a major deviation.

00:40:55 This cohort is group of trials that require credentialing for everybody on this trial. The CALM trial is one of, actually, the first ones that ever had credentialing. It just revolved around doing a questionnaire and was, I believe, in the early '80s. There it brought down the deviation rate to 5%. But you can see in this later trials from 2000 to present day, B39 being the last one that closed, there were hardly any major deviations, 0.3% to me is not a major deviation. Credentialing has brought down the major deviation for us. But now we have advanced technologies and clinical trials, SBRT, IGRT, gating, protons. So now we're back to that black box. We don't know what's going on. And so we needed to come up with an end-to-end QA audit tool to verify the intended treatment goal and make sure that the correct dose is being given to the correct location as planned. We designed a cohort of anthropomorphic phantoms and here are examples of two, this is a prostate and this one is our lung. They mimic the anatomy of a patient and they are water-fillable. They have dosimeters and they're both film and TLD. We send these to the institution and we tell them to treat it like a patient. So they get it, they CT it and SIM, they plan it, and then they treat it. And everything is then sent back to us and we evaluate the dosimeters against what their treatment plan said they delivered.

00:42:40 From what you can see, we've had a lot of these radiations. A lot of phantoms have come in and out of our office. We still have a 17% failure rate in head and neck plans. In our spine, approximately 25% are still failing. Now if there was another physicist in this office here, they would tell you this is fairly generous criteria and we have looked that if you bring down the criteria that was used in the clinic, it almost doubles the failure rate. It's very important when looking at this that to understand QA is such an important part of trials and making sure that institutions understand, we'd rather them practice on our phantom than practice on the patient. Some of the findings we have from our anthropomorphic phantoms is we found that treatment planning modeling for IMRT delivery was deficient, incorrect lung tumor dose calculations for SBRT were being done, deficient dose calculation algorithms for both protons and x-rays, and incorrect institutional modeling of treatment x-ray beams. And when an institution fails a phantom, they go back and they look at their processes and try to determine what has gone wrong. It's not easy because it's a black box. Many times they go through and remodel and then they come back and pass the phantom the second time.

00:44:15 Radiation oncology practice is evidence-based. For us, our gold standard is clinical trials. Low quality undermines these trials which will potentially conceal the true outcome of them. Therefore, there's a continued need for radiation oncology quality assurance within clinical trials.

00:44:36 Thank you.

Sharma: 00:44:43 That's great. Thank you, Jessica. Do we have questions from the audience? Tim?

Illidge: 00:44:49 Thank you for a very informative talk. I wonder if you could help delineate between how much of the failure of achieving the required radiation doses due to the, essentially, the radiation oncologist's defined volume versus the process as we might call it. In particular, in the study that you showed, the famous one in the head and neck cancer where there is a very clear survival difference of 20% difference between those that stuck to the protocol. Was any of that related to the radiation oncologist's defining the wrong volume?

Lowenstein: 00:45:33 In the paper it doesn't come out and specifically tell you for the TROG trial where it was (laughs) What I do know when they did the retrospective review for that one, there is a radiation oncologist who's a staff there and looked at the volume drawing so there were comments made, most of it was dose, but if the volume was too small then potentially, you know, if you have a small volume and they thought it should have been bigger then they might have said, yeah you had not done the dosing correctly, in the same way if you've done the volume too large.

Illidge: 00:46:09 That's the reason I'm driving the question because essentially there are two potential problems here. One is that what you've addressed in your talk and the other is actually about radiation oncologists working together and cross-checking each other's work. They require different approaches.

Lowenstein: 00:46:28 So I know from these trials, a lot of them, atlases have been created so that there are for radiation oncologists, like, [inaudible 00:46:35] for them to go look at the atlases to see how the volumes are drawn. Also, another form of credentialing that has come about is called the pre-treatment review where the plan is sent, we do the volume analysis, but a radiation oncologist looks at the contouring also and if they don't approve the contouring, you cannot start treatment on that patient.

Illidge: 00:46:57 But at the moment you don't know from U.S. data as to which is the risk factor for falling short...okay.

Speaker 3: 00:47:09 There are a number of organizations now that provide credentialing or quality review for practices like ACR and ASTRO. Do you know if a practice goes through that process, does that correlate with better pass rates if they're participating in clinical trials?

Lowenstein: 00:47:30 We haven't looked at that. I know the ACR when they go and review, they ask to see if you're monitored by IROC. But I can't definitively tell you they do better or worse.

Speaker 4: 00:47:48 I was actually just gonna follow up on Tim's question which is that there's another part of IROC, which is QARC, which is over in Rhode Island, which as mentioned does a pre-treatment planning review, to get to the individual question of the radiation oncologist and the volumes drawn. The TROG study also, to remind folks, that was large-field radiation. That was not IMRT necessarily. So we're working with smaller volumes and a lot more investigator judgment and so the importance of doing pre-treatment radiation plan review has escalated dramatically to ensure we get good quality for the radiation part of a radiation-drug combination. It's a huge issue.

Sharma: 00:48:36 Great. One last question?

Speaker 5: 00:48:38 Just one thing that struck me is that when we think about drug trials it remains focused on the FDA. We think about the quality of the drug product, the variability of the drug product is a very big deal obviously in manufacturing. So going back to the recent slide that was looking at radiation as the drug, it really would be the view of everyone to make sure that the variability in the radiation is as low as can be because that can really screw up your trial. And then even further if you want a huge trial and use, say, cluster randomization and you got sites being randomized, you can imagine how that would also be potentially a problem. It's a very interesting topic.

Lowenstein: 00:49:19 Excellent. Thank you.

Sharma: 00:49:25 So it's my pleasure to introduce my co-Chair here today, Fei-Fei Liu.

00:49:29 Fei-Fei Liu is from the Ontario Cancer Research and she's going to talk to us about clinically relevant endpoints for radiation therapy combination trials.

Liu: 00:49:37 Thank you, Ricky. And thanks for the invitation. This is really a fantastic workshop and I'm sure this gonna be serving as a fantastic launching point, we're hoping, for more of these types of radiation therapy combination trials.

00:49:52 I've been charged to discuss relevant clinical endpoints for these types of combinatorial trials. I have no conflicts to declare. So as we've heard over the parts of the days already that the gold standard endpoints are overall survival and the advantages are clear. There are very hard. It's quantifiable. It's binary, alive or dead. And it's indisputable. It's obviously very meaningful to patients but one of the potential disadvantages of course is it usually requires large number of patients and very long follow up particularly when you get out to these disease like breast and prostate cancer with very long natural histories, so you have to follow them up for more than 10 years.

00:50:33 The quality of life is another gold standard. There are a lot of validate tools. I'm not gonna be spending too much time in discussing this but again this of course these are very meaningful endpoints for patients.

00:50:46 In the context of radiation therapy combinatorial trials, of course as we've already heard repeatedly, radiation therapy is a local therapy. And in the context of curative treatments, the ability to be able to achieve local regional control or endpoints reflective of that are obviously extremely important for the patients and also for the evaluation of the clinical study. And then ideally these types of local regional control should also be able to translate into improvement in overall survival and/or disease-free survival.

00:51:18 We're also gonna talk about similar types of approaches and endpoints for neoadjuvant and adjuvant clinical trials. Another endpoints that are also extremely important as we've also heard about this morning is that these endpoints are relevant to the particular anatomical tumor site. So head and neck cancer can be different from gynecologic malignancies to CNS malignancies, lung cancer, and so forth. That has to be really important. The target population is also very important whether we're looking at a curative setting or whether we're looking at oligometastatic setting or whether we're looking at widely metastatic

patient population. And then stage of disease of course is also important whether we're looking at very limited early stage disease in contrast to locally advanced malignancies.

00:52:06 And there are few emerging endpoints which I'm just gonna very quickly mention and then of course there's a whole afternoon session later on about PRO or Patient Reported Outcome which I'm not gonna be touching up on.

00:52:18 So over the course of the next 17 minutes or so, I'm going to be discussing each of these endpoints as a function of the anatomical tumor sites: head and neck cancer, lung, breast, GI, GU, and CNS malignancies.

00:52:32 In head and head cancer, we all agree overall survival are important. I'm just gonna describe a little bit about events-free survival and comparing it to local regional control, progression-free survival and quality of life as one study. So this is a really great meta-analysis which was published in 2009 comprised of more than 22,000 patients and 116 treatment comparisons. What you can see here is that in the solid green line is the overall survival curve and in the solid blue line is the event-free survival and so this is any kind of event whether they're local failure, regional nodal failure, or any kind of recurrences, distant metastasis or death. And so you can see that the green and the blue lines track very, very well. And then in contrast, in this particular meta-analysis, in fact, the local regional control actually didn't track quite as well as overall survival. So in the context of head and neck squamous carcinoma, an event-free survival may well be a very, very important and valuable endpoint.

00:53:42 And this is a second kind of another kind of head and neck cancer, nasopharyngeal cancer, which is intimately associated with Epstein-Barr virus, and in this review of 316 patients with nasopharyngeal carcinoma, and patients were treated with CRT compared to radiotherapy, here again in the green solid line is the overall survival for the CRT population and here the progression-free survival in the solid red line track very, very parallel and reflective of the overall survival. And then similarly for the group of patients who were treated with radiotherapy alone, indicating here that in this particular disease, nasopharyngeal carcinoma, utilization of a progression-free survival may well be a very reliable surrogate endpoint.

00:54:33 And this is a really nice study conducted by our colleagues in the UK whereby the primary endpoint was actually one of xerostomia or dry mouth and they were comparing two different types of radiotherapy, one is kind of a conventional radiotherapy for head and neck cancer, and then the blue here is actually parotid-sparing intensity-modulated radiotherapy or IMRT. And here, they're plotting basically a score of dry mouth, we can clearly see that there is a very different score between patients who were treated with conventional radiotherapy, the higher score indicative of worse xerostomia or dry mouth; and in blue here are the patients who were treated with the parotid-sparing IMRT. So this is a nice study whereby they were primarily actually using a functional or quality of life endpoint demonstrating the advantage obviously in parotid-sparing IMRT if the primary tumor allow that. They also use the LENT-SOMA as a late normal tissue toxicity score to look at some of the late normal tissue endpoints which are very important.

00:55:42 In lung cancer, overall survival, progress-free survival, disease-free survival and also the possibility where we could have an image endpoint. So another very large randomized clinical trial meta-analysis published just in 2013, where there were 60 randomized clinical trials evaluated for patients with non-small cell lung carcinoma, more than 15,000 patients,

you can see here that the overall survival here in blue and then in red we have the disease-free survival for patients treated with a combination CRT tracks very, very nicely. And then this applies also to the patients who were treated with radiotherapy alone. And here, the progression-free survival is another readout, an important endpoint where also tracked extremely well with overall survival and this is progression-free survival again for patients with the participants in this particular meta-analysis.

00:56:44 This is an RTOG study whereby they had looked at FDG PET and so this is a metabolic endpoint of reflecting presumably from glucose metabolism in patients who were non-small cell lung carcinoma and this is looking at PET-avidity at the end of treatment of CRT in patients who were treated with concurrent platinum-based chemo radiotherapy. On the panel on the left-hand side, in the blue is the overall survival for patients in who they still had PET-avid tumor in contrast to the group of patients who have less PET-avid tumor and this is for single-institutional assessment of the PET FDG SUV or if you had a centralized review, it was also similar. Suggesting the possibility whereby an image-based endpoint could be potentially useful for patients with lung cancer.

00:57:44 In patients with breast carcinoma, lots of experiences obviously, where overall survival, disease-free survival, quality of life measures, all very important. I just wanna talk a little bit, touch a little bit on the concept of the pathologic complete response. There are increasing number of patients who are now managed with using a neoadjuvant approach whereby in this particular study of 220 patients with locally advanced breast cancer treated with an anthracycline-based chemotherapy followed by a Taxane-based chemotherapy, and then patients undergo surgery and then there may also be radiotherapy administered as a function of the particular indications. What they found here is that the group of patients who were able to achieve pathologic complete response from the surgical sample, that this was associated with a significantly superior recurrence-free survival comparison in contrast to the group of patients who did not achieve pathologic CR. This applies to all subgroups of breast cancer whether they were hormone receptor positive but Her-2 negative, triple negative breast cancer, or the group of patients with Her-2 positive disease only. So suggesting that in the context of neoadjuvant treatment for patients with breast cancer, the achievement of pathologic CR could well also serve as a potential endpoint.

00:59:10 For patients with GI malignancies, we have overall survival, disease-free, quality of life, and again the concept of the pathologic CR and also ability to be able to achieve a complete resection. I think this is one of the earlier reports whereby the correlation between disease-free survival and overall survival extremely strongly correlated and this is a meta-analysis of more than 20,000 patients with colorectal carcinoma, 18 randomized clinical trials, or be at least are just patients treated with chemotherapy only, but I think that everybody would agree that DFS and OS are comparable.

00:59:52 In patients who were treated with esophageal cancer were oftentimes approached with preoperative Cisplatin or 5-FU chemoradiotherapy regimen and then subjected to surgery, here on the left-hand side here we have again the patients who achieved pathologic CR, they had a superior overall and disease-free survival compared to the patients who were not able to achieve pathologic CR. And they also score the ability to be able to undergo a complete resection which of course is related and that was also advantageous for the group of patients in whom they were able to undergo a complete resection indicating that the PCR and complete resection may potentially also serve as important endpoint for these types of clinical studies.

01:00:44 This also applies of course in patients with rectal carcinoma who were treated with preoperative CRT and you can see here that the ability to be able to achieve pathologic CR associated with superior local recurrence-free survival, distant metastasis-free survival, disease-free and also overall survival, indicating that the pathologic CR for this group of patients treated with preoperative CRT for rectal carcinoma is also applicable.

01:01:19 In the GU world, there is overall survival, disease-free survival, and also recently this metastasis-free survival is appearing to be important. Quality of life is obviously important and also biochemical readout. So this was a large meta-analysis just published last year in JCO where had analyzed 28 randomized clinical trials of more than 28,000 men with localized prostate cancer, 90% of these patients received radiotherapy as one of the modalities, and there was a really, beautiful, almost overlap between overall and metastasis-free survival suggesting that MFS could serve as a very useful and valuable endpoint which will eventually then lead to an advantage in overall survival.

01:02:11 This is a review conducted by Anthony D'Amico where they had combined the results from two randomized clinical trials of men with prostate cancer treated either with radiotherapy alone or radiation therapy and androgen deprivation and the ability to be able to achieve a low PSA nadir level defined as less than or equal to 0.5 ng/mL. They had much lower risk of experiencing prostate cancer specific mortality in contrast to patients who had a high PSA nadir level and obviously there are a lot of clinical trials in prostate cancer where the PSA serves as a realistic and applicable endpoint.

01:02:59 And then finally in CNS diseases, overall, progression-free survival, and I wanna introduce this newer functional quality of life endpoint of cognitive deterioration-free survival. Of course that's also related to quality of life. And so as we heard a lot this morning, this is I think a very landmark paper that was just published last year in New England Journal where this group of multi-center study looked at the role of radiotherapy and temozolomide in elderly patients with GBM, elderly being defined as over the age of 65, and they found that there was a clear advantage in benefit of the combinatorial treatments of radiotherapy and temozolomide over radiotherapy alone. And this applied actually regardless of your MGMT status although the benefit was greater for those who had methylation. And this is a really nice study conducted by Paul Brown and multi-center study in looking at the role in comparing whole brain-

01:04:00 Our study, in looking at the role of, and comparing whole brain radiotherapy compared to SRS or stereotactic radiosurgery for patients who had already undergone a resection for their brain metastasis. And we know that in this population, your overall survival is not going to be affected by your particular kind of radiotherapy, but what is important and valuable to the patient, however, is the ability to be able to maintain cognition.

01:04:28 And so the endpoint, the primary endpoint of the study was actually cognitive deterioration free survival. They had six cognitive tests, and more than one standard deviation drop in any one of these six tests was considered to be having a deterioration in your cognition. Clearly, this was greatly advantageous for a group of patients who were treated with SRS in contract to whole brain radiotherapy, and so I think this and many other studies similar have shifted the management and standard of care away from whole brain radiotherapy as opposed to SRS.

01:05:05 As already mentioned this morning, the ability to preserve organs is extremely important in patients with head and neck cancer. For example, the time to tracheotomy or the survival duration with an intact larynx and esophagus are obviously very important for this group of patients. And then organization and preservation is also obviously very applicable to patients with bladder and rectal cancer. And then of course, the toxicity endpoints need to be considered as we want to all achieve improved cure, but reducing the toxicity. And then the CTCAE, apparently there's a version five now that's just been published at the end of last year, rolling out this year, with something like 886 variables to be considered.

01:05:49 And I didn't touch upon these, but the breast cosmesis is obviously very important, where there were these global cosmetic scores looking at induration, asymmetry, telangiectasia in women with breast cancer, and these scores have actually demonstrated the disadvantage of accelerated partial breast radiation therapy for women with breast cancer. And then there are other scores that are relevant for prostate cancer, such as the time to the first proctoscopy, obviously indicating that there is rectal toxicity as a result of the radiotherapy for prostate cancer, and there are also these other scores, such as the VRS or Vienna Rectoscopy Score, looking at mucosal changes and telangiectasia as a read out of the normal tissue end point, which are very important.

01:06:36 So, in conclusion, then, I think that we'd all agree that the overall DFS and quality of life endpoints are the gold standard. Everybody would accept that. But in context of combinatorial radiotherapy studies, additional endpoints obviously is local regional control, event free survival, progression free survival, metastasis free survival are also very important, as are organ preservation. And specifically, as we've already mentioned, the site of the tumor, the stage of the disease, the treatment dependent endpoints are very relevant, such as pathologic CR, complete resection, biochemical points and also neurocognitive evaluations. And then we've already talked about the relevant late normal tissue toxicity endpoints.

01:07:22 So thank you for your attention. Happy to answer any questions.

Sharma: 01:07:30 Thank you, Fei-Fei, and thank you for keeping to time so well. So, we have questions.

Le: 01:07:34 So Fei-Fei, is the data rigorous enough to say that for phase III randomized study for head and neck cancer, we can use PFS rather than OS as the primary endpoint?

Liu: 01:07:46 I think it depends on how confident you are. I think definitely ... So I think the short answer is probably not 100% confident. But I think definitely the overall survival is the gold standard. What are your thoughts on that, Quynh?

Le: 01:08:05 You know, we've been pushing it. And CTEP has always been OS as the primary endpoint for phase III study. But if you look at all these data come out for NPC and non NPC, PFS is ... They parallel to it, and you get to it sooner.

Liu: 01:08:19 Right.

Le: 01:08:20 Rather than OS. So that's why I'm trying to push the issue here, raise it up.

Liu: 01:08:24 Yeah. Certainly from the meta analysis that was published, that definitely suggests that it is indeed applicable.

Sharma: 01:08:32 Microphone three.

Chen: 01:08:35 This is Chen. I'm a statistician working on clinical trials and radiation therapy. It's a great program. Thank you very much for organizing that. So I have a question that's motivated from your talk, more or less related to the platform trial idea that was discussed earlier. So in the context of drug-radiation therapy combination. And if we are thinking about doing some platform type trial, I would imagine that first, you probably want to have some kind of end point or end points that incorporates both the toxicity and efficacy to some degree.

01:09:12 In addition, because you're simultaneously evaluating multiple disease or subtype, you probably also want some uniformity across different disease subtypes. So just now, you presented different endpoints for different disease. So, how can we overcome or have some discussion to reach something like that to help with develop some platform trial?

Liu: 01:09:36 So your question is that if you're looking ... You're trying to find common endpoints? Is that what you're saying ?

Chen: 01:09:43 Yeah, common endpoint of any sorts, yeah. I just feel that this probably also may be important, especially when we're talking about platform trials. Because otherwise, if you're thinking about some platform that at least in the more conventional setting where we're looking at different mutation types, you at least would look at some common endpoint across different disease subtypes, say, or something like that.

Sharma: 01:10:13 I think he's referring to basket, basket trials.

Liu: 01:10:16 Yeah. I guess it just depends on the specific hypothesis that you're addressing. So, if your design is going to be based on mutation status, then that's obviously going to be defining your specific baskets; mutation or not mutation or different kinds of copy number changes, et cetera. And then you would then design your intervention as a function of that, say for molecular targeted therapies.

01:10:43 For radiotherapy, I guess it gets a little bit more complicated, right? Because your dose of radiation could be different, and the toxicities may well be different. So I think those would be what I would probably consider to be more hypothesis generating designs. But when it comes to your phase III studies, I think that you're going to use harder endpoints as we've just described.

Chen: 01:11:08 Thank you.

Sharma: 01:11:08 Ted?

T. Lawrence: 01:11:09 I want to go back to Quynh 's question, 'cause I think it's important just in and of itself, but it's also particularly important in the context of this meeting. So if we're thinking of what's the quickest way to work with Pharma to get registration, and we're thinking that a common way we're going to do that is a clinical trial in which there's already say, a chemotherapy-radiation gold standard like treatment for head and neck cancer, and then we're adding a new agent. If we can shorten that time to a positive study, that's crucial in getting a rapid approval of the agent.

01:11:40 And so, is 5000 patients enough?Is 10,000 patients enough? Is 20 ... How many thousands of patients does one need to see the correlation and say it's a valid correlation that progression free survival's good enough?

Liu: 01:11:55 Yeah. The meta analysis that I presented shows that. And event free survival, metastasis free survival for prostate cancer. So, I think if these meta analyses are already showing that, I think that that's what we push for. Let's design those trials with those shorter endpoints as a primary endpoint. And of course you're going to have other secondary endpoints also.

01:12:20 So I think that as a community, that is what we should definitely be pushing for.

Sharma: 01:12:27 Okay, one last question.

T. Lawrence: 01:12:29 I just was going to respond to that. 'Cause I was involved in the metastasis free survival ODAC, and so moving registration endpoints up is a significant thing in different disease areas. And so with head and neck, some of the things we thought about during that ODAC, just to put it into perspective was, is local progression going to be as meaningful as metastatic progression. And it was thought at the ODAC that in prostate cancer, it changes the whole disease space when you get into metastatic, and that's a whole different type of clinical scenario.

01:12:59 And so that's where it came to metastasis free survival. And it was brought up that local progression is common and would strengthen, would power up your trial, et cetera. But it was felt tat that time that metastasis free survival was important.

01:13:11 Now in head and neck, that may be a challenge. I don't know what the propensity is for metastasis versus local progression, or what the timing is between those two. But that's some of the work that should be done in the field so that you can see whether MFS makes sense in a curative head and neck space.

Liu: 01:13:28 Yeah. I agree.

Sharma: 01:13:29 Okay, thank you. That was fantastic, Thank you very much.

Liu: 01:13:38 So I'd like to invite up Tatiana Prowell. Oh, there you are, hello, yes, thank you. So talk to us about the route to registration.

Prowell: 01:13:47 Great. So, thanks very much for inviting me to participate today. I'm not ambitious enough to try to cover 25 different endpoint disease combinations in 17 minutes. I've never seen anything like that, but you did a great job. So, I'm going to take the much simpler question that I've been asked to speak about, which is end points, really, and approval pathways from a regulatory perspective. So I have no conflicts of interest.

01:14:13 So, it occurred to me as I was preparing this that radiation oncologists aren't generally in the business of thinking about the process of getting drugs approved very much. You work with an entirely different construct in your discipline than we do in medical oncology. And so it might be useful to just actually pause for a moment and review the differences in the two primary drug approval pathways that are used in the U.S.

01:14:38 So, this is a simple chart that I think outlines the major differences, and I think will probably be helpful to you as you go forward in the conference talking about the possible endpoints that you might want to use in drug-radiation therapy, combination trials going forward?

01:14:53 So, let's start with regular approval. So, in contrast to accelerated approval, which is really limited to drugs being approved for serious or life threatening diseases. The regular approval pathway applies to both those sorts of diseases, but also other diseases that would not be considered serious or life threatening. So everything from migraine headaches to seasonal allergies as well as cancer and other serious diseases.

01:15:19 There's a comparative efficacy requirement that is not present in regular approval and is present in accelerated approval, and let me explain what that means. If you are showing direct clinical benefit, and I'll get to how that's defined in regulatory terms in a moment. If you are showing direct clinical benefit, for example, overall survival, your comparator arm can essentially be any therapy that would be considered a reasonable standard of care for the patient population you're studying So that might be, in renal cell carcinoma, for example, any one of a number of tyrosine kinase inhibitors. Or, in breast cancer, subtype, triple negative subtype, that might be any one of a number of chemotherapies.

01:15:59 In diseases or lines of therapy where there is no standard therapy, one could even compare to placebo. And because you are demonstrating a direct improvement and clinical benefit, you can get regular approval. In contrast, if you are not demonstrating direct clinical benefit, so if you are instead relying upon what call in very poor terms, a surrogate endpoint, that statisticians hard solve pause for beat when we say surrogate, because most of these are not true surrogates in the statistical sense. But when we're relying on something other than clinical benefit to approve a drug, for example, response rate. Just response rate by itself, then there is a comparative efficacy requirement.

01:16:41 And what that means is that your new drug that you're trying to bring to the market under accelerated approval needs to be either better than the best available therapy, or you need to be studying it in patients who are refractory to all available therapy. And available therapy, too, sounds like common parlance. But in fact, in regulatory terms, this also has a definition, and it's really drugs that are on the market for that disease, that patient population, under regular approval. It dopes not include other, say competitor drugs of the same class that might be on the market under accelerated approval. So that's an important difference to know.

01:17:16 And that sometimes constitutes a higher bar if you will, for drug companies seeking an accelerated approval pathway, because really, they need to beat the very best of what's out there on the market already.

01:17:27 The endpoint, as I've already alluded to, and you've heard a little bit from Dr. Liu’s talk right before, for regular approval we require clinical benefit. That's been historically overall survival, and in some cases progression free survival, and/or demonstration that a product helps patients to feel better, for example, function better. I'm going to go into what this means a little bit more in the next slide.

01:17:47 It could also include a validated surrogate. So that could be something like three year disease free survival in adjuvant colorectal cancer, which has been validated to predict overall survival. In contrast, accelerated approval relies on any endpoint other than those

things, basically. So a surrogate endpoint that has not yet been validated as predictive of direct clinical benefit.

01:18:08 And then finally, there's a post marketing component to this, and this is an important aspect of drug development, that pharmaceutical companies don't necessarily think through fully, particularly smaller ones who may be less experienced, and that is that when you bring a drug to the market, under regular approval, effectively you're done with establishing the efficacy of that drug. Now there may be post marketing studies that will be conducted to move the drug up to say, an earlier line of therapy. Or there may be post marketing studies that will conducted for safety reasons, for example, to assess whether or not a safety signal might have been an issue with the registration trial, is in fact a true one, or whether or not the drug needs to be dosed differently in patient's with organ impairment. But effectively, the study of efficacy of that drug is done at the time of approval with regular approval. There's really no further obligation on the part of sponsors in that way.

01:19:01 For accelerated approval, the drug company needs to continue to study that drug. So they have to establish that that drug ultimately does demonstrate clinical benefit. And that can be done in one of two ways? It can be done in the same study by simply following the patients out for longer maybe, or getting response rate earlier in a randomized trial, and then you're going to follow those patients out for overall survival. Or, it can be done by doing a second trial, either in the same line of therapy, or for example, moving that drug up to an earlier line of therapy. So, the two pathways are very different. So, let's talk about now what constitutes clinical benefit. So, I have to tell you, I was a former English major, and a little piece of me dies every time I read this, so I didn't write this. But clinical benefit has a regulatory definition and that is, I t's a direct measure of how a patient feels, functions or survives. It's awful. Let's all pause. How a patient survives. I don't know. But anyway, it's a direct measure of how a patients feels, functions or survives.

01:19:59 So what do we actually do with that? How do we interpret that as regulators? Well, in the advanced cancer setting, clinical benefit has historically been overall survival or PFS if it's sufficiently large. Suddenly I'm not advancing. Okay, here we go. So, let's take overall survival for a minute, because overall survival is becoming increasingly maligned, and there's some very well founded criticism about this endpoint. And we'll get to that in a moment. But why do we still care about it?

01:20:29 We care about it for a number of reasons. It captures the bottom line of both safety and efficacy. That's really the most important point. So we know that some of our adverse events, unfortunately, with oncology agents, will be fatal, and we know that we may improve how long patients are going until their scan looks worse or what not, but the bottom line is, are patients living longer? This matters to patients uniformly. FDA spends a lot of time talking to advocacy groups, a lot of time talking to patients in a variety of diseases, and never have we been told, survival is not an issue to us. That's not something that we care about. We've been told that about a lot of other endpoints; progression free survival, response rate, certain patient reported outcomes that don't necessarily translate into something that the average patient would even notice had improved. But overall survival routinely matters across the board in every disease and every patient population.

01:21:20 It's measure precisely as you all know, so there's no need for interpretation by a radiologist, for example. And the data are rarely missing, and if they are, they can generally be obtained, and they can be source verified if that were needed. And the reason that we've become

maybe increasingly interested in overall survival again though, in the last few years, is the recognition that it might actually better represent treatment effect for a drug compared to progression free survival, at least assessed at the median or other endpoints in certain settings, and I'll show a few examples of this.

01:21:50 So, for those of you who work in the lung cancer space, you're probably familiar with this paper from Julia Brahmer and colleagues. So, this was nivolumab in advanced squamous cell lung cancer, a drug that's of course now approved for this indication. And if you look at median overall survival here, so at the 50% patients having died in the trial, you have an absolute improvement of 3.2 months, which everybody would agree in this disease is a meaningful improvement. On the other hand, if you look at progression free survival at the median, again here, these numbers are almost indistinguishable. You've got a 0.76 month improvement in progression free survival. And had you looked at this as the only endpoint, I think nobody would have felt that this drug should be on the market for this indication. Right?

01:22:34 Likewise, if you look at overall survival measured at the median, you've got a 5-1/2 month improvement with nivolumab in metastatic renal cell carcinoma. When you look at progression free survival, you've got a 0.2 month improvement. Again, here looking at the median. And there are a number of reasons for this.

01:22:50 Statisticians are perhaps the better ones to really be commenting on this that a medical oncologist, but I think that this has to do with proportional hazards. I think this, to some extent, a phenomenon that seems to be not entirely unique to immunotherapy but certainly much more common in immunotherapy. And it speaks to whether to not we need to be either using different endpoints or different statistical assumptions as we design our trials that include immuno-oncologic agents. Because I think that using medium progression free survival, which has many other advantages for all the reasons that have already been alluded in the last talk, and in the conversation that followed it. I think that medium progression survival is problematic in this class across a number of diseases.

01:23:34 So where are we with overall survival as and end point in 2018. Well, the challenges that we have is that conducting randomized trials requires equipoise. You really shouldn't have, although you might personally believe in the drug that you've spent the last decade of your career working on, or the pathway that you've spent the last decade of your career targeting, you really shouldn't be confident that one am is going to outperform the other. You personally might be, but if everyone is, that trial should not be done. And that frankly was a scenario that we were never in 20 y ears ago in oncology. We seldom had a situation where everybody was sure that arm A was going to be better than arm B. We've faced that scenario much more frequently in the last five to 10 years, and that's a great thing for patients, but it makes trial design complicated.

01:24:17 So, if we need equipoise or ethical considerations, who's willing to put their patients on a clinical trial where they have a 50/50 chance or even a 30/70 chance of being randomized to the "wrong arm." There are feasibility considerations with being able to even accrue such trials to get an answer. And this had led us to use a lot more single arm trials as the basis of accelerated approval, and even in some cases, regular approval. And the challenge is that in a single arm trial, we really can't interpret time to event endpoints. So things like progression free survival or overall survival, those things may be impacted by the drug therapy, or the radiation therapy we're giving, but they may also be impacted by things that

we aren't measuring. Differences in supportive care, differences in the biology of the disease, and as result, we tend to request that objective response rate be used in single arm trials if there's any idea that this may be done for registration purposes.

01:25:14 There's also this issue of crossover. So even in the case where there's not enough of a loss of equipoise that a randomized trial can't be done, there may nonetheless be enough background data to suggest that it may be reasonable to cross patients over at the time of disease progression. And when that's done, this will confound interpretation of overall survival. It doesn't mean it's going to totally negate an overall survival benefit, but it will likely make it smaller, and it may make it no longer statistically significant, and that's a challenge certainly in general, but definitely when you're talking about trying to get a drug approved through regulatory agencies.

01:25:47 Sensitivity analyses can help here, looking at the patients who did and did not cross over, but nonetheless, we're left with this issue that overall survival might be tough to interpret. And we've heard repeatedly from industry that although in the U.S. we've been more flexible about this phenomenon of crossover and how it will impact interpretation of endpoints, that other regulatory agencies have been less so, and that particularly other payers abroad have been less so. And they have expressed concern that drugs would not be approved globally, or perhaps would be approved but not reimbursed, not paid for by countries, if overall survival improvements are not demonstrated. And I think that's a reality that we have to face recognizing that drugs and combinations are being developed in a global environment. So let's talk about response rate for a moment. The power of response rate is that it isolates the treatment effect from the natural history of the disease. So the reason for this is that with few exceptions, we don't see spontaneous regression of tumors, and therefor if something shrinks, you can be confident that that's due to the drug. Now, is the drug interacting with their biology? Sure, but it's not that supportive care has improved since 10 years ago or something. That's not going to make a tumor shrink. So if we see shrinkage of a tumor, we're confident that it really reflects the impact of the therapy we're giving.

01:27:01 So as result it lends itself well to use in single arm trials, because we can essentially assume that the objective response rate in the control arm, if we had one, would be zero. And we don't, therefore, need to have a control arm. The problem with objective response rate is that it doesn't account for stable disease, and stable disease is a benefit to patients in many respects. Certainly this is true in more hormonally driven disease settings, ER positive breast cancer, prostate cancer. Stable disease is a large part of the benefit that our drugs provide. And so we don't capture that with objective response rate at all. It poses unique advantages and challenges in certain settings, but the challenges I would focus on would be the issue of bone metastases, peritoneal carcinomatosis or other fluid collections. It's very difficult to discern whether or not a patient is responding in the setting of disease that's confined to those spaces or predominantly in those spaces.

01:27:52 And then finally as many people, I'm sure, are aware, immuno oncology agents have the additional challenge in part addressed by the use of immune related resist criteria, but nonetheless have the challenge that they may cause pseudo progression, probably on average in about five to seven percent of cases prior to subsequently demonstrating response.

01:28:13 But nonetheless, objective response rate has been a commonly used end point for accelerated approval, and in some more recent examples, actually has served as the basis for regular approval. So what features of the response do we think matter clinically and matter to us as regulators when we're reviewing these applications? Duration of response is of course one that we're all familiar with. It's great if you can get people to respond, but if their disease is progressed six weeks later, I think most people would argue that we've not done patients a tremendous service. T

01:28:40 The other features that we've started to focus on more, though, are persistence of response. So, particularly with the drugs that may have late or long term toxicities, even drugs that frankly are very expensive, because financial toxicity is a real issue for patients, and even in the case of drugs that may produce a very rapid and very dramatic response where it's not clear that we need to continue treating the patient, we're very interested in what percentage of patients actually have continued response, or continued stabilization of their prior response after the time of treatment discontinuation whether for toxicity or a plateau of maximal efficacy.

01:29:19 We're also interested in depth of response and association of response with symptomatic improvement, and I'll show you some examples of this from published papers in the next few slides. So, this is a slide from my colleague, Edan Blumenthal at FDA, and it's sassy in a way that, Edan's better at this than I am. But response seen from across the room versus response where you need an arrow to point it out. So on the left, this is actually Crizotinib in a Ross I rearranged nonsmall cell lung cancer, and I don't think anybody needs me to use the arrow to show you where that is. Those lungs look dramatically different in the before panels on the left versus the after panels on the right.

01:29:57 In contrast, here you've got the exact same drug, but now it's being used in a Ross I rearranged IMTS spindle cell tumor. And yes, this was categorized as a response by resist, there's no question. But nonetheless, it takes a minute, right? You have to say, wait, where is is again? Oh, right, okay I see it, there and there. Yeah, that's better. Now, does this still qualify as a response? Absolutely. Is this person going to be categorized in a yes group for ORR? Yes. But whether that patient's going to feel any better, I would argue they won't. Are they going to feel better in our clinic room when we say hey guess what, your scan looks better. Your tumor's shrinking. Yes, they're going to feel psychologically better. Are they going to feel physically any different? No, because I would argue that probably this patient didn't even know these things were here, and therefore couldn't possibly feel any better when they're no longer there, or when they're smaller as they are in this case.

01:30:48 So what about depth, durability and persistence of response. So these are again, I feel like we talk about immunooncology so much, we forget anything else exists now, so I tried to find some examples from the rest of the world. And I'm a breast oncologist, so since I'm looking to push my borders a little, I thought I'd tried to find online breast examples, force myself to read some other things. But again, this is Crizotinib in Ross I rearranged nonsmall cell lung cancer, and you see here on the waterfall slide that we have very few patients here going the wrong direction, which is to say their tumor burden is increasing on therapy. Almost everybody's tumor burden is going down, and in fact we see that some of them, the ones in orange, have stable disease. But frankly most everybody responds, and we even have a few folks shown here in the blue or violet color whose tumor is gone.

01:31:35 And this is a very powerful visual, I think, when we think about characterizing objective response rate. Likewise here in the swimmer slide, when we look at duration of response, when we see responses that are lasting here out for two years, three years, three-and-a-half years, when we see responses that are still on going after we've followed these patients for a long period of time, or still ongoing even after treatment has stopped, that's very powerful and that's very different than the short lived response.

01:32:04 We've begun grappling with this issue of when is response clinical benefit, because when you see something as objective and data driven and precise as we try to be in giving our advice to companies about where the bar is set, the question we get asked most often, nonetheless I can't change the fact that I'm a clinician first and I'm a human being first, and it's very hard to look at these pictures and say that's not clinical benefit. So this is vismodegib in basal cell carcinoma, hedgehog inhibitor, and if you look at this patient who's really got disfiguring disease here, in the before panel, and in the after panel most of this is healed, you know that this patient is having a better quality of life. Would I like you to ask that patient. Absolutely. Would I like you to do it in a rigorous way? Yes, of course. But nonetheless, no sensible person is going to think that person has a different experience at Safeway than this person. This person is going to be less likely to be stared at, less likely to get an infection, less likely to be in pain. This matters clinically.

01:33:03 Likewise this patient with cutaneous T cell lymphoma before and after romidepsin, these are the patients ... I haven't taken care of one of these patients in many years, but these are the patients I remember from residency and fellowship as being the most miserable patients. They were so itchy. I remember being told by an attending when we had one of these patients who was septic from a staph infection through the skin in our ICU that cutaneous T cell lymphoma patients have the highest rate of suicide of any cancer patient.

01:33:31 And so when you see something like this and you've seen even one of these patients to know how they suffer and then you see that afterwards, how can you not call that clinical benefit. The same comments as before. Do I think you should measure that in a formal way? Do I think you should do the work of doing the focus groups patients and saying what matters to you? Yes. But do I need that to believe this is clinical benefit? Frankly, no.

01:33:53 So one last example is a sort of approach that I think we've not seen that much and I'd like to see more of, and that's really composite endpoints that include a feature of objective response rate with some improvement in symptoms. So Paul Kluetz from FDA, my colleague, is going to be giving you a talk about patient reported outcomes, so I'm going to limit my comments on this except to say that this is an example of how to do this right. So probably most of the people in the room don't treat a lot of myelofibrosis I'm guessing, but this is a disease that has a variety of manifestations, one of which is massive splenomegaly. And when the company was originally developing this drug ruxolitinib or Jakafi, they noticed in their early phase studies that patients had very dramatic reductions in their splenic size going from on average about 10 times the upper limit of normal really looking very pregnant at presentation to having dramatic spleen volume reductions, and they had considered coming in for accelerated approval based on splenic response rate and came to meet with the agency to say would that be okay?

01:34:53 So we accept response rate. Splenic response rate was a little bit of a bridge too far, because this is not the only place this disease manifests. So the advice they were given was, look if you really believe patient's spleens shrinking is such a benefit, why don't you just show that?

And so in fact that's what they did. They did the work to develop a very simple six item symptom score with patients who had this disease capturing the things that bothered them most. And they showed both the improvement in spleen volume reduction, the initial endpoint they had proposed, here in the Jakafi group, 42% of patients met their criterion of response of a spleen volume reduction on MRI of 35% or more versus virtually no one in the placebo arm, and that was statistically significant.

01:35:39 But they also showed that you saw a similar delta , about 40% between arms in patients who had met their criterion of symptomatic response which was a 50% or greater reduction in the total symptom score of these six symptoms. They had done the work to show what mattered to patients with this disease. And here I show this, not something from the paper, I show this from the drug label, and I do it to make a point, which is there are p values-

01:36:00 The paper I show this from the drug label and I do it to make a point, which is there are P values on both of these tables, and anybody who's interacted with regulators even briefly knows that you don't get a P value unless that was part of your statistical analysis plan. So they really put effort and sort of their money where their mouth was in focusing on both those endpoints. And likewise here you see the waterfall plot for the jack [inaudible 01:36:23] arm versus the placebo arm. This group going the right way this group going the wrong way. So I'm almost finished here, I'll just conclude by saying, you know what were the lessons that I think can be learned from this development program that frankly any company who's interested in a response plus symptomatic improvement end point should learn.

01:36:41 The enrolled patients who were symptomatic from their disease and therefore there was something to improve. This is something we do wrong in oncology in a dramatic fashion in my opinion. We tend to limit trials to patients who are E-Cog performance status zero or one, and they frankly are mostly E-Cog zero. And so if you're going to try to show that symptom improvement good luck with that, because no one was symptomatic going in. I think we need to enroll people who are more like the people we're actually treating in clinic who are not E-Cog zero and one majority.

01:37:08 They met with us early about how they might go about doing this once they saw a signal of efficacy. They didn't rely on an off the shelf seven page long, hundred item instrument that while validated might be burdensome for patients with a lot of drop out, and patients simply not completing the tool when they feel poorly, which is the time we're most interested in their data. They had a six item PRO tool, that was important to patients, and they captured and submitted that data electronically, which was not burdensome to study staff or patients and it minimized missing data. They actually gave patients something like a palm pilot, it was that time, but now everybody's got their own device and simply you make an app for it. People carry that device everywhere you take it to dinner, you take it to the bathroom, you have that device all the time your ready to do your PRO and in an instant.

01:37:54 And they assessed response rate and change in symptom score and the relationship of the two, which was plausible. And finally they aimed for superiority because they had enrolled symptomatic patients who could improve and they had a real statistical analysis plan to show that their findings were robust. So my last slide here, just to conclude, regular approval requires demonstration of clinical benefit or an improvement in a validated surrogate for it so this is overall survival PFS in many diseases when of sufficient magnitude, objective response rate in some cases with certain features, and potentially other issues like

organ preservation and so on that we can talk about in the panel, accelerated approval in contrast realized upon demonstration of an endpoint that's reasonably likely to predict clinical benefit. And it requires improvement over available therapy, so a bit higher bar to get over and it requires continued study of efficacy in the post-marketing setting.

01:38:44 And the most appropriate design and endpoint is going to vary of course based on the disease, the line of therapy, the patient population, and the context of what else is available to treat those patients. So that's all I have, thanks a lot for your attention.

Sharma: 01:38:56 We have time for one question, but while the person is asking the question, come up, sorry so you can hear me. If I could ask the speakers to come sit on the panel make themselves comfortable, Andrew you got a question.

Sharabi: 01:39:17 Thanks for that really clear and informative talk. So I had a question regarding the endpoint going back to the OS versus PFS-

Prowell: 01:39:24 Yeah.

Sharabi: 01:39:24 So clearly in the metastatic setting the IO agents many times don't show a significant improvement in PFS but do in overall survival. What are your thoughts in the locally advanced setting, I mean looking at the pacific data, which led to approval for development huge three-fold increase in PFS do you think in the locally advanced setting that PFS still may be valuable for the IO agents?

Prowell: 01:39:45 Yeah, it may be, you know PFS, I think this is something that you really need to kind of talk about which disease you mean because I think that you know for example in breast cancer we lump locally advanced together, locally advanced incurable together with metastatic whereas we take locally advanced potentially still curable, meaning resectable even after chemotherapy and lump them into the early stage trials. So I think it matters a lot, the specific disease, I'm not sure I can comment on that in a broad fashion, but I will say that if you are seeing you know, three-fold improvements in PFS and the absolute magnitude that you're talking about is large not three-fold from you know, one week to three weeks, but three-fold from something meaningful to something much more meaningful then sure, I think that's reasonable. But I don't think we can make a blanket statement that therefore PFS is always going to be adequate in every disease and every line of therapy. Am I supposed to keep taking questions or do you want me to sit down?

Sharma: 01:40:41 Well yes, well we got four people who want to ask questions so are any of your questions relevant to the panel discussion? Or are they specific for Tatiana?

Speaker 6: 01:40:49 I think they're relevant for a bigger panel discussion.

Sharma: 01:40:52 Well then why don't you sit down [crosstalk 01:40:53] and we can deal with them as a panel. [crosstalk 01:40:59]

Speaker 6: 01:40:59 Having said that, there was a particular point of clarification. So, I agree with your comments about overall survival, being the most meaningful endpoint, it has to be from the patient's perspective. However, I thought, and I just wanted the clarification that you skipped over a really important area which is this area of cross-over with a trial. So, you, when you have a study whereby the majority of patients have cross-over and the survival of

both arms actually appears to be better than the standard of care, albeit all the caveats of looking back on historical data, how do you go about addressing that?

Prowell: 01:41:38 Yeah, it's a challenge. So I did have one slide about the cross-over issue, but we were well aware that when patients cross-over that you're likely to diminish the size of the overall survival improvement and in some cases you might completely negate it. You're asking a different question at that point right? You're asking a question of experimental drug early versus experimental drug late? As opposed to experimental drug early versus control, so in some respects you've tainted the scientific question that's being asked. I would say that we think about this in a few ways. So one is that if there's such compelling data that we know that every single patient is gonna wanna cross-over increasingly we're asking industry, you know, are you sure you need to do a randomized trial here should we in fact instead do a single-arm trial looking at objective response rate and these other sort of features of objective response that we're talking about and be creative in how you might confirm clinical benefit for that as opposed to proceeding on with a randomized trial. I think that the days when we were demanding randomized trials with overall survival, in every situation have really passed because we're seeing drugs that are so much more efficacious than diseases than we had in the past that in some cases is just really not ethically appropriate or feasible to do those clinical trials.

01:42:58 But I think that the other issue is if you have a clinical trial. Well say that it started and at the time there is genuinely more equipoise at the trial design point, than say halfway through and now it becomes clear that you really need to cross people over. Say we've got data from another drug in the same class or something like that and patients will drop out and simply drop out and take that drug if you don't allow cross-over and you need to amend your protocol to allow it. There are statistical approaches to this for example you can do statistical analyses of how patients did before crossover was allowed in the trial versus after once the trial was amended to permit it and so on. And to think that the US regulators tend to be more flexible about this than regulators elsewhere in the world or more to the point payers elsewhere in the world, where really we've seen a number of therapies that are approved in the US that don't end up getting approved even in Europe.

Speaker 6: 01:43:48 That's the reason I'm driving [inaudible 01:43:50] because it's really quite critical and there is a mark difference I see between what's happening in the US and within Europe.

Sharma: 01:43:58 So at this point I'd just like to introduce three people on the panel who weren't speakers. We have two representatives from industry we have Zelanna Goldberg from FISA and we have Geoffrey Kim from AstraZeneca and consumer representative we've got Helen Bulbeck from the brain trust in the UK. So we have three more questions, I'm hoping they're broad enough for panel not just for Tatiana.

Speaker 7 01:44:19 I'll try to broaden it. So one of the ... actually something that was interesting when I spoke with a breast medical oncologist, Mark Robson in terms of ... he led some of the studies with PARP inhibitors and metastatic breast cancer. I pushed back on him a little bit in terms of, if we've shown that [inaudible 01:44:37] patients respond to PARP inhibitors we also know that correlation with cisplatin, why not just use cisplatin? But actually he provided very insightful answer to me, is that for some patients orally given drug we can improve patient quality or in terms of how they feel and how they approach disease management. So, it might be a little bit different than how we traditionally approach approval or thinking about it; but is ... had eluded to in terms of feeling and looking at response and just patient

benefit. Is that also another pathway for combining different agents with radiation is to look more towards patient quality of life during the therapy.

Speaker 7: 01:45:20 Also the other question that is sort of broader as well is that partly, in terms of the paradigm that we function as a local therapeutic is that we do for some indications ... we cure some of these patients and were we a victim of our success in terms of trying to push that even higher where the bar is a little bit different in advanced metastatic drug only type of approach. So just, is that something that, you know, FDA would be interested in ... and then that would help inform an industry collaborators about how to design these trials and think about this. Thoughts from everyone.

Prowell: 01:45:56 You made eye contact with me the whole time, so I feel obliged, and you also said "is that something FDA", so I'll take a little stab as a regulator and then I'll let the industry colleagues speak to that. I think what you're really getting at is kind of a non-inferiority design where you say this works as well as this other thing but patients tolerate it better, patients prefer it and certainly non-inferiority trials can be the basis of approval. The reason that industry, and maybe industry can speak to this more, but the reason that industry doesn't necessarily pursue that pathway as often as you might think is because those are big trials.

01:46:27 So especially if you're talking about a scenario where you're going to use overall survival, already a big trial potentially or a long, expensive trial and now you're going to make a non-inferiority trial that's a big sample size and if you're going to take that to the early stage setting, that's a huge sample size. So frequently that's a level of resource allocation that industry doesn't want to pursue but of course ... it's absolutely ... if you show that a drug is tolerated better or the patients prefer it; this drug doesn't cause [inaudible 01:46:56] and it works just as well as the one that does. Is that going to be something that could bring that drug and radiotherapy combination into the market? Of course. But maybe the industry people should speak to that.

Goldberg: 01:47:08 Sure, the points that you made are exactly on. Non-inferiority studies are huge and they're much too expensive and they're very very unappealing. One of the challenges with even going to overall survival ... and we think about it in the context of combination with radiation studies, if we want to move these drugs into the earlier stages; overall survival takes years and years. That's a massive investment with a very long time to pay off, which means the net present value of that study is much lower than a comparable study that industry can run in the first line metastatic setting with a clear one year PFS endpoint. So, automatically if you stick to an overall survival end point and you want to move things earlier in the treatment paradigm you can't structure it in a way that is economically feasible for even the largest of drug companies. Let alone the fact that most drugs in the United States are actually ... most of the early work is done by small Bio-tech that live ... you know going between funding rounds. Which means you do exactly what you have to do and not one experiment more. So, going back to our first speaker, it's a capitalist system and the economics will dictate what happens and what, even our endpoints options really are.

01:48:31 It's all driven by what will the FDA will even accept, that's one big piece. But another big piece is what will get funded when we go to Europe? The Europeans are much less flexible in many respects and it's ... you know to some degree, to their credit I suppose, but mostly it makes it really difficult to more innovative things.

Speaker 8: 01:48:50 And I'll just add one more thing to that. Sometimes you want to strive for both and so going back to PARP inhibitor, the recent PARP inhibitor approval in breast cancer for the G Bracka breast cancer population did show improvement in quality of life. Now, Paul Kluetz will talk about quality of life next and then the difference between using the same data for regulatory purposes and the PR reimbursement diverge and how they look at that. Where payers actually take into consideration quality of life data, very much so. This is global health related quality of life whereas the agencies looking for very specific measures, where in the quality of life was I improved. And sometimes, you know, when you go head-to-head versus chemotherapy, with an oral medication, you're looking for that improvement and unfortunately in this trial it did read out.

01:49:41 So hopefully with the advances of new drugs I think the promise of immunotherapy where the toxicities, the immune related toxicities, are of serious concern. However, they're in such low frequency that overall the benefit to the patience and the extension of survival is also a coupled with disparaging of cytotoxic chemotherapy. Now we're kind of taking a step back because now we're combining with chemotherapy all over again. But one day ... is this a step forward for radiation where instead of chemotherapy perhaps spot radiation retaliation and then quantitating the patient experience and demonstrating a benefit is the challenge. And this is, I think, where we have to get away from some of the traditional endpoints and methodology that we're used to and start looking novel methodologies to quantitate the patient experience and then define the benefit in a real meaningful way. I think ... I used the example that, you know, where I trained in New York City, you know, the old Physicians could tell right when the patient walked through the door, who was going to do bad and who was going to do worse. Then whether a drug doesn't work or whether a drug does work without looking at labs. I don't need to look at the labs and everything and they're often right.

01:50:57 It was amazing to see and experience and experience is knowledge but it's the recognition of things we have not been able yet to quantify in objective fashion and reliable measure and I think we're getting to the point and I'm looking forward to Adam's talk where he's gonna talk about wearable and the next wave of technology. Can we use that to redefine endpoints to avoid nine year studies in melanoma? Are we really going to wait nine years before the next generation of affective therapies ... now that we've built up and learned about the science and we want to capitalize that but if it OS's the bar and now drugs are working and Oncologists and Radiologists have choices, this is going to get very complex very quickly. So I think we need to continue to push to innovate and to adapt in order to keep pushing the field forward.

Sharma: 01:51:47 Okay I think we'll probably come back to endpoints in the discussion but we have two more questions to deal with first.

Mason: 01:51:53 Hi, Sam Mason from Reflection Medical, thank you so much for the wonderful presentations today. So my question relates to indications for use, especially in the immunotherapy world. We're seeing some studies now that are these basket designs where you have multiple histologies entering in and with the advent of bio markers and the importance of bio markers in potentially predicting response or even survival. Is there going to be a shift towards bio markers specific approval versus histology specific approval? Or is there a potential for that? Especially in the advanced stage setting.

Sharma: 01:52:33 Tatiana you should probably go first.

Prowell: 01:52:42 I'm missing my mic here but yeah I think that we're gonna see more of that, you know I think that as soon as we have the first anything, industry tends to say "Oh wow, if that worked for them let's try that too" and this is why you have two dozen immune check point inhibitors being developed for example. So I think that as soon as you have the first successful example of a tissue agnostic drug approval with the MSI-High tumors of any tissue of origin with [inaudible 01:53:09]. I think we're going to start seeing that sort of approach, not only for other immune check point inhibitors that are already working their own drug development programs for that same indication, but you're gonna see that kind of strategy being pursued for others. I mean we do have some cautionary examples of how that doesn't always work with BRAF. So one of the challenges we're facing as regulators, and I think we're all facing really, as clinitions and industry is facing too is that when we do a clinical trial, a phasery clinical trial in HER2+ breast cancer we really have a pretty solid idea of what the background, natural history of that disease is. Both in general and at this moment with he available therapy.

01:53:49 When we instead do a clinical trial or a granted drug approval for a tissue agnostic indication we're effectively defining a new disease, right? We're saying now the new disease is MSI-High cancer and absolutely no one knows what the natural history of that is. With the exception of colorectal cancer because until a couple years ago, we never checked that in anything except in colorectal cancer. So that's okay, if you're approving drugs based on response rate in a single arm trial because again the presumed response rate in a control arm, if you had one, would be zero. But none-the-less it begs this question of how much benefit are we really providing patients if we don't know how well they would have done with MSI-High, to take that example, MSI-High whatever specific rare tumor may be, those people maybe that little subset of that already rare tumor actually had a great prognosis and those people lived for a long time. So we're struggling with that as regulators and we're struggling with, what if we grant these broad approvals that are tissue agnostic and there are one or two histologies that actually don't benefit or might even be harmed by use of that drug and we don't have a great way to know that. So, I don't know, other people in the room may be ... I'm sure have thoughts about this.

Speaker 9: 01:54:59 Yeah, just a follow up points, I think it raises into question about the use or indication of radiation in the metastatic setting; to improve outcomes with immunotherapy. So, what are some measures of that? I mean, one of the studies I'm running we look at a 33% in relative improvement in the objective response rate. Which may or may not be the best endpoint because some ... just scientifically some of the preclinical data shows that radiation can increase the breadth and depth of your response and have a more broad response. So immune response. So that could potentially help to control the rate of growth and prevent immune mediated adaptive resistance. So, could a composite endpoint, including, clinical benefit rate and rate of stable disease ... that might also be helpful in trying to get an indication for radiation and the pallet setting to improve immunotherapy, which would be entirely new and novel indication for radiation. And we're still awaiting that data and multiple trials are ongoing but it will be interesting to see.

Sharma: 01:56:09 So I'm aware that we have now got queues at all three microphones so we're gonna end up with more people standing and sitting at this rate unless we get on with the questions. So let's move to microphone number one.

Wang: 01:56:19 Andy Wang from UNC Chapel Hill. So, for much of what we do as radiation oncologists we're doing it in the curative setting. So we're in the upfront curative management regiment

chemoradiation. We just heard the perfect rationale for not looking at radiation with another drug with a survival as the endpoint because the time line is long. So aside from a few of these diseases where people die fast, I don't see a way to change the current state. Which is part of the reason we're having this workshop. So, to me, my bias opinion, is that we need a surrogate endpoint and I'm wondering what the FDA's take on say [inaudible 01:57:06] which is really the radiation oncology objective response rate as a surrogate endpoint because much of what we do is ... there is no metastatic disease that's what we see. The other thing is, I'm intrigued by the organ preservation line in your last slide. You didn't expand on that, I would like to hear more about that. You know, are you suggesting that is also a possible surrogate endpoint for approval?

Goldberg: 01:57:34 I'd like to pile on that question because, is the FDA willing to look at organ preservation as an endpoint? [inaudible 01:57:44] you've approved drugs, as you well know, with breast cancer, but that's the only example that's out there and having proposed to study, to remain nameless right now, looking at it in another agent or another disease state, you know, the immediate response was well it would be a review question. That is a very challenging position to fight back from within an indust where we're still competing from funding for studies.

Prowell: 01:58:13 Yeah so, [inaudible 01:58:15] something that I've been working on within in the agency in breast for several years now, and I think that this is something that is becoming of increasing interest in other disease areas. In fact, there is a conference that the FDA is co-sponsoring next Friday, March 2nd in Bethesda. Not in this hotel, but in Bethesda with IAS Cell-C that's actually looking at the question of using maximum pathological response, NPR which is similar to Path CR but not exactly the same in early lung cancer as basis for approval. So people are starting to think about this and there are regulators as co-chairs of that conference and I'm talking in that conference about the breast experience. So I think that we're ... there is an increasing level of interest in looking at response in a more granular way as a basis of approval. I would say that there is a lot of effort within the walls of FDA, one thing that I didn't really say in the basis of time, you know there is a lot of effort trying to quantify these other features I told you were important. For example depth of response, durability of response and whether or not those in fact could be response plus that other factor.

01:59:22 For example depth could be validated as a surrogate end point that is then able to support regular approval. Some of you might have seen, if you work in the lung cancer space, you might have seen an article by a bunch of my FDA colleagues in annals of oncology this summer I think in July or August where they actually looked at depth of response in four trials. Two trials in Alk inhibitors or Alk ... I don't know what you want to call them anymore, but [inaudible 01:59:48] that do all those things. And you know immuno oncology agents, immune checkpoint inhibitors and basically showed that if you looked at depth of response across those two drug classes in non- small cell lung cancer for patience that were sort of in the third and the fourth quartile. So greater than 50% depth of response, greater than 50% reduction in tumor bursts [inaudible 02:00:09] less than that. That actually correlated very well with both progression free and overall survival.

02:00:16 So I think there's a move ... you know we recognize that this is a problem. We recognize the strength of overall survival as an endpoint as I said, it's a powerful endpoint but none-the-less it's not very practical and it's not always the right endpoint, clearly. None-the-less it would be nice to instead of just making it up, saying "We can't do overall survival let's do

something else" it would be nice to find something that we think is really simple to do in a single arm trial where we do have a very promising drug scene in early development and we're confident that if you show an objective response rate of whatever plus, you know, the majority of patients having a greater than 50% reduction in tumor burden that that's likely to predict overall survival in those patients. I think that's a very powerful thing to do.

02:00:55 Organ preservation, you know I'm a breast person so I'm really the wrong person to ask about this I mean the organ is always partially removed, at least as of 2018 even in patients with Path CR. So probably this is a question I should maybe deflect to other people in the room that do tumors where organ preservation is a real endpoint that you think about clinically if not in a regulatory fashion. I don't know who those people are, I'm sorry. But [crosstalk 02:01:20].

Sharma: 02:01:20 I think that we can benefit from the panel there because we have expertise on the panel. So say for example in bladder cancer, where radiation might result in the bladder being preserved rather than a cystectomy. Can I ask the members of the panel, are there particular endpoints that you think matter to patients that wouldn't necessarily be recognized by the regulators? We've heard about quite a few already I'm just interested to know what others, for example from Helen the consumer representative.

Bulbeck: 02:01:53 I think it comes very much down to the individual and there attitude to risk and what their context is and what their values are. I would always say when you're looking at recruiting for trial you should stay low court and stay personal. So look at the people in front of you, have a talk with them, talk to them about future dis utility because that would be a big question for them. Very often it's about living with uncertainty, how resilient they are. I think there is a lot of work that actually ... there is an opportunity in scope for this group, I've just done the same four preclinical phase one trials with our experimental cancer medical centers in the UK. For producing educative material that demystifies things like equipoise for these patients that could come out of this group. Because it's a very complex game that patients are stepping into where you've got a whole range of medalists around radiotherapy and also around the chemotherapy as well and it's very very complex. It can be at any point in the journey ... my background, I've had head and neck cancer, I'm now ten years down the line and I have a huge range of side affects that were never explained to me. They are quite life changing, so there is all of that as well around that uncertainty and how resilient they feel. And what's important to them.

02:03:18 My charity I run is brain cancer ... my daughter had a brain tumor and if you've got somebody with a GBM you're looking at a very life limiting disease but you might have young father who is absolutely desperate to see his child being born and will do anything. And, you know, I was coming back to point I think you were making, there's two opportunities I think for trials to be developed at disease progression. We're very very thin on the ground with that it's certainly in brain, in the UK and my experience of talking to thousands of patients and their caregivers is that they are more willing to take risks at that point in the disease trajectory than earlier on because they haven't got quite so much to lose.

Sharma: 02:04:00 Thanks, Helen. So Zelanna were you going to say something about this.

Goldberg 02:04:04 I was gonna say that certainly from an industry perspective having land mark analysis accepted by the FDA would be game changing in the EME and so on. Game changing,

because one of the things RTOG can do is two year survival endpoints. And we can't take that to a regulator.

Wang: 02:04:25 Right, so, just a quick comment, I would love to see FDA develop a surrogate endpoint for chemoradiation regiment for much of what ... for many of the diseases across the board. I mean it's very similar for many cancers and I think that would be potentially a game changer because then the industry partners would be a lot more enthusiastic about finding us and doing trials.

Sharma: 02:04:48 Thank you for your question, we're gonna, move to microphone three because you've been standing there the longest.

Speaker 10: 02:04:52 Thank you, so my question actually is a very natural follow up. So ... but maybe from a little bit more statistical perspective because of my background. So what observation I notice is that in local and locally advanced [inaudible 02:05:07] where RT is involved the number of trials ... actually the availability of a number of trials is actually much smaller than the metastatic setting where you can typically use some standard mass to evaluate a surrogate endpoint. This is some issues that I've noticed as statistician, so I was just wondering in the context of developing ... to expedite the clinical development in early stages and early trial [inaudible 02:05:38] is it ... how it will be received if we try to evaluate some surrogate end points by pulling data from, not only randomized trials, but also static trials.

02:05:57 Because my observation was that ... so in many cases there are probably only a few trials for a certain disease and one maybe done RTOG and I know that because I am mostly involved with them and maybe a few conducted in Europe. And that's pretty much it and even in very extreme cases we don't really have a randomized trial before this practice being adapted. When such situation, I noticed, is at [inaudible 02:06:30] stage one non smokers' lung cancer for [inaudible 02:06:33] so SBRT was basically in use in practice based on a single arm phase two trial conducted by RTOG. And then it kind of became utilized everywhere. So I was just ... but on the other hand ... so this is actually motivated by my ongoing work, so now say we're trying to develop some phase three trial in the stage one inoperable non smoker lung cancer patients. So over survival just takes forever to do then ... but I don't really have much randomized trial data in hand.

02:07:11 So I was just curious in many institutions you probably have thousands of cases from your institution: Princess Margaret, from Stanford, everywhere. RTOG have a number of trials that they're setting up these studies but all are probably single arm and there is probably some other data out there somewhere and I'm just curious in some situations like that would the FDA, as well as industry would also be collectively be interested in creating some program or paradigm to collectively say that if we can maybe pull data together and see if there is something that comes up.

Sharma: 02:07:54 So maybe Andrew, do you want to comment and then Tatiana? He's asking about pooling data from non randomized trials.

02:08:00 Data from non-randomized trials. Or touch on it, do you-

Prowell: 02:08:07 I feel like I'm talking too much. There are a lot of FDA people in this room. I'm not the only one. And some former FDA people in this room. Why don't we have an industry who used to be at FDA until really recently?

Kim: 02:08:15 How about ex-FDA? So, yes, I think definitely industry would be interested in this type of data. I mean, this is what it needs. I think what I'm hearing, and what I would like to encourage this audience to do is not ... I know it's hard, but it's not to the point where you have to ask permission from FDA before you have innovative ideas. You just gotta go for it. If you think path CRs important for radiation, do a trial that does measures path CR, and the magnitude's big. It makes sense, just logically follows. If you have a tripling of pCR, that might be enough. One to three doesn't count, I get it. But if you go from 30% to 90% pCR, I think that's something that the field and what patients really want and are desiring. And if you have a body of data to provide that historical context, I think that's even more valuable to put in perspective.

02:09:13 There are so many pressures that researchers and industry, and even on regulatory, face right now. We have so many options. There's going to be a wave of new innovations coming our way with CAR-T cells by specific antibodies, all these other newer modalities that are gonna to challenge us of how to prioritize. Eventually, all of us are going to have to creep out of our comfort zones of what we are used to in developing and start to invest in other biomarkers, not only for patient selection but for patient benefit, like clearance of circulating free DNA. Perhaps in these early-stage diseases and whether or not they correlate with endpoints. But the longer we delay in starting these trials, the harder it's going to become to correlate that with long-term outcome. So, we need to make an investment at these key time points initially to understand.

02:10:11 If we can reliably curate that data to provide a dataset that gives us a comprehensive view of what the natural history of that modality, whether it's been verified in randomized clinical trials or not. And the example is the meta-analysis of the breast cancer pCR that the FDA did with the CT [NEO-B 02:10:31], where they did pull the datas from many different trials together to build that dataset to build a story and then launch into the endeavor of identifying pCR as a potential endpoint for regulatory approval. And I think the same rigorous exercise should be done. What is the data telling you right now? What do we know about the natural history of the disease? And then what is the therapeutic benefit of adding another therapy on top of that? That's the bread and butter of what we're trying to do without getting caught up in traditionally defined endpoints.

Sharma: 02:11:02 So, we've only got a couple of minutes left. So, very quickly, microphone two, then microphone one.

Speaker 11: 02:11:08 It's just to suggestion is that I think most of our trials of patients are young patient. The population's aging. Most of our cancer patient out there elderly with a lot of co-morbidity. It would be lovely to have a panel to discuss about an endpoint for that new, migrating patient population where their survival is to be the endpoint for that population. Cause we struggle quite a bit when we try to design these trials.

Sharma: 02:11:31 That's a good point. Thank you.

Buchsbaum: 02:11:34 To Quynh's point. There's a lot of space ... I'm Jeff Buchsbaum, NCI. There's a lot of space for long-term, re-use of radiation therapy that's not explored within the space. But the question is ... Well, part one, it's been a long-standing here. We're bringing out targeted radiotherapy with radionuclides as a focus with dosimetry, and I wanted to underline the importance of the dosimetry presentation that was put forth by [Ira 02:12:04] today. It's not something that one can appreciate until one is at the NCI. In some ways, the things I heard about aren't

necessarily all understood when you're in training or in practice, cannot be underlined enough how important doing quality work, as that does translate to preclinical space. And we're going to be demanding preclinical equivalent of good dosimetry in studies.

02:12:26 The question's this. We did not talk about enrichment, and it effects the entire panel. So, the enrichment of patients can shorten trials, can change trial design, can change trial endpoints, can change the interaction with patients because patients will feel like it's a trial for them as opposed to a trial for the group. So, I'd like to point this in an effort to help the panel have a panel discussion, which is what I think the panel chair has been looking for a little bit, is to look at enrichment and how we can use the concept of enrichment to accelerate the process and possibly reenergize the space.

Sharma: 02:13:01 So, I'm not sure if we're gonna have time to cover that, cause we're eating into the coffee break. But we might be able to come back to it in the panel discussion. So, unless anyone's got any burning comments to make on enrichment ... Andrew, do you wanna say something?

Sharabi: 02:13:13 Following up on Quynh 's question about the elderly population. I think that's a key indication. Many of these patients may be Cisplatin ineligible. There's even a question of whether in advanced age how much of a benefit there is to concurrent chemotherapy with radiation therapy. So, an indication and a use of immunotherapy in that setting, if it's better tolerated with similar efficacy, that critical point, especially in advanced age and elderly population.

Sharma: 02:13:42 So, I'd like to thank all the members of panel. I think we've got almost 15 minutes now for a tea break. Thank you.

Sharma: 02:14:33 Can you ask everyone to take their seats?

Liu: 02:14:33 So, I'm glad to see that everyone's having great discussions, but if we could all sit down so that we can get started again. So, this is the ... This afternoon ... Thank you, Ted. Can I tell a joke?

T. Lawrence: 02:14:33 I have another mathematician joke.

Liu: 02:14:53 Oh, no, no, no. Okay. No, I have a banker joke. I have a banker joke. A man goes up to his banker and said, "How do I start a small business?" And the banker's advice was, "You start a big business, and then you wait six months." Okay, sorry about that, I couldn't resist. All right, so we're going to ... We have three interesting sessions for the rest of this afternoon on talking about patient reported outcomes. And we're really looking forward to this session because I think it's interesting, it's new, and I think it's highly impactful and important for patients. And so we're first going to hear from Paul Kluetz, who is where?

Kluetz: 02:15:38 Right here.

Liu: 02:15:38 Oh, there you are. Thank you. So, Paul, please come up and you're gonna tell us about the PROs from an FDA perspective.

Kluetz: 02:15:47 Thank you. So, all I wanted to do was be up on that last panel. I was like, "Aw, such an interesting panel." So exciting about all these different endpoints. And I'm gonna actually touch upon some of those, too, with my presentation. So green means go, yes? So, I have no financial interest to disclose being from the FDA. So, as Tatiana said, regular approval ... I like to put these words up, regulatory words, but I like to highlight that what we look for is substantial evidence of a clinical benefit. And it's based on a prolongation of life, a better life, and an establish surrogate. Those are actual regulatory terms. So prolongation of life is your overall survival, and obviously established surrogates, we have PFS disease through survival, EFS, usually radiographic evidence.

02:16:33 So, but what about a better life? And that's what we're trying to dig into right now. So, a better life as a clinical outcome assessment. A clinical outcome is how a patient feels or functions. So, we have four different ways ... These are actually measurement types, and they're really based on the source, where is the data coming from. PROs are data from the patient themselves, and they're not amended. So, you give a questionnaire, it comes out with a score, that's the score. The clinician doesn't interpret it or do anything else. Clinician reported outcomes, we have a lot of, and the most common I would say is the CTCAE, or safety data. That's a clinician asking a patient, "How do you feel?" "Okay, I think it's probably more like this", grade it, etc. And it's relatively objective, but it's also subjective in how the clinician decides whether it's attributed to the disease.

02:17:16 An Obs-RO, or an observer outcome, is if you have a kid or an infant, or someone who has poor mental facilities, who might not be able to do a questionnaire, you can have someone observe them for observable signs, and that's important. We wouldn't want the observer to say, "I think my kid's in this much pain." It has to be observable, how many times did they vomit, etc. And then performance outcomes for measures like the six minute walk test. You ask someone to do something and you measure it.

02:17:44 But we'll get into PRO, first. So with patient focused [inaudible 02:17:48] and patient reported outcomes has become very big, and over the last couple of years I've been trying to dig into it, to really understand what the strengths and limitations of it is as a regulatory tool. And so, I'm putting it into the same bin, if we're going to use it as regulatory measure, as any other measurement. So what we look at for adequate and well-controlled trials for measures are ... we wanna know what the objective is of your assessment. We want the assessment to distinguish the effect of the drug, to the extent possible. And we want it to be well defined, particularly cause a lot of times we have to label this, and we have to communicate this information to patients.

02:18:23 So, as far as the objective, it can really answer a lot of different kinds of clinical trial questions. So, you can just describe the patient experience while on therapy. And that's typically what we get, they're mostly exploratory in many of our trials. Increasingly it's interesting to inform safety and tolerability so that there is a PRO version of the CTCAE that's been developed by the NCI, which is catching on and is very interesting. And then of course it can inform efficacy.

02:18:51 So, those are the objectives, but what about the endpoints? Where do you ... What's your US regulatory intent for this measure? So, you could just have it as support of data, and I'll show you a couple of examples of that. You can also get some data in the product label that's even descriptive. Remember, safety is descriptive data. It's not statistically tested and adjusted multiplicity. It's in section six, describing the safety of the product. Or you can use

it to make a claim of treatment benefit that you can market to say, "We improve pain." And radio isotopes like samarium were based on pain control endpoints and those patient reported outcomes.

02:19:33 So, a couple of labeled examples so you can kind of get your head around this. If you're gonna use it for efficacy, Tatiana mentioned the kind of gold-standard PRO in oncology example, more recently, was ruxolitinib. Again, myelofibrosis, you get a large spleen. They did the work to ask patients, "What are these symptoms that splenic enlargement's causing?" They started out with 40 questions, and they whittled it down to 6. So, again I think it's really important to remember that burden is real and duplication of questions is real. And they did see that, indeed, shrinking the spleen was also seen in association with an improvement in symptoms with the water [inaudible 02:20:12], and these are from the FDA label. So, these were labeled.

02:20:18 We've also got an example of using patient reported outcomes to describe and complement safety data from clinicians. So, in [inaudible 02:20:25] label, it was noted early on that there were a lot of ocular sort of side effects being reported by patients, that were kind of vague floater-type ocular side effects. And so they put in one of their trials a patient reported outcome that further explored what these ocular side effects meant to patients. And they got complementary information the frequency, how long these occurred, and also what kind of impact they had on the patient. And they were able to describe that even though it's a frequent event, it doesn't seem to impact patients very much.

02:20:57 Finally, this is a very novel use of patient reported outcomes, more recently, where you're comparing two very similar drugs, just a different way of administering it. So RITUXAN HYCELA, which is subcutaneous injection of rituximab, was head-to-head against IV rituximab. And a very novel sort of planned crossover trial design to where everyone got both types of medications, and it was found that 77% of patients preferred to get the subcutaneous injection rather than the IV injection. And they even asked why and it was because it took a lot less time. Rituximab you have to give slowly because of infusion reactions, and subcu they could give it in a matter of minutes. And also, interestingly, some people preferred the IV.

02:21:42 And so one of the things I've really realized in this space is we think we know what patients want or believe or desire or thinks important, and I overheard someone say, "Well, you know oral tablet versus an IV infusion. Of course everyone would want the oral tablet, that's so much better." But, actually there was study that showed the reverse, and why was that? It was really surprising to me. It was because patients didn't like to know they had cancer every day. Every day they wake up, they had to take their cancer pill, versus once out of every three weeks they get an infusion and they forget about it for the next couple of days. And so I thought that was really eye-opening.

02:22:18 So, what should we measure? This is a challenge and if I can solve this in the next year or two, I'll be really ... I'll feel like I've done something. Lots of patient reported outcomes are being put in cancer clinical trials, and there's overlap. And companies are getting pulled in five different directions because they need the EQ-5D for NICE, and they need the health-related quality of life for another group, and then they're trying to understand what we want for labeling purposes. So, there's a lot of duplication and there's a lot of burden, and we're trying to adjust that.

02:22:49 So, I'm just going to give you my perspective, and we're only one stakeholder, but we are working with international collaborators, including pairs as well as international regulators to try to get on the same page. This is from Wilson et al., it's a 1995 paper, just a conceptual paper about health-related quality of life, and I just wanna walk you through it.

02:23:08 So, we're trying to distinguish the effect of the drug for what we do, or the intervention in your case. We know that the radiation therapy is gonna affect biologic and physiologic variables. That's the most objective part, the most proximal part to what you're doing. That will cause symptoms through toxicity, and maybe it will alleviate some symptoms, EBRT for bone mets, let's say. And that constellation of symptom improvement and giving symptoms will then maybe affect function. And that function will affect a patient's perception of what their health is doing. And that health perception will affect their quality of life.

02:23:44 And as you step down that from very narrow to very broad quality of life, you can see all of these different inputs that start to come that are not drug inputs. So, you've got personal motivation, you've got values, you've got social, psychological supports, economic issues, spirituality for quality of life, etc., response shift, meaning when you get in your wheelchair for the first time since your spinal cord injury, you think your health or your quality of life is terrible. Same situation, no better in two or three years when you've decided how you're going to live in a wheelchair, your health-related quality of life gets better, no intervention. So there's this response shift, and it has a lot to do with emotional.

02:24:22 So, what we've decided is because we're trying to look at the effects of the drug, we want to look at these proximal symptom and functional measures. So, I wrote a paper in 2016 with a bunch of collaborators from the FDA to say, initially, as we really try to get scientific about this, we're gonna look at disease symptoms, symptomatic adverse events, and physical function, ability to work, as our first look for labeling purposes. It's not to say that's the only thing to measure because we know there's other stakeholders in health-related quality of life and social well-being and other things will be measured. But for labeling purposes, to put in the FDA label, which you can't put everything in there, we're gonna start there.

02:24:59 So, what about how can I measure it? I just wanna touch on instruments because that's a challenge. A lot of people who've tried to develop drugs from industry will come to the FDA and say, "We wanna measure skin toxicity, we wanna use this questionnaire off the shelf for durum, in the setting of a rash from a TKI. Can we do that? It's a different context." So what do we need from a well-defined and reliable assessment? This is from the clinical outcome assessment staff within the FDA, and they're giving you a couple of pointers about what is fit for purpose means. The instrument is fit for the purpose that it's intending to measure. So, it should be appropriate for the intended use, the study design, the patient population, and the therapy.

02:25:42 Quick example of where this goes awry is some of the prostate cancer, because I did a lot of prostate cancer work early, the instruments were really designed for the adjuvant setting, you could tell. They were asking about sexual dysfunction, they were asking about urinary issues, all of these things that you encounter with prostatectomy radiation therapy. And then they're applying it to the metastatic setting, like the third metastatic setting, where you're on ADT, you've got incontinence, NED that ain't gonna get better no matter how effective your drug is. And not surprisingly, patients are not psyched to answer that question when they know it's not gonna be better, and of course the data's not gonna be helpful. So, that's an example of it's not super appropriate, that you wanna ask the right

questions for the right context. And even though it's the same disease, prostate cancer, early versus late is pretty different. It needs to be valid and reliable, and that has to do with the measurement properties, so test, retest, to make sure that those analytic measurement properties are good. It should be clinically relevant. That goes again to the appropriateness of the context, and important to patients. And this third point is what we're working on. It has to be communicated and labeled in a way that's well-defined and people can understand it so that it's not misleading because the reason that Europe has a lot of [purell 02:26:59] on their label, and doesn't think about it maybe as much as we do, is because we have direct consumer marketing. And we really have to make sure ... We have a whole group that makes sure that the label's very clear so that the marketing is good and is marketed what the drug effect is.

02:27:15 So, an example of well-defined ... You can use physical function as an example. So, physical function is defined by pain to ... A person's assessment of his ability to carry out important and meaningful day to day activities, that require a physical effort. So, there's a lot of physical function scales out there. The PROMIS physical function has 104 items or something, you can build your own scale, and they're all sort of asking about these activities that require physical effort. Similarly, the QLQ-C30 has a physical function domain that also asks about varying levels of physical activity, and that score will give you a physical function score, so that when ... if there's an improvement, we can label physical function was improved in arm A versus arm B. These scales don't have a question about health-related quality of life, a question about pain, a question about something else that aren't directly related to that concept you're trying to measure. And we do see that in some scales, so they would not be considered well-defined. Myelofibrosis disease symptom scale, definitely well-defined. Six symptoms, cardinal symptoms of the disease, all within that concept so that when we said, "Disease symptoms were improved," it was not misleading. It was the cardinal disease symptoms. Again, there were no impacts on health-related quality of life, or physical function, it was just the symptoms.

02:28:26 So, you can see we're a little bit more narrow with what we like to see with the measures. And obviously with single symptoms, they're typically well-defined because they're a single question. And we can even ... Even if they're a little slightly vague in how they're asked, we can at least label it as the question. When patients asked this, X percent replied that etc. A lot of AEs, this is from the pro CTCAE dry mouth at its worst. This is a pain question from the MD Anderson pain scale.

02:28:56 Just a hypothetical fictional example of what is not well-defined, but we do see sometimes, is a fatigue score. So, we want to measure fatigue, we think we're improving fatigue. How tired are you? How much weakness do you have? What is your energy level? These are all fatigue-related items. What level of pain do you have? How much numbness and tingling do you have? And how would you rate your quality of life? Now, those are ... I see this a lot. And when you look at this group, it's kind of hard because pain and neuropathy may contribute to the development of fatigue. And yeah, health-related quality of life may be diminished as an impact of the fatigue, but it's not measuring fatigue itself. So then, now we label fatigue as improved, but it really health-related quality of life, and it was pain, and it was some other things. So, just wanted to hammer home. That's usually COA staffs, our clinical outcome assessment group that looks at the tools, that's usually one of their biggest concerns in oncology.

02:29:50 In general, you can develop your own instrument, but it's hard and it takes a long time, and on today's drug development timelines it's sometimes infeasible. So, understand, many measurement tools exist, we'll work with you to try to adapt tools, for instance, or select items from item banks that make sense for your trial. But you should definitely come talk to the FDA about that.

02:30:11 In response to my initial paper about focusing in a little closer, I got a lot of feedback from the health-related quality of life field saying, "You don't care about health-related quality of life, what's wrong with you?" And I understood that because they've been doing this for 30 years, and they believe ... They're an amazing group of people that really believe that the concept's important. And I think you can use it in certain contexts. So, in response to their scathing editorial, I just said, "We favor a thoughtful combination of static questionnaires," meaning these generic tools, "but also select symptoms that are very specific to your context with item libraries," like the PRO CTCAE. Yeah, it's got 80 questions, you can take the six that actually relate to your clinical trial context. And I've been working with all of the groups that create these large health-related quality of life tools, and they were working together to identify a way that everyone will be happy with it. Not everyone's gonna be happy with it. That's definitely not true.

02:31:08 So, the totality of the data. Getting back to this last session we had, which I thought was excellent, about endpoints. When we look at an application, we're not just looking at the primary endpoints. So, everyone's very focused. Should it be organ preservation? Should it be PFS? Should it be EFS? Should it be a biomarker? There's going to be different levels of strengths to that primary endpoint, but remember, it's a story. And so the more important endpoints that you can put into that clinical trial to describe the safety and efficacy, the better. So we're always gonna get our standard set of objective measures, of radiographs, or serum and biomarkers, of survival. And we're gonna get our CTC safety. But in addition these clinical outcomes, like PRO, like performance measures, like this cognitive scoring you can do with brain cancer, wearable devices, all sorts of things are going to be developed to really help us paint that picture of a patient benefit. Increasingly, healthcare utilization's interesting and I think that kind of gets to that organ preservation question. And so we've been sending out information requests to companies to say ... Cause we get this sort of in data sets, and we have to pull it out and figure out how to get it, but now I'm saying, "Just give us this. Tell us, for each assessment period, how many people got hospitalized, how many people in ED, opiates, antiemetics, antidiarrheals," so you can see supportive care meds. You can see palliative procedures, depending on the context, that can be important, that can really help us further understand the effect of the drug.

02:32:35 And so, why I really wanted to hop out of my chair when Tatiana was up and got asked the question, "Well what about organ preservation?" Cause that's a really good question, and that's a hard question to answer. What I can tell you is we did a workshop at the AUA for nonmuscle invasive bladder cancer, as well as prostate cancer, and it was this story. It was adjuvant situation, can't do the trial, wait too long. What can we use? And cystectomy came up because it's a very morbid procedure, it's obviously clinically meaning to the patient if they get it. It's an endpoint, okay? And as Jeff Kim said, and I think he's right, many times companies will forge ahead with the answer. It will be a review issue because we have no precedent for that endpoint. But what I can tell you is all endpoints have strengths and limitations. So, in that case what you're measuring is actually pretty strong. It's a direct measure of clinical benefit, right? I mean, if you're getting the cystectomy, you're not getting the cystectomy, that's pretty big. But how accurately it's being measured and its

susceptibility to bias is the issue. So, you have to be very objective how you stream those patients to cystectomy, and when you put them to cystectomy. Because if it's time to cystectomy, there's a lot of wiggle room in when that surgeon decides that it's time for a cystectomy.

02:33:57 Now, what can overcame that uncertainty? Magnitude of effect, obviously. I think that if you have a huge difference that would be something that would be helpful, but nothing is perfect. I just wanted to mention that that's how we think about endpoints. We think about what are you measuring? Is it a direct fields, functions, or survives type of endpoint? How accurately is it being measured and how susceptible is it to bias? And how much of an effect did you have on that endpoint. So I think if you think of all your endpoints in that way, you can kind of bend them. PROs no different. What you're measuring, important, direct clinical benefit. How you're measuring it? Pretty significant variability sometimes with some of these tools, potentially bias, we have a lot of open labeled trials. So, sort of wanted to leave you with that.

02:34:43 So, in summary, clinical outcomes are more than just patient reported outcomes. It's measuring the patient experience while they're taking the therapy, both objective things that happen, like getting surgeries or getting different kinds of morbid procedures, what kind of supportive care medication is he on? Remember, [abaradaron 02:35:01] has a timed opiate use endpoint labeled. So, we've done it before. Remember, skeletal related events, important regulatory endpoint, half of it is in an intervention. EBRT for pain, surgery for fracture, ortho-fracture. So, they're both, those events, are also generated from a physician and prone to bias. If you were going to use PRO ... Everyone's going to use PRO because that is what we do in clinical trials. We're gonna get it. We're not asking you to do anything new, but we'd like to see it a little bit more organized and a little more relevant. And we're working with patients like Patty to try to get a more concise, core group together that will be more consistent and have better coverage for toxicity. Remember the well-defined thing about instruments. Try to keep your instruments well-defined so we can communicate the results clearly. And I think there's an increasing interest in healthcare utilization, mobile device data, including wearables, and again paint a picture of benefit and not just your primary endpoint. So, thank you.

02:36:09 Are we saving questions?

Sharma: 02:36:12 No, we've got time for questions.

Kluetz: 02:36:12 Okay. Do you have any questions?

Sharma: 02:36:16 So, I have a question. So, the flexibility that you've demonstrated is really interesting actually because in terms of NICE and registry based commissioning, for example, is relatively inflexible because of its EQ-5D, or there isn't much scope for creating, for example, questionnaires based on item libraries as you showed. So, what do you think about flexibility in cost-effectiveness models? How can we improve that in terms of commissioning?

Kluetz: 02:36:51 So, thankfully the FDA doesn't take cost into consideration because it's incredibly complicated. But I do think about it because we've been thinking of cost as the third [inaudible 02:37:03] in the FDA, cause we really don't regulate it. But we do have a role in the sense that if value is benefit over cost, we know what clinical benefit is. That's all we do every day, is try to define what clinical benefit is, and if payers don't understand why we're

making our decisions based on response rate and PFS, etc., they may overvalue a drug or undervalue a drug. So, we're working to try to make sure at least they understand what that clinical benefit piece is when they put it into their models.

02:37:35 As far as EQ-5D and NICE, I do know that that's an issue and that comes in ... Luckily it's only five questions. There's a benefit to consistency, I think. So, I agree with them. Now it's not super sensitive, so it'll see big benefits, it'll probably see big toxicity and moderate benefit. It's that intermediate benefits or incremental benefits that some of those measures may not see. Again, when we're working towards this core PRO set ... On June 22nd, 2018, by the way, we're doing a workshop on this exact topic. It'll be at the FDA in the Great Room, and it's free, and it's on WebEx, so look at our website. But we need to have pairs involved because we know if we come up with this great idea that doesn't include EQ-5D, everyone who's in the industry's gonna be like, "Well, that's not going to be helpful for us because we need that." So, point well taken.

Sharma: 02:38:29 Any other questions? No, great, thank you. That was a great talk, thank you.

02:38:33 So next we're gonna hear from Patty Spears on the patient's perspective on PROs. Is Patty here?

Speaker 12: 02:38:47 She's right there.

Sharma: 02:38:47 Okay, great. Measuring what matters to patients. Thank you, Patty.

Spears: 02:38:54 Thank you. So, thank you for inviting me. I never turn down the opportunity to talk about patient reported outcomes. I think Paul knows that, because I have a lot of opinions on this. So, I'm a breast cancer survivor of 18 years. I've done two clinical trials, and one did involve some questionnaires, quite a few questionnaires. And one did not, but I also did some observing questionnaires for my dog who was on a clinical trial. See, you can add that to your list of children and dogs. We had to look at her and see whether she was in pain or not. She was on a new pain medication, so as long as she wasn't barking we thought she was okay. So, anyhow.

02:39:37 So, we'll get started. And I work the University of North Carolina Chapel Hill in patient advocacy now. And so why do we do PROs and what PROs consider? I think this is what the take-home message is, I always talk with what I want the take-home message to be. But it considers not only what matters to the patient ... What is the matter with the patient, but it also measures what matters to the patient. And one of my friends coined this at a ...

02:40:00 Matters to the patient, and one of my friends coined this at a triple ABV meeting and I think that's really important because you get the information directly from the patient without interpretation from the physician.

02:40:13 That's what patients want to hear about in the clinical trial. So one of the things that I get... I think there's a lot of confusion sometimes about pro assessments, especially in regulatory and in clinical care and in different avenues, so PRO assessments are being used in clinical care.

02:40:31 I actually volunteer a lot with Ethan Basch at UNC and, you know, testing the use of PROs in just clinical care, and he had a big presentation at ASCA that showed that it was a benefit and that's one way that you can use PROs to improve patient care.

02:40:48 Also in registration clinical trials, there's... It's usually about, "Okay, can I use this end point for registration," and everybody focuses on that, but I would like to challenge the industry and say there's another use for PRO data in registration trials and that's information for the patient.

02:41:07 I think there's a lot of competing drugs out there with different side effects and different effects on patients and so the more we can tell our patients about the different drugs and our colleagues, you know, what to expect because it's the unexpected... Like somebody said earlier, that really makes the patient very confused and not knowing what to expect. So I think that's really important to collect in a clinical trial, whether its registration or not.

02:41:32 And then in clinical trials just answering intervention questions. I volunteer a lot with one of the cooperative groups, the NCTN groups and you ask a lot of different questions and I think it's really important for all of those groups to use PRO CTCAE along with CTACAEE and along with other questionnaires so we try to work on incorporating those.

02:41:51 So there's lots of different ways to incorporate PROs. And why do we do that in clinical trials? I usually focus on the clinical trial area rather than the clinical care area because patients have to make a lot of decisions these days and so what do they need? They need to know what the benefits are, which are usually pretty well communicated as efficacy but a lot of times, the harms are not communicated quite as well to patients and they're just as important because they make these decisions based on the proportion of benefit versus harms.

02:42:25 And the clinical landscape is changing and I think you probably noticed that, that patients are more involved in researching clinical trials and in their own care. A lot of wearables I've got on my [inaudible 02:42:36]. Patients want to have a voice, more patients are speaking up. They need this information to be well informed patients and as you heard, the process of approval is changing so the endpoints are changing, they're being more patient-focused, patient-centered, more breakthrough designations and the precision medicine initiative has really changed the landscape of patient care. It's really come down to the personal patient rather than the big group of patients that are gonna do better. It's about individually, how well am I gonna do?

02:43:08 So what's the problem? Why are we still talking about this years later even though it's been in clinical trials for a long time? They've been around since the '70s. The health-related quality of life came in about the '90s. Short forms, there's tons and tons developed. And also for specific side effects, there was just a lot of different forms out there. So why is it still a challenge? Why are we still doing this? We tend to do the one-size-fits-all approach and that usually doesn't work.

02:43:43 And now that we've got new therapies, not just chemotherapies, which are poison and have certain side effects that we all know about, but the targeted therapies kind of pushed it into another realm and now immunotherapies are pushing us into another realm. And now we're talking about not only combination therapies of different drugs but also different modalities of the radiation therapy and the chemotherapy.

02:44:04 So one size will not fit all. Although health-related focus questionnaires are focused on health-related quality of life, they're still very, very broad. New short forms are added on top of each other and so you get a lot of redundancy and a lot of forms to fill out. I think I filled out like 10 pages of forms during my trial, and the measurement on the... The items are not necessarily related to what the patient is going through.

02:44:32 If I'm going through something I really don't want to be asked a spiritual question or you know, if I'm going through a chemotherapy treatment, like for the breast cancer fact sheet, if I'm going through chemotherapy, that's very different than a surgery outcome where cosmesis is really important. And so asking me about how I feel about my breast as I'm vomiting in the toilet is really not appropriate.

02:44:54 So really, asking that question that is direct to the patient experience is important. And it's not a primary objective a lot of times. A lot of times, it's not even a secondary objective. And the analysis is important, and that's where I think I'm going to at the end of the talk because I think that's where we're really missing the boat on what we're gonna tell patients in the analysis part. And it's done at a different time than the primary analysis.

02:45:19 And it's not getting back to the patient, so how are we gonna get this information back to the patient so they can use it in their decision-making? So there's lots of, lots of, lots of challenges. So I actually did a questionnaire at Paul's suggestion and asked patients, you know, what do you think the barriers are to participating in... not only participating in clinical trials, filling out the questionnaires, so I hear this all the time. "There's too much missing data. There's too much missing data. Patients won't fill out the forms."

02:45:49 Well, when you have 10 pages of forms, I can tell you, I missed a page once. A whole page because they're very complicated and you get tired of filling them out. So what are the barriers? Redundancy. So when you add those forms together, you get the same question several times. I would actually look back and see what I answered before and answered again the same because I noticed that I had been asked that before.

02:46:13 Complexity. A lot of the forms are complex. They're getting better. They're better than the ones I filled out in 2006. The ones today are much better, but still, how you ask the question and just changing one word can make a big difference in a patient. And that you want the right answer. And so, you know, kind of passing this over patients, just regular people and seeing how they interpret it is really important.

02:46:44 Time. The time it takes to fill it out. So the shorter amount of time is better. Too many questions and too long becomes very burdensome to the patient and they feel very rushed. A lot of times, which is not the best time to give questionnaires to patients, as far as my survey was concerned, but most patients get it during the clinic visit. They would prefer before and after.

02:47:05 Now with our options of electronics, we really should consider that. Because having it in the clinic when you're really nervous about the appointment and things like that, you're not gonna feel very good filling it out.

02:47:18 What do they think will help? Is, you know, if what you're asking is really important to them, they will be happy to tell you the answer. So making it relevant to their experience. No... Let the patients know why you're asking the question and that it's really important to answer

and giving them feedback on it too and let them know how you're using the information. If they know that it's really important... Because I can tell you as a patient, I get every CT scan that's ordered, I get every test like that that's ordered, but if you just haphazardly give them a survey or send them a survey and don't tell them that this is as important as that CT scan, they're gonna treat it as unimportant as it seems when you give it to them like that.

02:48:03 So really make sure that they know that it's important. And length of time matters, so if you ask a lot of questions, you can't ask them very often, you ask a short number like the Jakafi study, you can as them more often. So what's needed? Usually we just put them in phase threes, but I think they need to be pushed forward in phase ones. And I think with a lot of the information that I heard this morning that was relatively new is that going into phase ones with not a lot of pre-clinical on the combination might be important to collect this data in an early stage trial so you can really get an idea of the toxicity, especially for the off topic..

02:48:39 The, yeah, effects, but I think that that's important to do in phase ones, which a lot of people push back on, but I still think it' really important. It needs to be analyzed along with the regular data that's published in a reputable journal and the information needs to be shared with the public and patients. And instead of instrument validation like we have now where you have to add the whole forms together, we need the item validation, which is the PRO CTCAE where you can pick out different items.

02:49:16 And so the combinations are not specific and get away from the global health-related quality of life and go more towards the targeted measurements. So I think that's where we need to go and I think that we're kind of heading there. I think Paul is kind of leading the charge in a lot of ways, but how do you effectively do it? You actually collect PROs early and I think if you collect them early in your phase one and two, you can inform what you really wanna ask in your phase three?

02:49:47 Right now, we wait 'til the phase three and we throw everything in there and ask everything and it's not a very smart way to do it, so I think doing it early is better. Targeted precision PROs for all trials. Ask patients to report what matters to them, that it is acceptable to the patient to complete. Really think about the patient as you're making these PRO assessments and putting them together and that the endpoint is meaningful to the patient, just like the efficacy endpoint, the PRO endpoint needs to be meaningful as well.

02:50:19 So, you know, patient-informed PROs, asking the right question at the right time in the right way. What do we do with the PRO data? So this is where I think a lot of work needs to go in. I think there's a lot of good work going on out there and I'm really encouraged by what's going on. The toxicity over time... Right now we just do percentages and averages, individual items, but can we do things by patient level? And when the analysis is conducted, we need to do it when the primary analysis is done. And who sees the data?

02:50:54 Clinicians read journals and they need to see it in journals that they actually read and then patients, how can we get the information back to patients? How can we get the information to clinicians and patients?

02:51:08 So clinicians, we need to publish with the primary objective. That would be the best thing to do because they all read that article when the primary objective comes out, or publish it at least with the secondary objectives, but publish in a well-read journal that clinicians read.

02:51:25 And patients, you know, I think identify what they want to hear about. Present it in a way that they can understand and dissemination. So is it in the drug sheet? Is it in the cancer center materials? Do you go through non-profits and go through them and get the information out? So I think it needs to be intentional and there needs to be a plan for dissemination. It just doesn't happen just because it's done, so I think we really need to think about that as patients and people that work with patients. I kind of started making a list of what would I wanna know if a trial was done and there were PROs in it, what would I wanna know about? And really, it's about how you feel and function and how it affects your normal life. Can I still work during treatment? Can I still do the things I normally do? Does everyone experience this side effect, any side effect? Is there a chance I'll experience any, or is there a chance I'll experience none, or all of them?

02:52:26 We don't really know and what's the most severe side effect? What's the most burdensome side effect? How do other patients handle this side effect? You know, it's not only having this side effect, but how can you manage it treat it? How long did they last? Did they... Was it a short-term side effect? A lot of chemotherapy drugs, it's very short-term side effect and then it wanes and then you get hit again, but some of these other drugs have long-term side-effects and we really need to know that as patients, especially in our management of the side-effects and whether there is available medications to treat them.

02:52:59 And as we move into immuno-oncology, I think we're moving into a different realm where we have to talk to other people that actually deal with auto-immune diseases and say how do you manage these side-effects? Because they're a little bit different. And so now I'm gonna go into my pet peeve about the problem with the current analysis.

02:53:18 One of the things that I like to talk about is the problem of averaging... What you measure actually matters, and can we get away with grouping everything together and kind of look at patient-level data? We do that with other things, with the benefit. Can we do that with PROs?

02:53:36 So the problem with averaging. So I kind of modified this from Patty Gantz who gave a talk for Komen and gave a talk for NCI and I love this slide because it's about the global quality of life scale and I think I've been asked, like, "Well, would you feel better if it was a three versus a 3.5? Is that significant enough of a difference?" And I'm like, "I have no idea what you're talking about as a patient."

02:53:59 Because the global score kind of averages together, so if you look at this, they're both threes. Both patients have a three, but they're both experiencing something very different 'cause these are very different scores, social function and functional status and disease symptom, but they're experiencing very different... even though their global score is the same. So averaging is really something that I'm not a fan of.

02:54:25 And what's being measured matters. If you take this one hypothetical... This was published as a hypothetical example. So if you do time to deterioration, treatment B is the best. If you group all the means over time, just do that averaging thing, then they're both identical because you can average them and they're identical. If you pick a set time point, then the other one wins. A wins.

02:54:52 It does matter what you measure, but in doing this, we really lose a lot of the data because we collect all this data and then we just pick one point and we lose all of this information so

can we use the information better? Because I think that this is one reason why health-related quality of life has a hard time being accepted because of some of these problems that we have in the analysis.

02:55:13 When you start looking for these things, you start to find these things. Can we look at adverse events by patient? And that's what the toxicity over time... There was a publication out about that, and they actually looked at all the individual patients and kind of grouped them, 'cause I'm thinking, can we really look at the patient and say, do patients that have... 20 percent of patients have diarrhea, 25 percent have vomiting, do they over lap? Are they the same patient or are they complete different patients? You really never know because you just get a percentage of patients.

02:55:47 This kind of tells you, this is just looking at diarrhea over time and all the different patients in the two different groups and you can see really different... really big differences, and I think this is where we need to go with looking at the data. Look at it as big data. Look at it as lot of data that you can look at.

02:56:03 And I know that Bill Wood at UNC really wants to look at these side-effects and how they interact with physical function. Can you kind of do some interaction analysis type of thing if you look at all the data? So I think that, you know, things are changing and I think that's really good.

02:56:19 I don't know how we're gonna present this back to patients. If you have any good ideas, let me know. But I think that that's the next area that's gonna be really important. But I think that this is really looking at patient-level data. And so, considerations of combination therapies to go along with this session, it's been really interesting is you know, is... One of the things I think about when you do the multi-modality is that radiation and chemo are given in different places and different times so, you know, kind of that coordination of care thing needs to come in from the patient side of things.

02:56:56 New drugs used in combination, you know, immuno-therapies give really unknown side-effects and so management is really important of those side-effects. And that's becoming a really hot topic in consideration. I think it's well worth it in many cases to do that, though, because it has really extended the life of so many patients.

02:57:15 The abscopal effect, not knowing what to measure... So you have the added benefit of that effect, but you also have the added harms of that effect. So we really need to know what to measure in that way too, so from a patient perspective. I think the benefit is great but I also think we need to know what that harm is so we can make sure that we're giving the right patient the right time.

02:57:37 As I said earlier, collection of PROs early, especially considering logistics of two disciplines targeted of all trials, find out what matters, the more complex the treatment regimen, the more the patient needs to say what they feel, so I would ask patients what they feel. More acceptable to complete, ask the patients. Important part of the trial, make sure it's deemed as important and let them know why it's important to them, why you need to know that information.

02:58:11 So with rigor, include patients as stakeholders. I know a lot of pharmaceutical companies do that. I know the FDA is doing that. I know a lot... The NCTN groups do that and I think that's

really important. I think that one size does not fit all and so what the treatment is matters, what the disease is matters, the stage of disease, early stage versus late stage is very different, so you really need to be intentional in what you measure and what the endpoint is and what measurements are needed and how often they can be collected and how they will be analyzed. You need to think about that up front.

02:58:47 I think that the potential benefit of gains is less missing data. I get up at meetings and say, "Well, if you ask the right question, don't ask a lot of questions, I think you'll get the data that you need. I think they're more likely to fill it out. We should try that." Relevant information that is important for decision-making, that's the most important thing, and really it will be value added, especially with all these new agents that are the same type of drug category but have different side-effects. I think that's just an added benefit for everyone involved.

02:59:21 Thank you.

Liu: 02:59:21 That's great. Thank you, Patty. Questions? Uh, Tim.

Illidge: 02:59:33 Thank you. Thank you for a very helpful talk. I wanted to ask you the patient's perspective about the balance of the common side-effects, and you talked a little bit about the incidence of those side-effects, like diarrhea, nausea, and then the very severe side-effects that are maybe exceedingly rare, but they may be very important if they happen.

02:59:59 And I was quite struck having spent some time in the U.S. on how different that is, the balance of what is presented in somewhere like the U.K., so I exaggerate to make my point, but in the U.S., there's a very, very long list that would take an awful long time, and it seemed to me at times overwhelming to a more modest list where you might actually focus on the common things that might happen. My question is how do we get that balance? What do patients really want to know? Does that change over time?

Spears: 03:00:33 Yeah, I think that does change over time and patients want to know but I think it's... We inform our patients very differently I think whether it's in a clinical trial where we do that massive, long, exhaustive list of everything possibly that could happen in the different categories, versus in clinical care. And I think the thing is in clinical trials, we have a certain way of doing it, and once you get that information, how do we take that information and bring it to clinical care so that in clinical care, patients can make that decision?

03:01:02 And in clinical care, it's done all different ways. Some patients are given a lot of information and other patients are not given much information, or maybe a one-pager that either came from the company or was made by the institution and that's where I think this would go, like for informing patients. And the severe side-effects that cause death are definitely important to know and what percentage they are. And then other side-effects... And one of the things that I worked on... I did focus groups and interviews with [inaudible 03:01:34] about early-phase side-effects with breast cancer and they actually found that one of the side-effects that they added to a PRO was the bad taste in your mouth side effect from all these drugs that was never really mentioned, but it was a high burden for patients and things like that.

03:01:56 So sometimes things seem like they're not important for a physician to tell a patient, but if you ask the patient, that's what they wanted to know about, that type of thing. I think that's different.I don't know how they do it in Europe or the U.K., but...

Illidge: 03:02:12 So what's your advice on the best way to do this? 'Cause it can be a very, very long conversation that can evolve over a number of times, so I guess my question is, is it more important as a patient in that first initial conversation to know most about the common side-effects that may happen or do you want to know at that point the potentially rare, but potentially serious problems?

Spears: 03:02:39 I think you need to know both.

Illidge: 03:02:40 Okay.

Spears: 03:02:41 Yeah, I do, 'cause the rare ones... It might be rare, but if it... I actually was one of the lucky ones that had the anaphylactic reaction to Taxol, but I had been informed that that might happen, so I knew what to do sitting in the chair, you roll the little ball thing down and stop the infusion, so if I had not been told that that might be a reaction, I would've been really confused as the elephant was sitting on my chest.

03:03:06 But, you know, I think that you really need to know about those so that you can do something about it and call the doctor at the time, versus... But the common ones, definitely you need to know.

Speaker 12: 03:03:18 Can I ask you a question, Patty? You talked about informing the patient with these PROs, so you're talking about like, during the clinical trial or after the... So what were you referring to exactly?

Spears: 03:03:30 [crosstalk 03:03:31] After you collect them in clinical care.

Speaker 12: 03:03:33 And then giving them back for the entire population and also patient-specific? But that sort of, heat map you showed was extremely confusing, I guess as what you're reaching out for.

Spears: 03:03:43 Right, that wouldn't be a patient-facing thing. It's just a different way to look at the data that might, if you look at that data and then you can tell how many patients had a lot of side-effects versus none. There were patients in there that didn't have any diarrhea, right? And it was a trajectory over time type of thing, so I don't know how you would extract that and give it back to patients. I haven't seen anything that I think is appropriate yet, but I think that's an area where people are working on it.

03:04:13 But I think, you know, in clinical trials, you really don't have a choice. You're given what you're given on that arm, but in clinical care, I work a lot with patients that have to make all these really tough decisions and I'm not sure if they have all of the information that they need.

Speaker 13: 03:04:29 This was an excellent talk.

Liu: 03:04:30 [crosstalk 03:04:31] Last question.

Speaker 13: 03:04:30 Just as a sidelight, we put out a request for applications for grants for small businesses to set up patient report outcome apps and it was extremely well-received. And so the community's gonna have access to technology and companies are actively doing this so that patients can not only give us data when we want it, but they can give us data when we didn't know that there was data to have.

03:04:56 So it should increase granularity. But this should be a relatively free or low-cost thing for the community and enhance your ability to ask questions.

Spears: 03:05:05 Yeah, and I think in the clinical care realm, a lot of those apps are becoming really more common because you can do them in many different formats, so... And you need to be able to do them in different formats so different patients... Some are comfortable with paper, some are comfortable with the phone. I tested something for Ethan and I did it paper, I did it on the computer, and then they have a phone-in thing, and they would call you. Oh my god.

03:05:29 I was like, "Don't call me ever again." 'Cause I'm never ready. Text me with a link... I was like, "Don't call me." It freaked me out, but anyhow, that was me and I preferred the computer, which I told them. But, you know, I think that you need it every way and you need to test it on real-life people and what they feel, so...

Liu: 03:05:48 That's great. Thank you so much, Patty.

Spears: 03:05:54 Thank you.

Liu: 03:05:55 So our last, but not least speaker of the session is Adam Dicker. This segues very nicely where he's gonna tell us all about wearables, although your title's a little different.

Dicker: 03:06:08 Yeah, I changed the title. I felt it was a little pretentious, what I initially proposed, so thank you. And thank you for the organizers to allow me to share this.

03:06:22 These are my disclosures. I'm gonna talk about a couple technologies. I have no financial gain or relationship with the companies other than... I know, I know.

03:06:36 But we'll change that by the time we do this again, so I just wanna acknowledge a couple people. Heather [inaudible 03:06:43] who's a health science research outcome behavioral psychologist at Moffett, is a close collaborator. And some other people on this slide have helped me and I've also received funding for some of the work I'm gonna talk about from the Prostate Cancer Foundation and NRG. This is a great publication that was put together during the Obama administration about connected health within cancer. Really, it has a superb amount of information that talks about rural versus urban, different types of self-identified disparities, all sorts of information. But there's no question that patients are, as you know, are using the internet more and more. Digital health, there are a lot of definitions. This happens to be from Naomi Fried, but it's really to use technology to deliver care and information to patients and providers. It's really an add-on to health science to health science research outcomes.

03:07:48 Oncology is actually a late-comer to this field. Other fields like cardiology have been way ahead of this, certainly telehealth and telemetry for NASA has been one of the first applications of it. And there are certain institutions that have done a lot of work in this area. Princess Margaret is one. M.D. Anderson has done a lot of work in this area, particularly in cancer.

03:08:10 And I had a trial that I was writing, an immunotherapy trial I was writing a grant for, and I was struck by so... Related to toxicity, most of toxicity does not occur at clinic. It occurs outside of clinic and we really don't know what goes on and I was really struck by, especially

with these idiosyncratic somewhat, immune-related events, and I just felt there had to be a better way.

03:08:41 And then as Patty and Paul have alluded to, and Tatiana, there are a lot of dynamics in the room, right? You know, when you wear a white coat... And I've... All of us are patients, right? So you don't necessarily... You know, there's a hierarchical issue about power. You kind of forget about, you know, there's this recall bias to the symptoms that happened most recently but not what happened last week, and I just felt that there had to be a better way.

03:09:13 This is from my colleague, Heather, who studied sleep, which is a huge question that we rarely ask patients about. This happens to be in patients being treated for gynecologic malignancies. The bottom... The top graph is showing from an actigraphy, this is an old model, how when you're not receiving chemotherapy, how your sleep is not being interrupted, and then when you're receiving chemotherapy, your sleep has significant interruptions.

03:09:44 But the technology has really improved quite significantly, particularly in the consumer realm. The FDA has been incredibly active in the past couple of years in this space. I refer this to you both for the wearable space, the software space. There are now software therapeutics, there are... This is a huge area and I encourage you to learn more about it.

03:10:10 There are now journals that didn't exist only a few years ago in this space. ASCO has a journal, Clinical Cancer Informatics, that I'm involved with, Eric Topol and Steve Steinhubl. [inaudible 03:10:24] Nature of Medicine, Journal of Medical Internet Research has an impact factor of around five. And Digital Biomarkers by Ray Dorsey and the University of Rochester, and there are others, right?

03:10:35 So I think this is a very fast-moving field that's touching all aspects of healthcare. I'm gonna ask four questions and I'm gonna show... The data I'm gonna show is relatively immature, so I don't have the benefit of showing the Jakafi data that Tatiana and Paul showed. I'm gonna talk about... How do you fill out PROs with new drugs? And I'm gonna show an example of Citizen Science that I just recently started.

03:11:04 I'm gonna ask the question, what's the opportunities for wearables and/or E-Pros? And I'll talk about trying to pick up on toxicity early and I'll show you what we're doing, but there... It's not meant... I'm not trying to review the literature, so this is totally biased to stuff that I'm touching.

03:11:21 I'm gonna talk about adherence vis a vis medication. So if you're developing a drug with radiation but that drug has its own toxicity issues, what can you do? And there's an excellent example that I was not involved with but I'm completely jealous about that I'll show from Percy Ivy and a group from Dana-Farber and GOG Energy Oncology. I'm gonna pass on that example vis a vis remote monitoring, and I'm gonna talk about how do we nurture and develop this space for the next generation?

03:11:55 Okay, so this is Bonnie Adero. I've never met her, but I've met her husband, and she started... She's a 12-year lung cancer survivor and

Dicker: 03:12:00 And she start ... she's a 12 year lung cancer survivor. And she formed a foundation developed by patients for patients to do research by patients. So they created a registry not

too long ago. Actually a little over a year ago. It now has 600 patients. It's an international registry. It asks a number of questions. So about a year and a half ago I approached them because the pro-CTCAE that Paul talked about was developed in the chemo-radiation era. It wasn't developed in an immunotherapy area and we don't know if those questions that it asks are relevant in this setting. So how do you develop the measures for an immunotherapy pro-CTCAE et cetera.

03:12:48 So I approached them with Heather to ask the question, could we use the registry and ask an immunotherapy question? So this just got launched. It's actually a very soft launch with them to ask patients who are receiving immunotherapy, this is a cross sectional survey. So anyone with lung cancer who speaks English or Spanish can log in. Patients, they sign up, there's a whole whatever, there's an informed consent sort of approach. We partnered with [ISLAC ? 03:13:25], we partnered with the American Lung Association, with [SITCE ? 03:13:29]. So it just recently launched. It asks a number of questions, again, in across sectional survey. It's relatively international, although, it's kind of North American-centric. And in the lung cancer registry, it tracks a lot of patients without "targeted therapy." In immunotherapy, we have about 80, now probably about 100 patients who've answered. We've submitted an abstract to ESCO that kind of talks about the patient characteristics. But we think this is going to be very valuable for trials, for observational studies, for measure development tools. We can do this then to drill down. There's been a lot of work from Hopkins and other places about arthritis-like symptoms and other symptoms for immunotherapy so we can drill down for that. This is going to be available to researchers, so we think it's a way to start and it's a way to empower patients to participate in this type of science that Patty talked about. So more to come.

03:14:34 So how do we try to predict for our talks? So I'm going to show an example in lung cancer just because we have a couple problems in the field. One is the radiation pneumonitis. The other is the patients with metastatic cancer, kind of how do you remotely monitor them? So the thought was that we could use some E-pro, whatever it might be and some mobile health platform.

03:14:59 So a while back, because I'm interested in this field, I picked up on this pediatric device. So this is a wearable. It's meant for kids with asthma that can count coughs and respiration, and wheezes, and heart rate, and temperature, activity, and a variety of other things. And has a lot of different features. I approached the company. I said, "we'd like to study it with you but in a cancer population." And for them this was gravy because it extends their market. So it's not just having a wearable, it's having an app, it's having a web portal, it's being able to ... you have to have the whole platform, so to speak in order to do this.

03:15:43 There are a lot of benefits to a wearable, Patty talked about some of them. But you can monitor stuff and you really know in real time what's going on with your patient. The pediatric asthma field happens to be very active in the digital space because this is a very serious problem for kids. The app is really about ... it's easier to journal. In the olden days when we asked about pill diaries for patients, everyone knows both in the industry and at the FDA that pill diaries are not the most valuable source of information in terms of adherence and compliance. So we think the app is better.

03:16:25 So this is a pilot study for patients with lung cancer. We're combining this with a variety of e-pros because we don't know what the right e-pros are. And maybe this is too much, but again, as Paul mentioned from an inventory, we're trying to figure out what works and what

doesn't work. We're trying to fail fast in a software development standpoint to know what to bring to a larger trial.

03:16:55 This is Nitton Ari and Nitton is ... I'm going to shift gears to chemo-radiation across solid tumors. Nitton is a former trainee. I think he's the first trainee to give an asco plenary talk when he was a trainee. And he's been studying wearables. He's at Albert Einstein Montefiore right now. I think there's significant opportunities for wearables. Someone mentioned the geriatric oncology space, trying to understand who is fit, so to speak, from a performance status, there are more accurate ways to do that. So he published a paper in the Red Journals that looked at continuous monitoring for patients getting chemo-radiation. I think it's a really novel paper and I just want to highlight a couple features.

03:17:42 So this is a patient population in the Bronx who are getting chemo-radiation for lung cancer, head and neck cancer, any GI tumors, et cetera. And what really showed up, and they're using the Garmin Vivofit 3 at the time. It doesn't need to be recharged, battery life is a year. Does not detect heart rate, but your step count on the weekend was the greatest predictor for hospitalization in this patient population. Nitton developed an activity score to predict hospitalization. And if you ask the question, so is this better than ECOG performance status? The answer is yes. And if you ask regarding a PRO questionnaire, the ORTCQLCC30, turns out the wearable trumps that.

03:18:35 So I think this is early data, it's a limited number of patients but it's quite provocative. We took this to then go the next step. So this is Noelle Williams, she is a senior trainee of ours finishing, she'll be at Levine Cancer center come July. And she developed a trial that really asked the question, using Nitton's data and what he has come out with, with e-pros and can we try to do better. So she developed a trial that actually she presented and took to the ASCO Vail course and she got the Dan Van Hoff award for this for its novelty.

03:19:19 So this is a trial that we're looking to implement at our health care system. Again, standard of care for patients getting chemo radiation where against activity tracker and weakly e-PRO's for triggers for intervention. So again, so we have the right e-PRO's? I don't know, but we're going to learn something. We're going to learn about how do patients related to these types of devices? Does it interfere? Do they take them off? We're new in this space and we don't know how well or how poorly this is going to work out but this is our way to try to build on the prior work.

03:19:57 I'm going to talk about drug toxicity. What do you do if you have a drug that is relatively toxic or challenging and you want to develop it with radiation because the potential is so great. So the example I'm going to show is an example with a drug [sedaranid? 03:44:03], the veg FR2 inhibitor that Tim talked about earlier and [elapronid? 03:20:23] the parp inhibitor. So sedaranid, the toxicity is hyper tension and there's some data that in the prior trials with that drug that some centers had better survival rates than others in terms of being able to handle the toxicity of the drug. Elapronid the most common toxicity is diarrhea. So when you put them together ... and this happens to be a trial in recurrent ovarian Fallopian cancers. There happened to be this incredible response rate from Dana Farber that was then taken the GOG energy oncology of like 60, 80% in women with recurrent disease. But these drugs are not trivial to combine together.

03:21:13 So Valentus is a French company and with support form AZ they developed an app, which is both patient facing as well as provider facing and both the site and centrally that

information is updated simultaneously. So there's secure access for patient, there's a blue tooth enabled blood pressure cuff that takes the measurements. Patients are asked some simple questions about do they have any other symptoms that might be relate to hypertension. Similar questions are asked about diarrhea. And then, what's interesting about the app, is the app then tells the patient what should you do for this constellation of symptoms. Whereas, most of us in the room, the way we operate, so we get a phone call or a text or an email from a patient and we're playing ... we react to what the patient is telling us and we're always one step kind of behind the situation. Here, the app in this particular select setting is really ... has the algorithm already plugged in. And this was provider developed. Then if things escalate, there's a way to get the real time help.

03:22:31 So I thought that was pretty novel and I think this is going to get published in JCO Clinical Cancer informatics. I think it's the way of the future for a lot of the stuff that we do because we don't have enough resources in oncology worldwide to be able to help patients.

03:22:48 So how do we promote and kind of build the pipeline? So this is my view of the digital health landscape. There's a lot in there, but when you look at the scholarship in this, it's quite small. There's a lot of activity, there's a lot of money. There's not a lot of data, or the data is in the different type of data, not the type of data that necessarily this crowd would appreciate more data. So we think the problem is that there are silos and there are silos within silos. There's a design silo, a technology silo, a healthcare silo, and our goal is to create a cross trained type of individual.

03:23:28 So we're looking to create a new approach that is kind of tech centric. There's also a significant informatics piece to it to create degrees that didn't exist before. We appreciate that there are health care learners and there are design learners and tech learners. And when I talk to the tech folks, they really have no idea about what a clinical trial is, and when I talk to the people in health care space, they don't appreciate what the technology can do. So I think there's a role for cross pollination.

03:23:59 I teach a class now in our medical school. I got now 16 students, just got another the other day. And each one of these has a project in digital health, it's not all in oncology unfortunately, but I think these are the future in terms of being comfortable with these types of tools, asking questions about how's it work, vis a vis, the workflow. How's it relate to Epic and other practical issues that confront us. I should mention that in NRG we have a digital health working group that fairly nascent within the NCTN. Nothing like a grant to get the juices flowing. So when the grant ... so Monica Bertinolli had a meeting in September and we appreciated that there were a number of us in the room from the various NCTN groups who were working in this space. But everyone kind of was looking through a different lens in terms of what they were working on. And this became a part of all of our grants for the grant renewal and it's now lead to a number of things and mini symposium where we're trying to find best practices and how do we not reinvent the wheel and chair.

03:25:19 So I think this is a slide that Percy Ivy gave me so all of us in the room are into this in terms of selection of patients and the various different types of [inaudible 03:25:31] mix to enrich our populations as Jeff mentioned earlier. I think what we're trying to figure out an integrate is that those client histograms, no one's really integrated this stuff so well, and really relate it to what Paul said. This is just another type of layer of information. So the PRO layer, the functional layer passively collected through a wearable or other types of information

combined with a translational imaging, gives us a real complete picture of the patient. So thank you.

Liu: 03:26:09 Mic one.

Speaker 14: 03:26:09 Sure, very interesting talk. I know that in pathology they've had kind of a bio informatics focus and there's almost fellowships or at least opportunities for the residents to develop kind of on a dual tech track and on the medicine side. How much buy in have you had, or at least noticed among other radiation oncology programs? You'd think with the number of engineers and people that come from more of a technology background for our field, that this actually probably could catch on fairly well.

Dicker: 03:26:45 Yeah, so a number of programs, UCSD in Toronto are very interest in radiomics. Also, Fillip Lamblin has a very strong program in that. So I think there's ... you touch on a variety of things. There's kind of a radiomics approach. Fascinating. I have a resident who spent his year doing that and helping his career. There's a data science aspect in informatics, which I think our field needs to address. Kent Mow and I, with the support of Astro have a paper that's being submitted to the Red Journal. Anyone that reviews it, be nice. And what we did was we queried chairs and people in training et cerea about ... not only about informatics, it was about immunology because obviously these are [inaudible 03:27:39] in our field.

Dicker: 03:27:41 So, you know. Some people have drank the kool aid and some people haven't. I'm a drinker.

Liu: 03:27:47 Great, thank you Adam.

Illidge: 03:27:53 Thanks a lot for-

Dicker: 03:27:54 Let me ... let me make this clear.

Illidge: 03:27:57 There's a group later to see you.

Dicker: 03:28:02 I don't even drink koolaid. I don't drink any soda. I'm vegetarian. Okay.

Illidge: 03:28:09 Thanks for a very stimulating talk. One of your slides, the very busy one with essentially the number of different areas in digital health. On that slide you had quite a large circle on social media without actually sort of covering it during the talk as to how any of this might link to social media. So, that's the first question. How might you link it? And potential problems associated with that.

03:28:33 The second question is, is there any evidence that you've come across where actually the adverse vents associated with drugs are reported on social media to a higher level than you might get actually in the PRO's.

Dicker: 03:28:48 Yeah, so I'll try to address both. So I think it's huge and it's totally untapped. So a lot of people are into Twitter Sentiment. There's a whole ... you can go on the Symplur, S-Y-M-P-L-U-R, there's some very powerful tools that allow you to kind of look at various things that relate to cancer, immunology, some other stuff like that. We have a project in that space about how can you use social media to pick up on stuff much earlier. I think it's incredibly important. SWAG has done an incredible job for social media to push out information, not

only ... well certainly to patients but also to investigators. It's an international organization. I think the answer is yes.

03:29:43 And then, as you know, there are some really fascinating papers by the group at Microsoft doing Bing searches and picking up on lung cancer before ... they went retrospectively and they could pick up on pancreas cancer and lung cancer before patients even developed overt symptoms because there are very subtle ways about key stroke patterns and other stuff like that that can pick up on disease. The former head of the National Institute of M<ental Health, if you analyze messaging, you can pick up on sentiment of patients and pick up on depression. There's a lot of different types of opportunities for this.

03:30:24 So I didn't ... this wasn't meant to be a comprehensive review and I just meant to kind of be someone titillating for the crowd and to connect with Paul and Patty, to build on what they were talking about.

Illidge: 03:30:36 But you think it's important?

Dicker: 03:30:37 I think it's huge, but it's a different type of skillset you need to be able to take from the Twitter fire hose to be able to analyze that. People have done it for HPV vaccination perception. There's a lot of things you can do with it.

Illidge: 03:30:53 And this issue about adverse events?

Dicker: 03:30:56 Yeah, so maybe someone from the FDA would like to talk about this because they're on top of this.

Speaker 15: 03:31:04 So I think there's a lot of interest in social media and mining that data. I think the issue is denominator for one thing. It's sort of a select population that's interested to get on that, and they may be more interested in reporting things, and so then suddenly you have this sort of selection bias issue. So if I was to guess, I would say clinical trials report less than PROs, which report less than social media if I was to guess. But I haven't seen the data on looking at those in a comparative way. So I think veracity is going to be the challenge in the social media space. Certainly interesting for hypothesis generation. I think it has a lot for patient engagement reasons. I think it's really nice to be able to reach out to patients in a very facile way and get some information about what's important, and are we missing important aspects to measure. But for making decisions or creating maybe associations but not causal.

Dicker: 03:31:58 Yeah, I mean, there are some companies like Patients Like Me. And they're very open to patients that they sell their data de-identified to pharma. Pharma's constantly monitoring the social media channels about their drugs because it's another way to pick up on real world generated data.

Sharma: 03:32:21 Thank you so much Adam. So [inaudible 03:32:27]. If I could ask the panel to speak as ... plus Zelanna Goldberg Pfizer, to come up onto the stage please, we'll get some kool aid delivered if it's cool enough.

Liu: 03:32:40 So I'm sorry I have to apologize. The traffic is getting worse to get to the airport and so I have to [inaudible 03:32:45] chair this panel somewhat [inaudible 03:32:52].

Sharma: 03:32:52 Okay, so before we start, I just wanted to ask the panelists, a lot of this lends itself very well to big data, which is obviously a very topical subject at the moment. Do you think we should be collecting the data in a certain way to allow it to be used in that context?

Speaker 16: 03:33:13 Yes, I mean, the analogy is when a surgical specimen goes to pathology and they take on e little thing and throw out everything else. I was on a grant with Nat Ellis from Baylor, a genome proteomics grant. In those days, when they were prepping for DNA, they threw out all this stuff that contained [inaudible 03:33:46] and proteins and stuff like that. So I think we're not ... we're tapping only about 1% of the potential information. And we don't know what we don't know, so we don't ... but that's okay, but I think now the machine learning algorithms are ... on e line of code represents 10,000 lines of code now. If you look at what Google has done in the tenser platform for machine learning.

03:34:19 So I think things are going to get better. The radiomics field is getting so much better now. So I think it's going to be applies to free text and data mining the EMR and other types of things.

Sharma: 03:34:33 Okay, so microphone two is very popular this afternoon.

Speaker 17: 03:34:38 So this question is for Paul and the other panels, but how do you advise us to address drop outs for patient reported outcomes and the biases associated with that because the sicker patient then did not report. You know, sometimes they don't fill out the forms. And the second thing is that, I'm pretty simplistic. When I design a trial, survival of one single endpoint, you develop a hazard ratio. Now you look at all these panels of patient reported outcomes, the big data, how do you design a trial using this type of data?

Speaker 18: 03:35:14 So the easy one first is probably missing data for patient reported outcomes. I think for one thing, I think it's helpful, as Patty says to make sure that the sites and the patients are aware of how important the information is that they're collecting. Because remember, there may be other surveys these patients are getting, even from the health care facility that they're being treated in. Clinicians are getting beat down on having to enter a lot of things in now. Now patients are starting to get a lot of questionnaires ask about quality and this and that in their hospital. So we have to be very ... I'm really trying to make things narrow. But I do think the the site education and the patient education about why it's important is also critical. And I think some kind of monitoring during the clinical trial is really important. In other words, you need to not monitor what the PRO responses are but monitor that they're being completed. And if you see a site that's way low you've got to jump on it. It's not dissimilar to other monitoring techniques that you can use.

Dicker: 03:36:08 Just before Paul answers the second piece, one of the things that's been nice, and Jonathan will talk about this tomorrow, is the NCI has a certain number of licenses with metadata to develop e-PROs with some of the ECTN trials. I've been helping Jonathan with one of the immunotherapy trials, heather and I. So the hypothesis is that if it's on their phone that you'll get a higher collection rate. So I think that's the way to go. Didn't mean to interrupt your second question that you're going to answer.

Speaker 19: 03:36:43 And I'll weigh in on that as well before you go to the second question. But I think things are changing and I think with the e-PR it's changing everything. You can send reminders. I'm on another project where we talked to a company that had like a 95% compliance for their

PROs because it was a really nice app, patients like it, it was easy to use and it wasn't burdensome and the questions mattered.

Kluetz: 03:37:15 So just really quick, there's a difference between missing data and compliance rate. That's something that people really need to understand. We will get drop off in a normal metastatic trial. You're going to lose half of your patients by six months. So if you're doing a time to deterioration type vent point, you're going to have 50% of the patients not reporting anymore unless you report after they stopped the trial, and that is very hard to do. So remember compliance is just data quality, you got a PRO and you answered the questions and we want to know that that's high. And that is pretty high. As we look through our data, we see 95 ... like the high 90s and that. So they're two different things.

03:37:56 As far as analysis of the data, it all depends on again, the study objective. You can do 30 questions and make on of the questions the end point and create an endpoint definition like we do anything else. In Jakafi's situation it was a 50% reduction in the total symptom score at week 24 or some cross sectional week. So it's very simple to make those end points.

03:38:21 When you look at the totality of the pero data, what we're trying to do right now is we're looking at the acute and sub-acute patient experience. We're going to do descriptive analysis like we do for safety within the first six months or so where you have the most data because if you go out three years, you're going to have five patients on each arm or depending on the trial. So that's how we're doing it.

Goldberg: 03:38:41 So let me ask you a question about that. A couple questions actually. The first is, we were challenges to use the PRO tools earlier in the clinical trial paradigm. Are they in fact valid in single arm phase one or phase two trials?

Kluetz: 03:38:58 Yeah. So the word "valid" is what people think it is. I think that's a very difficult-

Goldberg: 03:39:07 [crosstalk 03:39:07] what we wanted to hear.

Kluetz: 03:39:07 It's a very challenging word, like, "This tool is valid." If you read any patient reported outcome manuscript is says, "We used the validated blah, blah, blah." But I think most of the time in phase one you are going to be looking at it as an exploratory measure. And as I said, at the well defined single symptom level, I think probably most of the study objective you're looking at in an early phase is safety is trying to get a tolerability read. So yeah, I think you can definitely make something out of a categorical change in a question of how much nausea you're having. And that's in fact PROCDCA is suggesting that that's one of the big values of their product is that early. And then if you wanted to an end point like symptom improvement, you can still do an intra patient as their own control to say what was the change in symptoms, what percentage of patients as a responder had an improvement in symptoms to help power your other trial.

Goldberg: 03:39:56 Okay, the second part is, you discussed the patient journey and looking at it over a period of time. What, just being really, kind of blunt, what is the value to a company trying to get a drug approved to expose themselves to the potential of showing a much more ... a much worse, frankly, side effect profile when they don't need to do that to get it approved?

Kluetz: 03:40:31 Right. Yeah, I get that you're blunt. But actually, what I would say is that ... because I struggle with this. I'm very pragmatic. I'm like, what is the potential benefit for a company?

What we've actually seen is that with CTCA, with standard safety, there is no baseline. And so, if you look at a phase one clinical trial result or a single arm of [inaudible 03:40:56] approval, you see a super high frequency of fatigue, super high frequency of all these sort of symptomatic things that could be disease, could be treatment but we don't know. And in the setting of the single arm trial with no comparator, we just have to assume that it's at least possibly due to drug. So there's an attribution potential benefit.

03:41:12 This idea of taking baseline into consideration and saying, "Well, if you have grade II fatigue at baseline and it never goes above grade II, we're not counting that as a drug related adverse event." So you could see some of your symptomatic toxicities go down, that's one benefit. The other benefit would be potentially predicting better oses in earlier stage. But again, it's not a requirement, but it is what patients are asking for to do a better job. Oh, and I should say it's already being done. That's the other thing. If you look at any health related quality of life tool, they will symptomatic toxicities in. Just random ones that may or may not be relevant. They're the most common, but potentially not relevant to your drug that you're ...

Golderberg: 03:41:55 Well, and I ask the question actually from a very positive and support place because we are struggling to use these and we are very keen on using them. And particularly in implementing the PROCTCAE tool, but it's ... there is a very real risk that we're trying to work on how to address that it will not provide a benefit to ... and could harm the drug getting to market. And there are some legal issues, frankly, in terms of patients reporting these symptoms at home and then not reporting them to the physician.

Kluetz: 03:42:33 Yeah, that's a good ... so we just wrote a paper and then we should get to the next question. But we did just write a paper. This is a real issue and we've listened to companies. And they said, "We have three major problems with PROCTCAE. Number one, who is monitoring it and are we at legal risk of not acting on a high grade symptomatic AE? Number two, if there's a discrepancy at the end of the trial between diarrhea from the patient and diarrhea from CTCAE, are we going to get a site inspection violation for poor clinical reporting?" That makes sense too. Then there's a third that I'll get to, but the issue is clinical cancer research, we set down OHRP, the IRBs, our inspection folks and most of the key FDA leaders in that space and wrote a paper, it's in clinical cancer research that I can send you guys that spells out that we think the data is different, we expect it to be different, it shouldn't affect inspections. Whether or not you monitor that is at your discretion, it's not required by the FDA. And in fact, we've been looking at patient reported outcomes that have been asking the same questions for 30 years and not telling patients about it. Provided you inform the patients about how you're going to do that, and what PROCTCAE does is, on their first screen they say, "Your health care provider will not receive any of this information. Pick the next question." So yeah, those are totally valid and understandable concerns, but I can send you that paper, because we addressed them.

Sharma: 03:43:52 So that was a useful discussion. Thank you. So let's move on to the next question.

Speaker 20: 03:43:56 I have question and comment. One is in regards to trial design. A lot of these trials, especially if there's dual end point like an efficacy and a PRO or toxicity ...

Kluetz: 03:44:00 Trials, especially if there's dual end points like an efficacy and a PRO or a toxicity end point. We stratify by variables, often for the efficacy end point, whether it's stage, or disease, age, etc. My concern is, there's data, even from U of M, let's say a man getting prostate

radiotherapy. It's actually mental illness is the number one predictor of GI/PRO decline, so we would never stratify or try to balance that. There is a concern, A, is that being built into these trials? Are they actually, how do you know these underlying factors to make sure that these are truly balanced, not just solely relying on the randomization process?

Sharma: 03:44:44 So, it's a trial design question.

Kluetz: 03:44:45 Yeah, I think that's a concern for small trials, for anything that you're doing, that you're not stratifying for it, that there could be an unbalanced prognostic factor that you don't know about but, unless the safety - let's say it's a safety end point. Let's say you want to have less diarrhea and you're actually going to power your trial to that. Then, you should do the work to figure out if there are issues with respect to that particular end point. I know that you can only have so many stratification variables. It depends on how important that PRO is to your drug development program and how much you want to utilize stratification factors for it.

03:45:25 In GBM, if you didn't stratify by MGMT status, people would have a big step back if you wanted to approve something. Same if you're going to use, if there's some big variable that I'm sure exists in these patients that I don't see any stratification, that's sort of a point. A second point is a, more of a comment, is one of the dangers, even though I think PROs are excellent, is the ice cap initiative, the metastases we talked about last time. Where it's biochemical recurrence is not a surrogate endpoint for survival, I'd bet if you did PROs, patients who have a biochemical recurrence, you're going to see a massive difference in patient reported whether it's anxiety, or whatever the metric may be. You could show a very large difference and I'm curious, from an FDA sort of perspective, is, we could run that trial, show a massive difference, but again, there's almost no correlation to survival.

03:46:14 So, one point is that an improvement in symptoms or function is benefit and you don't need to correlate it with survival. So, it's not a surrogate, it's not PSA. More importantly, yeah, there is variability in biases potentially associated. My impression so far, in looking at the data, is that the broader you get, as I've showed with that slide, the more that feed in you get on anxiety, emotional stuff pushing it. I've seen health-related quality of life improved with the main domain pushing the whole thing, emotional in a breast cancer trial, to your point. But I've also seen super effective drugs flat line on health-related quality of life because things are going all over the place and they average out. I think there's a risk of under-valuing and over-valuing with the super broad domains, which is why I favor symptoms and, sort of, more proximal functional measures because I think it's a good point.

Spears: 03:47:12 I have another thought on the ... So, I've gotten that comment before, if we do the per CTCAE it might come out worse, and, Oh no. But, I think patients want to know that information and I think that it's under-reported now with the CTCAE. Per CTCAE isn't going to replace CTCAE. That's still the standard; it will always be the standard and it's actually a different scale. To think that you're going to match is really not going to so I don't know why people think it's going to match. It will be different and I think it will be different in different categories, or different drugs, or different patient populations. I think it's important information to get, even though it's different. That should be OK. It's still important information to get.

Goldberg: 03:48:02 And, I would add to that, we totally agree. The issue came down to the question of having to have that data monitored and have that data shared with the site staff. That is where the skew, and it's where, sort of, all of the complications come in because there is a concern

around the legality, the risk. As much as we tell patients, " No one's looking at this. If you put something here, you still have to tell your doctor." There is a risk, of course, that people will not. Then, if there's a terrible outcome for this poor patient, what happens then? The lawyers always say, well, you have to show it to your treating physician and review it as if it were a patient diary. Then, you end up with these reporting questions and instead of having this separate, very valuable patient experience data set, you have a muddling of the physician assessment because it's being impacted by the patient assessment that otherwise because of recall bias and other white coat bias, I mean, other things that come into play don't otherwise show up in your safety data set.

03:49:15 It's very challenging. People are very eager to do this. It's a lot easier to do it outside of an approval, a trial for regulatory approval. A post-approval commitment study, because then the logistics are much simpler and we're able to generate the data for patients and patient advocates. It's important.

Sharma: 03:49:37 So, sticking with the topic of trial design, the question for the panel, we've heard about a lot of new measures, some of which we might not even have considered as endpoints before. That's been really enlightening. We've also heard about bespoke instruments that could be created to measure the clinical experience. How does an investigator go about getting, doing the para-calculations as a primary endpoint for some of these new measures? Do they have to do a pilot study in order to get some level, some background level? Or can they go straight in with an ambitious para-calculation for the sample size?

Kluetz: 03:50:20 Pick an endpoint example.

Sharma: 03:50:23 Well, say one of your, say the spleen example that we heard about. That was a nice example. If they did a bespoke questionnaire with six questions, how would they calculate what the background level is and the magnitude of the effect that they would be looking for?

Kluetz: 03:50:39 That gets back to the question of why on God's earth are we put a PRO in a phase one clinical trial. That they did because we've been reviewing a lot of this data to really analyze it and better understand it. When we looked back through Jakafi, we saw that we have a metadata database now that says we want to find all the single arm trials that have PRO. Jakafi's early trials showed up. They knew what the spleen size reduction was going to be, percentage-wise based on maybe 40 patients, or so, and they also knew how many of those 40 patients were going to have an effect on the same instrument that they used, the six item instrument. They were able to have an idea at least of what the incidence of those two would be. I think, again, it's all about making sure that the PRO, you can have a thousand different endpoints in PRO, but pick. If you're going to use one for that purpose, which is an important purpose, you should treat it like any other endpoint and power it like you would, get some information from the early trials.

Sharma: 03:51:34 Could I ask Zelanna, is that popular within Pharma, that type of, using that type of endpoint?

Goldberg: 03:51:42 At Pfizer, essentially every one of our trials has a PRO component. Powering it, for us to do that we have to have a lot of solid preliminary data on what is a reasonable expectation of benefit and then to put that as part of our secondary endpoint. Of course, as you sort of alluded to, there is a cost every time you do another assessment in terms of sample size and

in terms of power. Those are very difficult conversations that our statisticians dominate and say we can have this or we can have this. What do you want?

03:52:24 You were showing a lot of, actually, the Pfizer data on Crizotinib which was lovely. It was a very easy time when the patient's symptomatology told this very clear story and it was very easy for us to use that as part of our power calculations and part of our label. In immuno-therapy and certainly with the radiation studies, it's more challenging because, finding the right time to take those scores and knowing how to build that in statistically, we don't have that information, frankly. All of the PRO tools in Javelin, for example, are exploratory so we are not spending alpha on them.

Kluetz: 03:53:04 I think in the Crizotinib case, it was a safety, it was to complement the safety finding of ocula-toxicity, so it wasn't so much a statistical issue. It wasn't like, we cause less eye-toxicity. It was, we know we cause eye toxicities and the patients say it's not really impacting them terribly and it happens as frequently, etc. It gives you more information that I think was useful for people who take your drugs. I think that objective of safety and tolerability is nice because it overcomes the multiplicity and the powering and everything else. It's really more about how we do safety normally, which is we describe the effect. The other benefit, I think, back to your question, your valid question, of why would we do this? There's really a lot of increasing interest on the trajectory. The way that PRO is systematically assessed you just get a better longitudinal data if you want to do things like [inaudible 03:53:56]the heat maps and stuff to better understand toxicity.

Sharma: 03:54:02 My final question for the whole panel relates to the topic of this workshop, which is drug rating, therapy combinations. Bringing it right back around to that in terms of these really interesting new measures that we've heard about. Are there specific ones that you think we should be thinking about in with regard to drug radio therapy combinations?

Dicker: 03:54:24 I think it goes back to Paul talking about, and Tatiana, how do you show clinical benefit? Part of the issue is, we don't know what baseline is from the patient's perspective. For physical activity, what is baseline for a patient newly diagnosed with multiple myeloma versus on second line therapy for multiple myeloma. We really don't know. What is baseline activity for a GBM patient at month three? Verily has a trial called Project Baseline, which is looking at 10,000 people. It's a micro-biome sleep activity tracker with the Google Watch to understand what is baseline. I think that's a huge component that we don't really appreciate for our patients.

03:55:24 Another thing that we didn't touch on is, in routine clinical care, PROs are frequently not asked. Right? We acknowledge that there's this disconnect that the providers underestimate toxicity by 30 - 50% compared to from the patient's voice and yet there are very few institutions in at least North America that routinely incorporate. Some are routinely, maybe your institution is incorporating them, UPMC is starting to incorporate some of the promise measures that David Sella has worked on with FDA, etc. Across the board, if you picked all the, NCI designated cancer centers, most of them do not incorporate PROs for routine standard of care because, when do you collect them? Do you collect them remotely? How's it fit with the work flow? How do I react to that? Banner fatigue on the MR. There are a lot of practical issues that haven't been addressed yet. I acknowledge that tension and that disconnect as you try to figure out what is going to be meaningful to a patient, what's going to help you provide better care and what's going to move the field forward.

03:56:44 I've completely avoided answering your question but ...

Sharma: 03:56:50 Patty, are you going to answer the question?

Spears: 03:56:52 Yeah, I can answer the question. I think it's really a unique problem. I think that you have two completely different modalities there and so you have to really be intentional about what questions you ask. I don't think I've ever seen a PRO for radiation therapy. I don't know if there is one. There probably is because it has to do with cosmesis and cognitive function, if it's brain radiation, things like that. I think that it's marrying the two and whenever you marry two treatments you have an unknown as well. I think it is going to be challenging to do that but I think it's definitely worthwhile to figure out what those different side effects that you think might get by combining the two different modalities.

Sharma: 03:57:40 Adam's going to have a second go at answering the question.

Dicker: 03:57:42 I just want to mention one thing. I do a lot of bio-marker work, as some people in the crowd knows, and it's just fascinating how it's perfectly acceptable to do bio-marker work for early phase trials that are meant to pick up on clues but very few companies are interested in early phase trials inserting PROs. It's just fascinating. They're willing to collect plasma for circulating tumor DNA and things like that and scanning the micro-biome for all sorts of things because it's relevant for checkpoint therapies and maybe other things. Trying to get in some early PROs, because it's a different group, if the economic health research outcome group had this same mindset as the bio-marker group you'd see it inserted more. It's just something I observed, not with all companies but with a number of companies. It would be nice to get them earlier to get clues as to what maybe, yeah, where's the signal?

Goldberg: 03:58:53 That flows directly back to the work we have to put in to getting people to actually collect them and get them from patients. The earlier studies are in patients who are sicker. There's more data gaps; there's a lot more work that goes in to trying to get those data sets. It's very unclear, often, what's going to happen with them. It's certainly not philosophic for at least any place I've been or at least people I've spoken to on our end. I mean, even putting it into a phase three study, I have to tell you, when I went to the Ad Boards, and I don't say this to embarrass anyone, the physicians that we were talking to about designing the studies, the head/neck study, they sort of all sighed deeply when we talked about the PRO stuff because it's so challenging to get patients to fill them out.

Dicker: 03:59:47 One thing I'll just comment on and Paul and Patty can comment, is that a caregiver can answer a PRO question as long as they're not inserting their own opinions into that. That is allowed now, unfortunately for many head/neck patients we know that the greatest predictor of survival frequently is the ones who are single and live alone, they have the worst survival for those reasons.

Speaker 20: 04:00:20 I just will say that NCI Ctep does not support PRO collection for phase one or two, only for phase three trials.

Dicker: 04:00:28 Yeah, but that's a financial issue.

Speaker 20: 04:00:30 Yeah, but by the time we go to phase three we don't have a baseline from the phase one or two to design the phase three especially if we want to use the phase three as a primary endpoint. The second thing is, everybody is telling me 95%. The trials that we have run, and

some of them were electronic, our returns rates drop off substantially after six months, in the about 70-60%. I will say that that's a real world experience.

Dicker: 04:00:59 They're comparing a Pharma-driven regulatory trial to an NCTN.

Kluetz: 04:01:05 I do agree that we generally see the best of the best in phase three.

Goldberg: 04:01:11 We spend millions of dollars to track down every one of those forms so that these guys are OK with us.

Kluetz: 04:01:18 I would also say, just because I am very pragmatic and I acknowledge the issues of dwindling resources, that if it's going to be done - and it is being done - every single phase three clinical trial we see randomized for the clinical trial has patient [inaudible 04:01:36] You just said every study we do has PRO data because European payers, because Europe really wants this. If we're doing it, we should do it thoughtfully and better, and I think we can. I think you guys are, judging from the commercial trials we're getting. Again, I think it's done a lot better. What we hope to do in the next year is to be done with the "what to measure" thing and at least have buckets and tools and then we can work on analytics and work on making interpretable decision-making from them.

Goldberg: 04:02:07 And I would say, as we're moved more and more electronic so that we can push these tools out to patients on their phone and we can insert wearables, it just makes it so much easier and our compliance is going to get a lot better and then our data's going to get better. And, it's going to be less of an economic and work flow burden.

Sharma: 04:02:27 One very quick comment from Tatiana and then we'll wrap up

Prowell: 04:02:29 Yeah, it's actually a quick comment on a patient perspective, of all things. Specifically because I wanted to know how hard this was, with all three of my totally healthy pregnancies, I actually joined healthy Volunteer OB trials that were be conducted by Maternal Fetal Medicine at Hopkins where I practice. They were looking at things like maternal stress levels and cortisol levels and fetal outcomes and subsequent outcomes. These people are still coming to my house to interview my children every year. They're now 14, 12, and 10, so I'm kind of regretting that I joined the trials. I did one per pregnancy so it's a lot of visits.

04:03:03 They had patient reported outcome instruments at every single visit when I was already there getting cortisol levels drawn and ultrasounds. I showed up for all those appointments, despite being a fellow for two of those pregnancies, I showed up there. What I could not finish were the PRO instruments. By the end, by the last trimester of pregnancy, when I felt awful, I was just done. I would get through like four pages and I'd be like, that's it. I'm out. I've answered that question six different ways. On the last two instruments, I'm done.

04:03:32 I was healthy and I could not have been more motivated. I went in a trial to just see what it was like to be a patient on a trial because I've been fortunate enough to be pretty healthy. You can't get a more motivated patient than that. I share that anecdote just to say that if we're talking about people who are living with metastatic cancer who've been through enough prior therapy that they're in a phase one trial, you just have to be very realistic about what you're asking of people. Otherwise, the quality and quantity of data that you're going to get back is not even something that you can rely on.

Sharma: 04:04:04 I'm sorry, we've run out of time for questions but I just wanted to make the point that these panel discussions have representation from Pharma, regulator, consumer representative and academia, worked really well, I think you'll agree. That's good for tomorrow. We'll have more of them tomorrow. I'm going to hand over to Stephen Hahn to just give a summary of the day. Thanks to the panel members.

Hahn: 04:04:30 Dr. Walker told me that I need to be brief since it's the end of the day. I also wanted to congratulate you, Amanda. I think force of nature was exactly the right term and hearing your FDA colleagues, I have to tell you, it warms the heart to know that you all are helping us take care of drug approval. Impressive, impressive. We learned a lot from you today so, thank you very much.

04:04:54 I will be very brief but just a few things to start. First of all, Amanda, your major mistake was asking a 12-year-old to pay attention, take notes and then summarize, so, we'll do our best.

04:05:05 Note to self, Dr. Sharma taught us not to double down on missing your anniversary two times in a row and no, I don't think anyone in this room told Dr. Camphausen that he would be rich and famous. That was also another falsehood. And, who knew that it would be possible to bore a tumor to death. That is fascinating. I got a lot of things at MD Anderson that we can throw at a tumor, let me just tell you.

04:05:27 I think we've done a great job of outlining the challenges associated with combining drugs and radiation. I've heard that collaboration between academia and industry and our regulatory colleagues is essential and that involvement at the early stage in the life cycle, maybe not with PROs, is important. I am incredibly fascinated by game theory. To me, it's all about, I'm philosophically aligned, but it's all about getting alignment of incentives. I heard a lot of that at the table here. I think there's something there, Dr. Lawrence. I kind of like it.

04:05:59 We've had some general guidance from our CT/Rad colleagues in the FDA about clinical trial design and the pathway to registration. A lot of very helpful information there. And Dr. Lawrence, the other Dr. Lawrence, I think we have established the pre-clinic models and studies were particularly important on the issue of developing rationale, potential bio-markers, and scheduling.

04:06:20 I still think that a significant unmet need and weakness that we have, and I didn't hear any solution to this, is predicting toxicity. It's a real problem for us. One of the points I was going to make is whether we can, like the medical oncologists are now leveraged big data, and Adam, I was so glad that you brought that up. Some of these things are so rare, and sometimes, although there's hazards associated with it, sometimes we need large data sets to help us figure that out.

04:06:46 Nevertheless, Dr. Sharabi, your recommendation that we think of bio-markers to guide field selection, dose, fractionation, etc. I think that's really important. Particle therapy versus photons, I think we need to get into that space pretty significantly. I'm going to ignore my comment about plea to regulators about using organ preservation as an endpoint. I think I got schooled on that one here today. But, Dr. Lou's comments about the fact that some of our endpoints are very much disease related and stage of disease related, I think is also an important point to focus on.

04:07:22 PROs have clearly emerged as important and, Miss Spears, I think I learned something from you and that is, less and more targeted is actually more. That's a really important thing for all of us to remember.

04:07:36 And, Dr. Dicker, this I love. Citizen Science. I cannot agree with you more. It's a really powerful and significant tool and I'd like to see us get more into that.

04:07:47 Past failures, Dr. Harari, really you and Dr. Camphausen helped us with that a great deal and I think the correlative studies, we have to think about how to help us learn from wide trials. Fail or succeed.

04:08:00 Just two things looking forward. What are we going to do about this issue of normal tissue toxicity prediction, surrogate end marks, endpoints for that, etc. I think we need to spend some more time thinking about that and then, how can we leverage big data and analytics to accelerate research. It's no surprise that Roche paid $1.9 million for a flatiron. That's not a surprise at all. There's something in there for us to learn as well.

04:08:26 Have a great night and it was a terrific day. Thank you.

Sharma: 04:08:32 Thank you very much and we'll see you all back here tomorrow at 8:00

FDA-AACR-ASTRO Clinical Development of Drug-Radiotherapy Combinations Workshop

Transcript: Session III: Immunotherapy

Tran: 00:01:46 Okay, good morning everyone. I think we're going to start. If everyone could take their seats, and give a few seconds for the webcast to initiate. 5, 4, 3, 2, okay, good morning. On behalf of the ACR-ASTRO FDA staff and my other co-chairs, welcome to our second day of drug-radiotherapy combinations.

00:02:23 So just remarking on yesterday one last time, I have no social media presence whatsoever but using the most archaic form of communication according to my sons, texting, I did receive texts throughout the day congratulating us on the superb excellent line-up. And again, so just congratulations to the speakers, moderators from yesterday. It was an amazing piece of work.

00:02:55 So yesterday was very much the how and the why of this drug-radiotherapy combination issue, and today we have the what, which are what is the set of agents that are going to be combined with radiation that lead to regulatory approvals but also bettering the lives of our patients.

00:03:18 So we have a similarly superb line-up looking at immunotherapy, which many of you would have guessed right off the bat. As well as other molecularly targeted agents and nanoparticles, and how we may combine those to again improve the outcomes of our patients. In retrospect, given the conversations of yesterday, and we did co-chairs, we did have these conversations regarding the importance of biomarkers and defining molecularly targeted subsets of patients. We have one lecture on that. I think, in retrospect, as I was saying we might have given a little bit more time, but as many of you know, when you're juggling the schedules and the timing, we thought that this lecture may at least give us a good introduction to what we're needing and they're very much like our co-chair Amanda Walker was, a force of nature. We're very lucky to have Dan Sprat, who's also a force of nature, for all of those who know him. Even in his very young career to date, he's already made very significant contributions to molecularly targeted biomarker discovery research and clinical trials. So I'm looking very much to his talk.

00:04:38 And then at the very end of the second half of the day we're going to have a very lively but friendly debate on what will be the first, the next, FDA approved agent combined with radiation immunotherapy versus something else. And that will be given by Doctor Lawrence and Jim Welsh from MD Anderson. And then we'll have a final panel set discussion to wrap this all up.

00:05:05 So, very proud, very honored to introduce Doctor Kirsch from Duke. He's gonna give our introductory lecture today. Doctor David Kirsch is a Physician-Scientist Radiation Oncologist who practiced primarily treating patients with sarcoma. He is the Barbara Levine University Professor and Vice-Chair of Radiation Oncology at Duke University. He holds joint appointments in pharmacology and cancer biology. He's internationally recognized for his work in sarcoma, as well as the use of state-of-the-art genetically engineered mouse models to study fundamental issues in radiobiology. He will give us his lecture entitled 'Which Molecular Pathways are Worth Targeting in Radiation-Drug Combination Studies'. Doctor Kirsch.

Kirsch: 00:05:53 Well, it's really an honor to be asked to kickoff the second day here. I'm very pleased to be here. This is a disclosure slide before I get started. And also, as program chair for the upcoming annual meeting of the Radiation Research Society, I'm going to put a plug in for this meeting. If you're interested in this topic, several of our speakers for this two day meeting are going to be presenting at this meeting in Chicago. And we have a really exciting line-up and several speaker spots are still open for tox query abstracts.

00:06:36 So I wanted to take a step back, I know we have a mixed audience both here and also listening in on the web. Especially from pharmaceutical companies. And you heard from Ricky Sharma yesterday, and this is from the workshop consensus statement from the CT/Rad group in the UK. But they really highlight the critical role that radiation therapy plays.

00:06:58 So approximately 60% of cancer patients receive radiation therapy as part of their treatment. 40% of cancer cures include the use of radiotherapy, and it can be one of the most cost-effective cancer therapies. And so, making advances in radiation therapy with combined molecularly targeted agents really has the potential to make major advances in the outcome for patients.

00:07:22 However, as you heard yesterday, there have been a lot of obstacles to getting drugs combined with radiation through the approval process. Part of that I think comes from concerns at the pharmaceutical company level. Part of it is the regulatory process may be more challenging. And Norm Coleman, Ted Lawrence, and I wrote this editorial in the JCO a few years ago discussing some of these issues. And as part of this, we started off by talking about some of the premises of radiation therapy, and I think these are worth reviewing just briefly.

00:07:56 I know this, for the radiation oncologists in the room, this is old hat. But for the pharmaceutical companies, I think these are really important concepts to think about as you consider combining drugs with radiation therapy. So first, radiation therapy is a spatially focused therapy. So we have anatomically defined dose distribution. That, of course is very different from systemic therapies that go throughout the body. And that limits the toxicity to a certain part of the body.

00:08:21 In addition, we have highly accurate radiation dosimetry to both tumor and normal tissues. So compared to drugs where we may know the PK and what the dose is in the plasma, we really don't know how much of the drug gets into the tumor. How much drug gets into the cancer and with all its heterogeneity. And contrast with radiation therapy, we know exactly how much radiation dose goes throughout the tumor causing double strand breaks in DNA damage. And finally, we measure success in radiation oncology by increasing local control or having improved survival. And this really speaks to the impact of radiation therapy and its ability to have a positive impact on patients.

00:09:01 And if you look at this curve here, this is an in vitro assay showing cell killing. We typically measure cell killing with radiation therapy, here with the Y-axis on a logarithmic mixed scale. So 100% surviving, 10% surviving, and so on. And the X-axis showing increasing dose is on a linear scale. And if you go back and think bout how we do our drug studies, typically we're looking at cell death with 100% down to zero so the Y-axis is a linear scale and our X-axis is on a logarithmic scale. We're giving nanomolar, micromolar doses, and so on. And so it's

really a totally different order of magnitude in terms of the potency of therapy that we have with radiation therapy compared to drugs.

00:09:51 Now the other thing I'd like to emphasize before moving on to some of the molecular pathways that I think are relevant to target, is that to cure a patient of cancer you have to kill many logs of cancer cells. So this is taken from Bob Weinberg's textbook on cancer. Tumors are first palpable, maybe with a centimeter of tumor with 10^9 cells. So here we're looking at 10^9 cells, and each time we give a daily dose of radiation, two Gray per day, kill off a certain fraction of those logs. When we see very nice ASCO plenary sessions, there's talk of partial response, complete response. Complete response may only have 3 logs of cell kill. And if we wanna cure patients, we have to get all the way down to 10^9, 10^10 cells log kill.

00:10:37 Because radiation is so effective, and can kill off so many of the cells, drugs that make radiation just a little bit better have the potential to really increase cure and get rid of all of that last logarithmic cell kill. So, which pathways are worth targeting with drugs to combine with radiation therapy? Well, together with Eric Bernhard and others, there was a National Cancer Institute workshop that was held to talk about the future of radiobiology, and this was recently written up in the Journal of National Cancer Institute, where we highlighted areas of current and future focus for radiation research. And I think all of these areas are going to be fruitful for the years to come and offer great opportunities for combining drugs that target these areas, these pathways, with combination, with radiation therapy. We'll be hearing about some of them today, later on this morning.

00:11:35 So one of course would be to modulate the DNA damage response increase radius sensitivity of tumors. The flip side would be to minimize radiation toxicity to normal tissues and stem cells. Cancer metabolism is an exploding area, and there's exciting opportunities for understanding how radiation affects metabolism and taking advantage of that to improve the response to radiation therapy. Cancer stem cells is a very important topic for resistance to radiation and other therapies, and targeting the cancer stem cells has the potential to also improve outcome.

00:12:09 And then finally is what we'll be talking about today, the role the tumor microenvironment has a critical role in the outcome from radiation and other therapies for cancer patients and combining radiation with immunotherapy is certainly a very exciting area with great promise. Hypoxia and targeting it is also another area that has great promise and we also highlighted other opportunities in the microenvironment, such as manipulating the extracellular matrix. And finally as Fu was mentioning before, there's great opportunity to expand predictive biomarkers so that we understand, which patients would be best to include in our therapies as we move forward with novel clinical trials.

00:12:53 So finally moving on to these molecular pathways, I also want to highlight this other paper that was published led by Norm Coleman talking bout improving the predictive value of pre-clinical studies in support of radiotherapy clinical trials. And here we outline the various types of preclinical studies and data that are needed to move forward into clinical trials. Of course, there are in vitro studies looking for drugs that can enhance cell death with radiation and a number of different in vivo models, typically what's done is with a regrowth delay assay where radiation causes a growth delay, and then one looks to see if adding in the new drug enhances the time for regrowth. This can be done with human tumors such as xenografts.

00:13:40 And then there's a more involved assay, the TCB 50, which uses higher doses of radiation to actually get local control in 50% of the tumors. This requires a lot more animals and is not done as often, but may have the most clinical translation potential. And finally I'd just like to highlight some of the other models. There's a patient derived xenografts and the genetic engineered mouse models that also have certain strengths and advantages. But like any model, as shown here with the Salvador Dali painting, they all have strengths but they also have limitations. And the critical thing is that we can learn something important from our models as we move forward to translate them into clinical trials.

00:14:23 So here I want to highlight two molecular pathways that I think are ripe for moving forward into the clinic. This is the P53 tumor suppressor pathway, and this really takes advantage of 25 years of sound basic science and translational research that's gone on in this space. P53 of course is the most commonly mutated gene in human cancer, and also plays a fundamental role in ionizing radiation and other cellular stresses, such as oxidative stress and oncogenic stress. When P53 is activated, it can then turn on a host of downstream targets, such as P21 which causes cell cycle arrest and senescence, and also can turn on genes like PUMA that can cause apoptosis. An important regulatory protein is the MDM2 protein or HDM2 in humans. And this causes ubiquitination of P53 and degradation. And this pathway that P53 MDM2 axis is now being targeted in the clinic.

00:15:29 I just want to highlight here the critical role of context for P53 pathway. We and others have shown that following radiation, P53 plays a critical role in the bone marrow to cause cell death and to promote injury but in other tissue types, such as the vasculature and the intestine, the GI epithelial cells, P53 I actually playing the opposite role in protecting. And then in the liver, it seems that radiation doesn't affect P53 at all and has no affect on the liver. So although we kind of give this cartoon of how P53 works, there's a lot of complexity here, and cell type and tissue complexity that we have to think about as we're translating these concepts into clinical trials.

00:16:14 So here's another schematic of what I showed you. After ionizing radiation, the kinase ATM is activated, which can then phosphorylate P53 and MDM2. This allows P53 protein levels to be elevated, and turn on downstream targets for various cell type specific end points here. When there's a mutation, and an oncogene classing hyper-proliferative signal. This can then activate P53 and usually in that setting, there can be inactivation of the tumor suppressor P19 or P14arf. And this allows the tumor to develop, in some cancers, where P53 is wild-type. And this then allows us to think about targeting this pathway by having drugs that can block MDM2. So there are now very potent MDM2 inhibitors that can block MDM2. And then given in combination with radiation, get an exacerbated P53 response and get increased cell kill. This is the work from Peter Houghton's lab published now a couple years ago with a rhabdomyosarcoma xenograft model. The tumors are implanted into the mice and they grow. When they're given the MDM2 inhibitor, they also grow. 20 Gray causes a growth delay but then the tumors come back. But when they give the MDM2 inhibitor plus 20 Gray of radiation, there's permanent cure.

00:17:37 And so based on the underlying sound rationale, for using MDM2 inhibitors and this pre-clinical data with the xenografts, the NRG is now moving forward with the Phase 1B trial of neoadjuvant AMG 232 MDM2 inhibitor with concurrent preoperative radiotherapy in wild-type P53 soft tissue sarcomas. This is being led by Meng Welliver from Ohio State through the NCI Experimental Therapeutics Clinical Trials Network. And I'm the physician translational scientist on this team. So through all of these patients, they'll be enrolled

either with the sarcoma of the extremity body wall or a sarcoma of the abdomen pelvis and retroperitoneum. So we've got two separate cohorts. They'll have a biopsy at the time of enrollment. And they'll have next generation of sequencing of P53 to determine of P53's wild-type or is mutant. Of course, if P53 is mutant, we wouldn't expect an MDM2 inhibitor to have any beneficial role based on our understanding of the pathway.

00:18:48 So the patients will be placed on AMG232 and there will be correlative science endpoints. And then, the patients will then go on to receive radiation with AMG232, if they're P53 status is confirmed to be wild-type. For patients that have a P53 mutant or deleted tumor, they have it's back to standard of care with just radiation therapy alone. And this is going to be a standard dose escalation trial, but given with a single dose of AMG232, 3 times per week with daily five days per week radiation therapy. Starting three times per week at the first dose level and then moving up to five times per week if that's tolerated.

00:19:27 Now another area that I think is really exciting to target are the upstream kinases proximal to P53. This is the schematic of PI3-Kinase family, the canonical PI3-Kinase and also family members mTOR, ATR, ATM, and DNA-PK. These kinases respond to ionizing radiation and other damage and phosphorylate key targets, including P53 to orchestrate the cellular response to DNA damage. There are now potent inhibitors that are going into clinical trials of these kinases and can be tested with radiation therapy. We and others have preclinical data to suggest that targeting these kinases can have a very impressive affect on outcome following radiation.

00:20:19 So this is work from Katherine Castle, a graduate student in my lab, using a mouse model of brain stem glioma generated by Oren Becher. In this model it uses the RCAS/ TVA system to generate primary brain stem gliomas in mice. This is a lethal cancer in children and they're been over 80 clinical trials over the past few decades with no improvement in outcome. And here Katherine's targeting the ATM kinase using Cre-LoxP technology. And when she deletes ATM, there's no affect on the growth of the tumors or the penetrance in this model. However, when she treats the mice with 10 Gray times 3 whole brain radiation, there's a dramatic survival advantage in this model. Typically Oren only sees improvement in survival on the matter of days here. This is a major shift in terms of survival.

00:21:13 And this slide was provided by Melinda Merchant who's here from AstraZeneca. AstraZeneca now has some potent ATM inhibitors that are moving into clinical trials. There's a microdose F18 study looking to see the exposure of ATM inhibitors getting into the brain of healthy volunteers. And there's also a first in patient phase 1 study combining radiation with the ATM inhibitor for the treatment of brain tumors. This is going to be done in glioblastoma as well as brain metastases.

00:21:43 Now, of course, whenever we move forward with combinations of drugs with radiation, we always worry about the therapeutic index. But it's going to be critical to test this combination and others going forward to understand in humans what the safety and tolerability is of targeting these critical pathways.

00:22:04 Finally, I'd just like to share some of our data with radiation immunotherapy. This is the work of Amy Wisdom and Yvonne Mowery in my lab. Here again using the genetically engineered mouse model, this is a model that I developed when I was a Post Doc where we can inject a muscle with an adenovirus expressing cre recombinase. This turns on oncogenic KRAS and deletes both copies of P53. When Amy then makes a cell line from these mice

with the sarcoma, she can then transplant them in a syngeneic mice. And as many others have shown, when we then give radiation or an Anti-PD-1 inhibitor, we see that there's modest affect but then when we add them together there's impressive synergy. What's been really remarkable is that when Amy and Yvonne repeated this experiment in the autochthonous primary model, now the same tumor model with the same treatment, we see very minimal affect.

00:22:56 So here the PD-1 inhibitor doesn't really have an affect and the combination also doesn't have a synergistic affect. And I think these data are important because they show that all of our different model systems have various limitations, and model systems that rely solely on transplant systems run the risk of missing out on the critical role that the tumor and the immune system have on one another as they co-evolve during development.

00:23:26 Now we've also generated an additional mouse model where we can delete P53 and then we can give the chemical carcinogen Methylcholanthrene MCA. We did this because our genetically engineered mouse model like others, has a very low mutational load and mutational load appears to be important to allow the immune system to respond to cancers. So here's our KP sarcoma model. Very low mutational load, but when we do the P53 MCA model, we now see that there is a very impressive response or very impressive mutational load, similar to what we see in human melanoma. This is for the TCGA dataset for human undifferentiated polymorphic sarcomas, which is what our mouse model is most similar to.

00:24:09 And then Yvonne Mowery then took this model and she did an experiment where she generated the primary tumors in the mice. Gave them radiation with or without the Anti-PD-1 antibody, then amputated the tumor and and then followed them for metastases. So about half of the mice developed one metastases in this model. And what Yvonne found here in this preliminary experiment is that giving radiation didn't affect the rate of metastasis giving the PD-1 antibody didn't affect the rate of metastasis, but the combination did seem to decrease the rate of metastasis in this experiment. And so based on this preclinical study as well as a clinical trial, SARC028, we're now moving forward with this concept, testing it in patients.

00:24:48 This is the data from SARC028, which was a multi-center phase 2 study of Pembrolizumab, the PD-1 inhibitor for advanced tissue sarcoma patients. 40 patients were enrolled, 10 per subtype. The patients that had the undifferentiated pleomorphic sarcoma, there was a 4 out of 10 response rate, so 40%. In patients with the pleomorphic liposarcomas, 2 out of 10 had a response.

00:25:13 This is the waterfall plot showing again that the patients with the undifferentiated pleomorphic sarcomas had the best response and here's one of the patients from the University of Michigan that was enrolled on the study. I'm showing the impressive response to Pembrolizumab.

00:25:27 So based on this clinical trial, SARC028, as well as the preclinical data, we've recently opened a trial funded by Stand Up to Cancer called SARC032, which is a multi-institutional clinical trial to test the safety and efficacy of Pembrolizumab and pre-operative radiotherapy to try to reduce the development of metastatic disease in high-risk sarcoma patients. Primary end-point is two year disease-free survival. And we also have a number or correlative studies of the tumor as well as the blood as well.

00:25:55 And here's the clinical trial schema. Patients with high-risk undifferentiated pleomorphic sarcoma or liposarcoma. Will be stratified by grade. Half the patients will receive standard of care, image guided radiotherapy, 50 Gray and 25 fractions followed by surgery. And the experimental arm will receive Pembrolizumab before, during, and after radiation therapy, have the tumor resected and the will receive adjunct Pembrolizumab.

00:26:22 So just to summarize, I think there is a tremendous opportunity for translation of cancer in radiation research into the clinic by combining molecularly targeted drugs with radiotherapy. And to maximize the success of the clinical trials, we need sound rationale based on solid understanding of the basic cancer biology and radiation biology. We need to carefully select preclinical models with complimentary limitations and strengths. And the preclinical data should really provide compelling data to support translation into clinical trials.

00:26:54 I've outlined a couple of what I think are the really exciting clinical trials moving forward. The MDM2 inhibitor for P53 wild-type sarcomas in combination with radiation. Targeting ATM with radiation for tumors in the brain. And PD-1 inhibitor with radiation for extremity sarcomas.

00:27:14 And these are the folks from my lab that did this work, our collaborators, and a funding source. I'd be happy to take questions.

Speaker 3: 00:27:31 Thank you for that David. So you've presented that data a few times with regards to your KP model, the autograft versus the autochthonous, and the differing response to radiation and checkpoint. Can you elaborate on perhaps why you see those differences?

Kirsch: 00:27:48 Well I think that the difference has to do with peripheral tolerance of the immune system. We're working hard to do the mechanistic studies to nail this down. But when you have a syngeneic mouse, and you inject in a million cells or whatever it is, the interaction between the immune system and the transplanted tumor is different then when the cancer co-evolves with the immune system over time, and peripheral tolerance has months to years to develop. And I think the threshold for overcoming that, the bar that we have to overcome is much higher than a syngeneic model may otherwise suggest. So that's our hypothesis.

T. Lawrence: 00:28:30 Okay, so we had a spirited discussion yesterday about the role of, I guess I'll say translational science, in trying to develop these clinical trials. In particular, how can we assess in patients whether we hit the target, whether the science is actually playing out in patients. So in the trials that you talked about, how can one do that, and how do you think that's going to enhance the outcome of these studies?

Kirsch: 00:28:53 Well I think that the MDM2 inhibitor, we're doing next generation sequencing up front to identify patients with P53 wild-type tumors. And so based on the really large body of work, we think that the AMD 232 will only be effective with radiation in the context of P53 wild-type tumors. So that's really an essential biomarker driven trial. In addition, there are P53 targets that are secreted, so there's an MIC-1 protein that's secreted, and that will be a biomarker that we'll study to see if we're able to enhance P53 response in vivo in patients.

00:29:32 You know, for the ATM clinical trial, I'm not sure what biomarkers are actually going into that study, but I think that it would be nice, it's hard to do in the brain, but if there are sites

that are accessible, it would be nice to see that ATM phosphorylation targets that that's blocked after radiation. So that would be the biomarker study to look at.

00:29:54 And then with the immunotherapy studies, we have a host of peripheral blood mononuclear site assays and others to look for the immune response.

00:30:05 Yeah.

Speaker 1: 00:30:07 [inaudible 00:30:07] NCI. I noticed that you used different radiation schemes for combination with immunotherapy. Do you have any recommendations for the [crosstalk 00:30:18]?

Kirsch: 00:30:17 Well, we're going to have a slew of talks coming up with real experts on immunotherapy and radiation, so I don't think I want to go there. I think what I would say is there's conflicting data in the preclinical literature. I think that we need to do the clinical trials and be open to the possibility that different tumors in different settings will benefit from different fractionation models, and I think they need to be tested prospectively in humans. But I think that for our clinical trial, I talked to sarcoma radiation oncology community about using hypofractionation but we can use 5 grade times 5, which is used in Poland for extremity sarcomas, but their rate of local control is only about 82-83%, which is lower than what we see with 2 grade times 25, which is more like 90% of the US and other countries. And there was discomfort in making two big changes. Going to hyperfractionation with Pembrolizumab, and so we stuck with 2 grade per fraction. That may not be the best and optimal fractionation scheme, but it was was the first step that we were able to do.

Sharabi: 00:31:24 Alright, I think we'll go ahead and get the third session started on immunotherapy, because we all know immuno-oncology is revolutionizing oncology in general. There are over, I think, 100 trials. Close to 100 trials now combining radiation with immunotherapy specifically.

00:31:51 We have a great line-up, so I want to thank Amanda and the organizers putting together such a wonderful line-up of leaders in the field. And so we'll get started with Doctor Crittenden. She's a radiation oncologist. She's a true immunologist. Trained classically as an immunologist and Director of Translational Research at Earl Chiles. And she's published one of the first studies combining radiation with immunotherapy many years ago, and so I'm looking forward to her talk.

Crittenden: 00:32:14 Thank you. And I'd like to thank Amanda for organizing such a great, great session. So, I'd also maybe not like to thank Amanda so much for the task of demystifying the abscopal effect. Which I'm happy to do, but I'm not sure I'm going to make it any clearer than mud. So.

00:32:35 Disclosures, I don't think any of the laboratory support, well, the NCI and NIAID stuff I may talk a bit about but nothing from the companies.

00:32:45 So, in this talk I want to give you a little bit of a mechanism of immune radiation interactions, and I had synergy up here but I learned not to put synergy. I learned from the question yesterday, and I learned from when I put it in a publication and then had to statistically prove synergy. So.

00:33:00 ... to statistically prove synergy. Then we're going to talk about aspects of dose, timing, and fractionation, which I think is a big part of what people want to know, and I'm afraid you're not going to come out with a direct answer. We will talk about prospective clinical trials of radiation in the metastatic setting in combination with immunotherapy and searching for abscopal responses, maybe what we can learn from what has been done so far, then go back to some the pre-clinical data looking at what we have learned in the clinic, maybe why we're seeing responses we're seeing and then maybe targets we need to be considering.

00:33:36 So the mechanisms for interaction for radiation I group into sort of two general areas and Andrew nicely explained this yesterday, but interaction one in the one that most people talk about. That's where radiation functions like an NC2 vaccine. You don't need to know the antigen, it's in the tumor, in order to enhance immune control of distant disease and this is what people are referring to when they refer to the abscopal response, the response then is seen outside the field of radiation.

00:34:03 Interaction two refers to the fact that the immune system really can function to enhance control of irradiated tumors because radiation will make changes in the cancer cell and the microenvironment that will make it a better target for the immune system and that's really a concept that Jim Hodge and colleagues have pushed a lot, immunogenic modulation. I think if I were in a company, this would be the direction I would be heading for because I think there is a lot you can do bringing it earlier into definitive radiation setting.

00:34:34 So this is just a nice cartoon for those of us who don't learn by writing or by reading, but this shows the tumor and as you can see there is cancer cells in the tumor but there is also other stromal cells including T-cells, very radiation sensitive. They die quite quickly with radiation, although may be variable based on effect or function. Endothelium, maybe more radiation sensitive at higher doses, less radiation sensitive at the lower doses. Macrophages, dendritic cells, those cells are a little more radioresistant because they tend not to undergo active division so they can be a little more resistant. You give radiation, as you can see, the T-cells are now gone. The tumor starts to die, releases adjuvant antigen, gets picked up by dendritic cells, traffics to the lymph node where it primes T-cells, and then those T-cells traffic back to either clear residual disease or clear distant sites of disease and that's predominantly the thought and theory behind radiation inducing an abscopal response.

00:35:36 There have been multiple mechanisms that have been shown between radiation and immune response that can contribute to this, specifically the cell kill increasing antigen release, damps released at the time of radiation. You delete regulatory T-cells and endergic cells in the environment, and you end up resulting in recruitment of more activated T-cells. You see up regulation of death receptors and antigen processing machinery, perhaps more to the second interaction that I talked about about better killing in the tumor micro-environment post-radiation. Recruitment of immune cells through cytokine and chemokine induction realize this is in the radiated tumor, not necessarily as much in the distant tumors unless you have got an immune response going. That results in enhanced immune cell trafficking.

00:36:25 So for those of you who are not immunologists, the two fundamental components for a vaccine is antigen and adjuvant. If you have antigen without adjuvant that typically leads to tolerance of the immune response. If you have adjuvant without antigen, that typically leads to an immune refractory period. So giving too much inflammation without an antigen there can lead to your T-cells being in a refractory period so timing can matter with how we

deliver agents. The adjuvants that have been associated with radiation, double-stranded DNA, uric acid, HMGB1, calreticulin, ATP I didn't put up there, but you can also use pathogen associated CPG, poly IC, LPS, all of those have been looked at with radiation.

00:37:09 The other thing I want to emphasize is priming versus boosting. Priming is referring to activation of naïve T-cells. It is a dendritic cell dependent mechanism, and it requires secondary lymphoid tissue. Naive T-cells do not circulate through the periphery typically so unless you're doing something to draw naïve T-cells in an artificial way into the periphery, that encounter really happens in the secondary lymphoid organs. Boosting on the other hand doesn't require dendritic cells. It can start sooner, typically three to five days, but you may have to overcome energy in the boosting system. It can occur in the tumor.

00:37:47 So what do we know about dose, timing, and fractionation, and I have divided them sequentially. So dose. This is about dose effects on the release of damps from tumor cells. This was publish awhile ago by Jim Hodge, but they did variable doses 0, 10, 100, and they compared it a chemotherapy methotrexate and they looked at ATP and HMGB1 and you can see that it's really, in this case, the higher doses of radiation that are causing the increased release of theses damps, and perhaps a more physiologic or a more clinically relevant dose range Dr. Golden from Fermenti's group looked at ATP, calreticulin, and HMGB1 over a rance and you can see the most is actually at the highest dose 20 gray presumably going up to the 100 gray would similarly do that.

00:38:38 And then here is another thing about dose published a long time ago Edith Flord looking at priming with either five fractions of three gray or one fraction of 15 gray and then looking at the draining lymph node. It uses ova as a model antigen, and you can see the most ova-specific T-cells by ELISPOT are in the 15 gray dose compared to the more fractionated dose and even the endogenous TRP2 binding to the class one highest in the high dose.

00:39:08 So therefore, everybody should be doing the highest dose of radiation, but wait, it's not so simple. Dr. Fermenti and colleagues have thrown a bit of a wrench in it in the fact that they looked at dose, and in their tumor models, at least, there appears to be an inflection point. They were specifically looking at double-stranded DNA that can activate sting and what they saw was that the eight gray times one, they saw a lot of double-stranded DNA, but in the cytosol of cells, radiated cells, but when you went to the higher doses, you lost it and this seems to correlate with T-rate expression coming up at the higher doses of radiation and perhaps degrading the double-stranded DNA leading to less sting activation.

00:39:48 So that's dose. So not so simple. Seems to be a little bit better with higher doses, but maybe you can go too high. So co-stimulation and check point regulation I'm going to use as examples of timing. We heard a lot about PD1 from Dr. Sharabi, Dr. Illidge yesterday. So, I'm going to talk about OX40 and I'm going to talk about CTLA4 as examples of where timing may vary depending on the agent you use. OX40 is not [inaudible 00:40:15] expressed on CD8 T-cells, it comes up very quickly following MHC engagement and TCR engagement of MHC. I mean it's pretty tightly regulated to within 24 hours of antigen presentation and recognition. CTLA4, unless you're talking about T-rates typically comes up later two to four days post antigen presentation. Both result in, well, the CTLA4 prevents contraction if you engage it. OX40 leads to a greater number of activated T-cells with more effector phenotype.

00:40:49 So what can we tell about timing? This was an experiment that Dr. Young did when she was in the lab, and we basically just did anti OX40 pre, concurrent, or post and then looked at where the best scenario is and based on what I told you about mechanism, you would expect close to where antigen release is, and what you see in fact is when you give radiation and OX40 one day post, that gives you the most effective scenario, although there is some efficacy of RT alone in this model, and the more delayed treatment appears to be a little less effective with pretreatment.

00:41:27 CTLA4 on the other hand, we did pre, concurrent, and post, and I would have said based on what I told you about the mechanism that it would have been later, not earlier, but in fact, the best immune responses are seen with the pretreatment, which makes all the scientific rationale go away except if you know that actually CTLA4 acts on T-rates and T-rate depletion before radiation is probably the mechanism in part by which anti CTLA4, because we used the depleting antibody. Is there anything we know from the clinic that helps support this? This is a retrospective look that Barker did at patients with metastatic melanoma and looked at whether they got their radiation during the induction IPI phase or during the maintenance IPI phase and retrospective, there is lots of caveats to this, and I think we need to study it in a prospective manner, but it seems radiation after IPI had started for a while looked better. So timing may matter, and it may depend on the agent used.

00:42:28 Radiation therapy and fractionation. So there have been lots of studies for decades published about lymphopenia following radiation. This is just a comparison of two studies, one that used standard 28 fractions of radiation in the neoadjuvant setting for locally advanced pancreatic cancer, and one that used a hypo-fractionated 8 to 10 gray times three all within one week, and we looked in the peripheral blood. The crit study, we just moved the letters around. The crit study is hypo-fractionated. The ICRT is standard fractionation, and you saw a significant decrease in lymphocytes that persisted in the standard fractionation. They dip a little bit in hypo-fractionation, but recover. Monocytes show no difference regardless of the system you use. And when you looked at the actual CBCs and the absolute lymphocyte counts you can see that normalization for two consecutive measurements occurred in 70% pf the patients, and the mean time to normalization was 50 days to 172 days, so a long time for normalization in the standard fractionation. So, if lymphocytes matter for what you're doing, you either need to figure out if that lymphopenia is going to affect the outcome or figure out a way to address it.

00:43:50 It terms of summarizing this dose, for an endogenous vaccine, higher may be more effective, but in some tumors, there may an inflection point. If you're not really looking for a vaccine or adjuvant release effect you may be able to get away with lower doses. Timing of radiation and immunotherapy combination is really going to depend on the agent that's used and fractionation is good, but too much fractionation may be bad.

00:44:15 So what do we know about prospective clinical trials, and I tried to group them by agents that were used. So high dose IL2 was actually used in 1992 at the surgery branch with radiation. They did five gray times two to four to multiple sites in the body, and their overall response rate was only 7%, so very similar to high dose IL2 use alone at that time. Second study in renal cell was done with eight gray times one, again, multiple sites were targeted, and again their response rate was only 12.5%. You might say this person doesn't know about repeating the same thing again, but the theory was that high doses seemed to make more effect and so the doses used were 20 gray times one to three to lung and liver mets because

that's where it had been shown to be safe to use that dose, and the reported response rate was 66%. This is now in a randomized phase two trial and has completed accrual and will probably report out later this year if this in consistent in the randomized setting.

00:45:16 Anti CTLA4 has also been tested, mostly melanoma, but also in all solid tumors in a range of doses, six to eight gray in this setting. This used a huge range, which makes interpretation a little tricky but maybe is more hypothesis generating, 2.5 to 25 gray. Multiple sites were radiated. Overall response rates of 18 and 27% were reported. Here is the response rate reported in Walchuck's recent paper looking at combination, 19%, so not dramatically different. Certainly not the degree of difference we see in the preclinical setting. This one you need to realize is solid tumors, not melanoma, so most solid tumors in fact, I don't think they had any except maybe a uvula melanoma, melanoma in this case using 6 to 12.5 gray and up to five fractions to lung and liver mets, and they saw 10% response rate. So again in a setting where maybe anti CTLA4 doesn't work alone, but not the degree that we see in the preclinical models.

00:46:16 This study I'm not going to talk that much about because they didn't report overall response rate. They reported best response in any abscopal lesion, so that makes it hard to interpret and compare. Anti PD1, we're going to hear a lot more about this later in the day but reporting a 13.2% response rate. Again, across all solid tumors, not melanoma.

00:46:36 So what do we know about clinical trials? Most have been single arm phase one, phase two, IO agent plus immunotherapy we don't really have randomized data yet. There is a suggestion of higher response rates when we combine RT in ablative doses with high dose IL2. That may not be true for all immunotherapy agents. Response rate with checkpoint inhibitors haven't shown the degree of combined benefit that we saw in the preclinical setting, and I want to talk to you a little bit about why that may be. So radiation is a bad vaccine. If you're British, you might call it sort of shoddy, but here's a good vaccine, listeria vaccinating against SIY, and you can see a strong SIY specific CD8 response, and this is going out past the vaccine. Untreated there is very minimal response. RT doesn't give you much response. You get a little, but it's not a great vaccine so really maybe we need to think about how to make RT a better vaccine.

00:47:29 And then the other thing I want to mention is anti CTLA4 isn't really known to make vaccines work better so this looks at OX40 and anti CTLA4 combining with radiation and CTLA4 doesn't do much more than the vaccine alone. OX40 actually expands the cell, so maybe you need to think about what you're combining to make a better vaccine.

00:47:49 And then I want to talk a little bit about what David referenced, which is the issues of our tumor models. When you implant a tumor model, and this has been known since the 80s, North did studies, you get an effector T-cells response and then you get a secondary suppressor T-cells response, and if you do concomitant, contralateral legs, when you inject that contralateral leg, you can reject it if you implanted it day six to nine in this window when you have an effector response. You give it a little earlier, you probably have more favorable immune environment in there. You give it late, you probably have a very suppressive immune environment.

00:48:23 So in order to mimic this but in our transplantable models, we used anti CD40 ligan in this block. CD40 ligan it's known to prevent priming responses when you inject a tumor and what you can see is that in the control, you see an antigen specific response and when you

use anti CD40 ligan at the time of implantation you lose it. But what happens when you use this CD40 ligan blockade and then you look at combination with CTLA4? And what you see is this is the normal response, we're seeing 100% cures when we combine RT and CLTA4. This is what happens when you block that priming event. So probably what we're seeing in a lot of these models is boosting with the radiation rather than priming and that may be some of the issue of why we see a smaller response rather than the dramatic response. It's not limited to PD1. We used central tolerance here with a SIY expressing pancreas and PD1 similarly response by itself and then response in the animals that are tolerized.

00:49:23 So in final thoughts, there is actually strong preclinical rationale for radiation and IO combinations to enhance the abscopal response, but dose, timing of the combination and immunotherapy that you're using and what fractionation you're using needs to be addressed and really thought out beforehand and maybe compared as Andrew mentioned yesterday. We need to exercise caution in interpretation in some of the preclinical results and make sure we're testing what we want to be testing so if you want to look at priming, transplant tumor models may not be the best way to see what optimizes priming, and then if abscopal response, as I said, basically that's what I just said. We need to maybe consider the IO agents that will enhance the priming in the clinic and so things that bring in DCs, things that optimize T-cells priming, adjuvants may be the way to go. Thank you.

00:50:23 Adam?

Dicker: 00:50:24 So Marka, can you talk about, so there was a lot of discussion yesterday about clinical benefit, so can you talk about abscopal response and clinical benefit?

Crittenden: 00:50:40 Yeah, so I think when you're talking about abscopal response, this is why I think you need to be cautious about looking at any response in any un-irradiated versus looking at response across all of it and the duration of the response because if you're just saying I see one or two tumors shrinking, but others are growing, then you probably aren't having a clinical benefit, and frankly, we could probably take out two more tumors with radiation, and we sort of know that that whack-a-mole game hasn't historically shown to be beneficial outside of oligometastatic disease. So, I think the caution with abscopal response is I don't think we can use, we can use that way to give us a signal, but we can't use that way in really looking at as an endpoint, so I think your endpoints still have to be progression-free survival or overall survival, or delay to next event and needing additional treatment potentially as the beneficial, clinical benefit that we can provide in that abscopal setting.

Speaker 2: 00:51:47 Is there a reason to think that the abscopal effect may be more effective in, is it microscopic or occult disease than in gross disease?

Crittenden: 00:51:56 Yeah, there is evidence that, the Pacific trial with [inaudible 00:52:03] will talk a little bit about may give hint to that and that we see a really good response rate in that setting and that's microscopic versus dual disease rather than gross burden of disease and so there is suggestion that metastatic lung responses better than say a contralateral large, bulky tumor in preclinical.

00:52:24 Great, so next speaker Dr. Minn, and he may defer his questions until the panel session because he's got a lot of really exciting data to share about bringing immune checkpoint blockade perhaps earlier into the treatment of cancer.

Minn: 00:52:43 Okay, Marka, thank you. I have to say I was starting to complain a little bit about the topic that I was assigned as well. So I think a lot about the mechanisms of response and resistance to immune checkpoint blockade typically in combination with genotoxic agents such as radiation, but the task I was assigned to address today was to also think about this in the context of the definitive setting as opposed to the metastatic setting where most of these agents have been tested. I have to say, it's very interesting question. Again, I don't think we know the answers to them, but what I like to do is maybe outline some concepts that hopefully will give us some guidance.

00:53:29 So all of you I'm sure are familiar with this slide. Basically tumors so an exquisite job at suppressing the immune system, and one of the ways that the tumors can do this of course is by enforcing the engagement of inhibitor receptors on immune cells, in this case CTLA4 on T-cells, PD1 on T-cells. But fortunately, we have antibodies that target these inhibitor receptors, which if it works, it can potentially reinstate the T-cells against the tumor. Experimentally in mouse models, we know this works. This is a seminal study Jim Allison's group published in Science decades ago just showing that if you give an anti CTLA4, you can really prevent the outgrowth of this mouse tumor.

00:54:17 We have many, many studies of checkpoint blockade, typically in anti PD1, PDL1, anti CTLA4 in the clinic. The vast majority of these studies have been done in the metastatic setting. This is an example in nonsmall cell lung cancer, unselected patients, unselected for PDL1 status and we can see [inaudible 00:54:36] map, which is an anti PD1 compared to chemotherapy alone. In unselected patients a response rate of about 20%, so you can see the progression free survival is not bad. It's maybe a little bit better in melanoma, but it appears that lung cancer and melanoma and other cancers with high mutations, which I will go into a little bit more, may be the primary, at least so far, beneficiaries of these agents.

00:55:03 As Marka mentioned, there was a recent study that came out called the Pacific trial where now they took the combination of checkpoint blockade, in this case an anti PDL1, with chemo radiation in the stage three unresected nonsmall cell lung cancer setting. And here you see that the combination, or the addition of anti PDL1 as consolidation, so after definitive chemo RT led to a substantially improved progression free survival compared to simply chemo RT alone. So the results of this trial are actually quite impressive, and we don't exactly know why. Is it because we simply shifted it to the earlier disease stage? I'm sure that had something to do with it. But could it also be that the usage of immune checkpoint agents such as PDL1 in combination with genotoxic agents such as chemoradiation may be particularly beneficial in the earlier stage settings were you have less gross disease and disease heterogeneity?

00:56:09 What we know so far in terms of the determinants of response immune check point blockade have primarily focused on a few things. First we know that we have to get T-cells into the tumor, so patients that have T-cells infiltrated into the tumor tend to respond to checkpoint blockade better than patients that do not exhibit that property. Patients that have tumors where there is a lot of sematic mutations also tend to have a better response compared to patients that have fewer sematic mutations and that's probably simply because more mutations equals a more likelihood that there is going to be a new antigen that the immune system can recognize.

00:56:48 So given this simple model of how T-cells are needed in the tumor, they start secreting cytokines such as interferon gamma, then a [inaudible 00:57:00] class one, which helps

present neoantigen, the likelihood of the good neoantigen being increased by the prevalence of mutations are all potentially predictors of response. Indeed, if you kind of look at the simple two variable model, if you have interferon gamma related genes on the x-axis and mutation load on the y-axis, patients that tend to responds to PD1 and other immune checkpoint agents tend to fall within this upper right hand quadrant meaning that there is T-cells, T-cells producing interferon gamma, there is mutations, probably more neoantigen. These are the patients that are more likely to respond. But many patients don't respond even though they're falling into this upper right-hand quadrant so clearly there is more that we have to understand.

00:57:51 In thinking about the questions of what may determine response to radiation, immune checkpoint blockade, and the combination therapies, one thing I find somewhat useful is to kind of go back and think about well, how does the immune system normally generate a response? What are the major discriminatory functions that the immune system has to engage and properly execute in order to mount an effective response?

00:58:15 So the first antigens [inaudible 00:58:17] so the immune system obviously has to recognize something I have already mentioned in the case of cancer it's neoantigen. But oftentimes as Marka mentioned, just having an antigen isn't enough. Just a peptide alone can oftentimes tolerize the immune system. You also need an adjuvant. This instructs the immune system on how to properly activate and what way to activate, how to differentiate all the supporting cells needed to present the antigen. And then finally, a key property of the immune system is what's call a feedback inhibition. That is the immune system is exquisitely good at apply a break whenever gas is applied. The reason for this is because the immune system needs to prevent immunopathology, immune driven pathology and potentially autoimmunity as well.

00:59:08 So in thinking about this framework and going back to the topic I was assigned, how are these immune functions influenced by disease stage, so early stage verus a metastatic disease, and how are these immune functions influenced by radiation? So at what part of this process does radiation impact? Again, most of you I'm sure are aware of this, that across many human cancers a number of mutations varies by a tremendous amount. The tumors that tend to respond best to immune checkpoint blockade lie on this side of the spectrum where the large burden mutation is more likely to degenerate a decent neoantigen. So have your lung cancers, your melanomas, and your bladder cancers over here. There is more to than that. It can't just be any neoantigen, and there is additional properties of the mutational landscape that seems to play a role.

01:00:11 So mutations and the neoantigen that are generated can be clonal, meaning that they're present likely in all the clones of the tumor or a large fraction thereof, or the mutations can be subclonal, meaning that they're probably only present in a very small minority of the cancer cells, and it turns out that response to checkpoint blockade is probably more strongly influenced by the clonal mutations as opposed to the subclonal mutations. Several studies by Charles Swanton and Tim Chan has nicely demonstrated this is in clinical samples. What you kind of see here is that if you stratify by mutational load in response to anti PD1, it's okay. But now if you stratify instead by the clonal mutational load, then that seems to do better, so again, the type of mutations matter in terms of checkpoint blockade.

01:01:05 Here's another interesting study that recently came out where George Miller's group looked at a patient with ovarian cancer that had progressed over many years, got extensively

treated, and there was biopsy material available throughout the disease course. What was noted in this study and maybe perhaps not surprisingly is that a lot of these mutations of course, many are clonal or in other words truncal in origin, but then as you start sampling from different metastatic sites, you can see that many mutations are actually kind of private or subclonal meaning that they're either not expressed in the primary tumor or they're expressed at low frequency. The frequency is shown here by this heat map.

01:01:49 What's also very interesting about this study is that because this patient was extensively treated with many genotoxic therapies, particularly chemotherapy, you can see that the therapy tends to generate a lot of the subclonal low frequency mutations, so not really the type that is associated with a better response to immune checkpoint blockade.

01:02:11 In terms of antigenicity and how radiation may fit in, as Marka already mentioned, it's unlikely that radiation has a large impact on generating new antigens or these new mutations lead to things that the immune system can't effectively recognize. In fact, radiation probably is more effective or has more of a primary role at just being a good adjuvant and maybe other effects as well. So what's some of the evidence for that and why is this important?

01:02:41 So again, if you just give the immune system a peptide or an antigen without any instruction on what to do with it, you're unlikely going to generate an effective immune response. But pathogens generally not only bring into the picture an antigen, but also a lot of what are called PAMPs, pathogen associated molecular patterns. These molecules engage pattern recognition receptors that can recognize for example viral DNA, viral RNA and that way activate the right dendritic cells to prime the T-cells and that then will lead to the proper immune response. In this case, a cytolytic T-cells activation. So viruses are particularly good at driving cytolytic T-cells responses.

01:03:28 And what we're learning is that radiation, chemotherapy, epigenetic agents, even targeted therapy seem to, on some level, mimic a virus. And the way they do this is by engaging the same type of pattern recognition receptors that a viral nucleic acids can also engage. So this includes DNA senors, cytosolic DNA sensors such as [inaudible 01:03:50] and sting or RNA sensors such as [inaudible 01:03:52] receptors or the [inaudible 01:03:54] receptors. In this case, it's endogenous DNA or endogenous RNA that's recognized leading to maybe the production of interferon in the tumor micro-environment, which really help to prime or active the proper dendritic cells, which can hopefully facilitate T-cells activation antigen driven expansion.

01:04:12 Here's just an example of how this could work. There are other ways too as well. In the phase of DNA damage, cells eventually get stuck in mitosis, but oftentimes those checkpoints wear off and then they progress through mitosis in the phase of DNA damage. When they do this, they start forming what are calling micro nuclei, and these micro nuclei appear to be scaffolds for CGAS, which is one of the DNA sensors or looked at another way, these micro nuclei perhaps are recognized as if they were little intracellular pathogens, if you will. What that does is it activates interferon stimulated genes, ISGs the same ones that would be activated by a virus, and if you look at some of the effects associated with this activation, so here is a mouse where you radiated one side, then you look at the other abscopal or the un-irradiated side, so there is no checkpoint blockade here, just radiation. If you track individual T-cells by TCR sequencing, the y-xis in the frequency in the un-irradiated tumor, the x-axis is the frequency in the blood. You see that just radiation of the opposite

tumor is able to expand the T-cells in the un-irradiated tumor. But you see the T-cells get stuck because they don't expand into the peripheral blood. They only do so when you add checkpoint blockade. Now you see that they also expand into the peripheral blood as well.

01:05:39 Skip that. So clearly radiation alone can have some effects on the immune system, maybe not complete effects, but it can do so in preclinical models. Early on, we tested some of these ideas like many others have in mice, also in patients, and here is an example of a phase one study metastatic melanoma where patients got treated with radiation ...

01:06:00 Where patients got treated with radiation, a single lesion. We see those lesions go away. And then, there are abscopal or non-irradiated lesions that with subsequent [inaudible 01:06:12] also go away. The overall survival of this phase on the study of the patients on this trial is about 38 percent or so. Don't know the contribution radiation of course, but in mouse models, we know that radiation combined with Anti-CTO4 can improve the survival of mice compared to the individual treatments. Perhaps better clinical evidence that radiation may have an impact on the immune system and the efficacy of immunotherapy is a trial where [inaudible 01:06:44] at the University of Pennsylvania is the PI. Here this is taking patients and dividing them into two strata. Stratum one includes patients with melanoma or non-small cell lung cancer who have already progressed on PD 1. Stratum two are patients that have a low a priori likelihood of responding to PD 1 monotherapy. Patients with breast cancer, pancreatic cancer, etc.

01:07:10 Here patients that progress on anti-PD1 and stratum one were then treated with radiation to again a single lesion. And then these patients went on to get more PD1. And what we see here is a patient with non-small cell lung cancer. This patient ... here's a tumor that progressed through therapy. Clearly progressed on anti PD1, was enrolled on the trial and this tumor was irradiated with eight grade times three. You can see that the radiated lesion disappeared, responded really nicely. But in this case, the unradiated tumor that actually progressed on PD1 also responded quite nicely. If you look at the responders in stratum one, well, it's melanoma, non-small cell lung cancer, which isn't surprising. And stratum two you had a reno- cell carcinoma patient and another adenoid cystic patient. I think the point here is that the patients that perhaps may have benefited from radiation are probably the same patients that have a higher likelihood of benefiting from checkpoint blockade alone.

01:08:17 Which kind of makes the point again that the radiation probably isn't going to do much if the tumor just doesn't have good antigens in the first place. It can help. But it's unlikely going to convert a patient that has poor neo-antigens, and it's unlikely to respond to a patient that is likely to respond. Finally, the third discriminatory function of the immune system, I think that plays an important consideration is this issue of feedback inhibition. Radiation and immune response, it generates these interferons that I told you about. They are generally immunostimulatory cytokines. They do, what are called, good things. They help regulate MAC. They promote antigen processing, immune cell activation and differentiation. But as also alluded to, these same pathways can also inhibit the immune system by regulating things such as PDL1.

01:09:13 What we've demonstrated is that when these pathways are allowed to persist, in other words, get chronic signaling because you just can't get rid of the offending agent, or in this case a tumor, then this prolonged signaling on the tumor side can actually increase additional inhibitory receptor pathways. Not only PDL1 but other [inaudible 01:09:32] for T-cell inhibitory receptors as well. Here, once again, you see that in our mouse models

radiation and anti-C34 it starts leading high levels of interferon gamma. So, it's probably reflective of the stimulatory properties of this treatment regimen. But if the tumor doesn't respond or it eventually relapses, we believe that, that prolonged exposure to what was otherwise good can lead to something bad. Experimentally that's demonstrated if you take these B-16 cells that are normally sensitive to the treatment, you just in culture, treat it with prolonged interferon in order to kind of mimic what may have happened to this mouse at relapse after therapy.

01:10:16 And what you find is that prolonged exposure sufficient to now render this sensitive tumor now completely resistant to the combination therapy. There's also some evidence in patients that we may also see this effect. So, melanoma patients treated with anti-PD1, patients that have high pre-treatment levels of interferon gamma serum, also seem to be more likely to progress as opposed to the patients with the lower levels. This type of feedback inhibition also not only happens on the tumor side but in particular it happens on the T-cell side as well. In the presence of persistent antigen the immune system normally does not differentiate from effector cells into functional memory T-cells, as one would hope. But instead, in chronic inflammation and chronic infection the differentiation pathways rerouted to an activation ... to a state known as a T-cell exhaustion. In here, these exhausted T-cells as opposed to the memory T-cells they kinda have poor effector function. They're still active but they just don't go a great job. And these cells are probably the target of immune checkpoint blockade, such as anti-PD1.

01:11:35 And so again, that's illustrated here. Exhausted T-cells compared to bonafide memory T-cells, that are generated when an immune response is productive, tend to have a poor effector function. As shown by the duel secretion of interferon gamma in TNF. These exhausted T-cells express multiple inhibitory receptors on the surface. In contrast to other T-cells. And because of this, these T- cells may be more deeply dysfunctional and also more terminal. In other words, they may have very limited effector function. And moreover, it may be very difficult to do anything about this. It's thought of course that immune checkpoint blockade acts on these inhibitory receptors on the T-cells. And you can try to combine additional new checkpoint blockade agents in order to improve T-cell exhaustion. But a very interesting and still outstanding question is, how much will this really help? There's accumulating evidence that exhausted T-cells may be what's called, epigenetically locked-in.

01:12:40 Meaning that if you treat exhausted T-cells with anti-PDL1 or PD1, the genes change. So, there's something that is going on. But if you look at the epigenome, or in other words the DNA and the chromatin state, the addition of anti-PDL1 to these exhausted T-cells is doing very little to epigenetically modify, or reprogram, these exhausted T-cells. And so, that kind of locked-in state is shown here. Kinda genome Y that kinda looks like this. Compared to the more plastics state shown here. There's also evidence in patients that this ... you can see some of the features of this locked-in epigenetic state in patients as well. If you look at peripheral T-cells they also demonstrate limited function, which may be related to what I just told you. Melanoma patients treated with PD1, most of them will have a peripheral burst in the peripheral CDA pods, PD1 pods that have T-cells. But most of them will only have that single burst. That single burst early on. And they will never have a burst again.

01:13:51 And in fact, if you then assume that these T-cells have limited function the patients that seem to do the best are the patients that have a, what appears to be, a high ratio between the magnitude of this peripheral burst and lower tumor burden. In other words, if you give

the exhausted T-cells less to have to deal with, in this case lower tumor burden. Then these patients appear to do better. So, you might be able to offset the limited function with giving the immune system less to have to tackle. Finally, feedback also applies to the tumor cells themselves. Tumor cells in contract, maybe to the T-cells, are actually quite plastic. And they will take advantage of the inflammatory microenvironment to potentially interstates of profound immune suppression. One of these tumor states that is associated with immune suppression are mesenchymal tumor states. So again, clinical evidence for melanoma patients. That those patients that typically respond to PD1, have lower levels of these mesenchymal genes, compared to melanoma patients that don't respond to PD1.

01:15:05 Experimentally, in mice mesenchymal tumors tend to have lower numbers of CDAT cells, higher amounts of Tregs, and these less favorable, or less abundant M1 anti-tumor cytokines. The mesenchymal tumors don't respond to checkpoint blockade, whereas more epithelial tumors do.

Crittenden: 01:15:27 Andy, we're gonna have to wrap up.

Minn: 01:15:29 Okay. We're gonna wrap up. So, just to show you that the mesenchymal state is dominant though, if you mix these tumors even one to nine, so one portion mesenchymal and nine portions epithelial, it appears that the mesenchymal state is dominant. Finally, going back to the metastatic setting. And going back to that study where I was telling you that this ovarian cancer patient was sampled across multiple metastatic lesions. You can see that this type of immune tumor microenvironment can be dramatically different from site to site. Some sites have very high abundance of CDAT cells, where other sites have very low abundance of CDAT cells.

01:16:15 So, in terms of metastatic versus definitive setting, one might argue that conceptually the definitive setting has certain advantages. There may be less heterogeneity in sub-common mutations, many of which may have been introduced by prior therapy. These also may be less heterogeneity in the immune tumor microenvironment as well, which particularly can be very important. And a decreased burden in the definitive versus the metastatic setting may offset the limited function that these reactivated T-cells have. And really any antigen cytoreductive effects of radiation potentially might be maximized in the definitive, low tumor burden setting, as opposed to the metastatic. Apologies for running over. Thank you very much.

Crittenden: 01:16:57 So, in the interest of time we'll move forward, defer questions for Andy to the panel discussion. And next up is Stephen Chmura, giving a talk on SPRT combined with anti-PD1 as a platform. Results of the initial phase one, two trial.

Chmura: 01:17:16 Hi. It is an absolute pleasure to be here today. And to really talk to you about how we have developed this platform at the University, to attest SPRT in combinations with IO agents. These are my disclaimers. Over the next 18 minutes, and I'm gonna try to stick to that, I'm gonna give you a different prospective and a rational for actually the multi-organ site ablative radiotherapy, or the idea of MOSART. And into the first clinical trial doing I-MOSART, which is combining it with anti-PD1. And at this point you can probably tell I enjoy acronyms. And then the actual ... a translational science, which unfortunately is only gonna be in humans, and not in any nearing models. I think in general we often think about treating our patients who have a metastatic ... a disease, using our systemic agents. And really to reserve local therapies for things like obstructions and palliation.

01:18:25 But if you really think about the first times that we have thought to use our SPRT or ablative techniques in terms of integrating it with a systemic therapy, it comes from the idea of oligometastases. Truly popularized by Helman and Wexlerbaum. And the idea that if in fact a patient presented who have limited disease, it may provide a true window to cure the patient by ablating everything you could see. And I think the interest in kind of integrating this has really evolved over time. If you just plot the interest on like a pub-med and you go back to 2005 when we had first launched our initial phase one trial, it was very little interest. In 2014, NCI approved actual randomized phased two, three trials. And now, in 2017 we actually have randomized data showing both overall survival and progression free survival. In addition, we now understand, there's a true, a molecular, basis for this phenotype. And that you can see this both in terms of patients and in term of animal model systems.

01:19:43 And now in 2018, doing this, actually integrating ablative therapy with a system therapy improves overall survival. If we look at the EROTC trial with long term follow up with colorectal metastasis, improves overall survival. You see a tripling in terms of progression free survival from the lung cancer trials. And the same idea, an almost tripling in the time of the need for ADT in terms of prostate cancer. And we are about halfway accrued now on energy BROO2 asking the same question, can we add SPRT to the standard systemic therapies to improve both a progression free, and ultimately overall survival? I think in terms of really using SPRT for a systemic control has grown out of the idea of oligometastases. And I think, we know, that treating the local mets with a bladed techniques, improves both progression free and overall survival. And we now have true biologic evidence driving this. And these ongoing trials are really designed to answer specific hypotheses as to, in which patient populations are we going to improve overall survival? So, though going beyond this though, why stop at oligo, right? So, we have heard a lot about abscopal. And I'm going to introduce one more acronym, ADscopal. And the idea there is that, could we enhance controls of larger or hard to treat lesions by combining high doses of radiation and the immune checkpoint inhibitors? If we have so many options on how to design these trials, how have we kind of thought about that, and how can we develop a platform? My colleagues and I kinda worked backwards, and said, "Well, what are the problems, and then how can we design a platform?" If we take a true working model of this T-cell inflamed phenotype, where if you look at the tumors, you have, let's see, the A positive cells and a type 1 interferon signatures, the kind of main immune escape seems to be inhibitory pathways. As opposed to the non-inflamed type where you really don't see CD8 cells, and it's really by a T-cell exclusion. Most immunotherapy responders have the inflamed phenotype.

01:22:22 Unfortunately, most of our patients have this uninflamed phenotype. And we are fortunate because, at least experimentally, we can convert the non T-cell inflamed type into the inflamed type, using large fractions of radiotherapy. We heard high disease burden also leads to poor response to anti-PD1. High disease burden leads to exhausted T-cells. And you see this impact, in terms of the melanoma trials. On not just resist response of tumors but even in terms of overall survival. And as has been previously pointed out. At the lowest amount of disease burden, one you cannot see, appears to have a dramatic response. And even if we look at this idea of abscopal, and you really look carefully. It turns out that it only works if you have limited oligo metastatic disease. Again, seeing this means that high volume seems to be a true inhibitor to the response. In summary then, I think the abscopal response is rare. Probably because immunosuppression dominates the inflamed phenotype of tumors, has the best response to IO agents. The bulky disease responds poorly to IO.

01:23:52 Ultimately, could we create an inflamed phenotype, produce antigens, and debulk a disease to actually improve both local and potentially a systemic control? Our first trial was combining the multi-site SPRT and the anti-PD1. In this trial we took 27 advanced solid tumors. We used the energy SPRT doses from a BROO1 and from a BROO2. And treated two to four metastasis per patient. Antigen pembro was a given until progression. And our assessment for the primary endpoint, being toxicity, is at three months. A few kind of notes about who was in the study. Again, this was 27 histology's unselected for PD1. It turns out about 20 percent had some type of PD1 staining. The median number of therapy are five. And if you had large tumors over like 65cc's, only 65cc's of tumors would be targeted with the radiation. And two to four metastasis were treated across all patients. This is our primary endpoint. Our toxicities are grouped similar to the NCI trials, into sort of seven anatomic cohorts. And in the end, we had 6 out of 73, grade 3 events, across all of the patients. And it seemed to be equally distributed into each cohort. So, how about any evidence that the systemic therapy actually augmented local control? I think if we look at these large lesions treated it was really interesting. So, in like 17 patients, had quite large tumors. Over 21 large tumors total. With the median size being 116cc's, compared to the other tumors treated being 7cc's. And so, to kind of give you an idea then, if the green is the actual GTV to actual target, we shrunk down our target to actually keep it at 65cc's. And so, this water fall plot shows you how much of the tumor was excluded. Our median isodose line, which covered the whole tumor, it was at about 20 percent. If we then look at this, I thought it was pretty exciting, because our control of these large tumors appears to be quite similar to the small tumors. Really suggesting that you have some interaction in terms of improving local control.

01:26:56 And so, what I think could be the first time ever, going from a patient into a mouse to try and figure out why. If we look, and we prevent new recruitment of T-cells into the tumor by using an inhibitor of sphingosine-1-phosphate, you can see that these T-cells are then actually surviving in the tumor. Only in the tumor, not in the [inaudible 01:27:25], or the lymph nodes. And are active and actually migrate throughout the tumor. So that you can actually treat half of a tumor, and yet you see a functioning CD8 cells move throughout the entire tumor. So, how about any evidence that the systemic therapy has been augmented by RT? Overall, this is our abscopal response, is like defined by resist non irradiated. Our objective response rate is about a 13 percent here. And if you break it down by PD1 staining, it appears to be a trend towards potentially having more CR's and PR's in the patients who have some PD1 staining. Again, only about 20 percent had any staining at all.

01:28:25 And this has been brought up earlier, how should we quantitate it? And I think this graph shows a true difference in why all of us have to use these same numbers. Again, if we use the more classic resist, like definition, as the sum of the target lesions, we see a resist response rate of about 13 percent. If you actually simply use the more information, which is a single lesion shrinking, it also doubles to 27 percent. In terms of progression free survival, this is exactly how almost every IO study looks. It looks to be about 3.5 months, is the median progression free survival. However, we have been quite excited by ... in this heavily pre-treated population, in terms of the overall survival. And that 12 percent of the patients enrolled on the study are now past 14 months, and have progression free survival. Our kinda primary translational endpoint, it was using a 4 gene score, which has been used in a number of the IPPY trials, to say on the post SPRT biopsies, can we correlate the interferon related genes to a distant response? And the answer is, we could.

01:30:08 And it was actually strongest out of these 4 genes looking at granzyme K. I have some new data back doing whole transcriptome affymetrix arrays, which is really trying to look at post-SPRT biopsies from the pre to the post-SPRT. In terms of an unsupervised clustering. And it shows ... and this is really exciting I think, because it shows in humans that the genes up-regulated post-SPRT really fall into three groups. It falls into the innate, adaptive, and into the DNA repair category. And this is even more interesting I think, because this is across 13 different histology's, all showing a very consistent trend, at these high ablative NCI sponsored doses. And I think this is really even more exciting in terms of ... if you sort of look at then, and you model this in terms of the major upstream regulators. And you think about the orange as sort of being pro-immune, and the blue being kind of anti, some kind of clear pathways come out. In terms of the interferon Jak-STAT, it promoting, and the Mik E2F Inhibiting.

01:31:36 In summary then, I think that this platform has shown combining these ablative doses to multiple sites is safe. That we had six DLT's, which is about what you would expect doing an IO agent alone, or SPRT alone. I think that abscopal responses are seen, probably. And more interestingly is the local control story [inaudible 01:32:04]. The primary endpoint of the interferon associated gene expression actually correlates to a distant response. And the ablative doses used in these NCI trials are in fact activating innate and adaptive immunity. And so then, I think now is the time to move on to actually specific hypotheses. How are we doing this? I am pleased to say the NCI sponsored trial in Markleville, actually randomizing anti-PD1, plus or minus SPRT, opened a few weeks ago. I hope everyone here will consider opening this. This is a huge effort. This is the schema here. They are going to be stratified and randomized to ... like pembro, compared to pembro plus SPRT.

01:33:03 And the primary endpoint is the abscopal effect, or the non-irradiated resist response. We are also in house randomizing in upfront lung cancer, doing a concurrent or sequential [inaudible 01:33:24] and SPRT. And we are obtaining both pre and post biopsies. Our hope here is to really say, you know, how is the ... at least the actual toxicity of concurrent versus sequential and then our ... be able to see any hints of improved efficacy at the concurrent regimen. I am excited about some of the newer compounds, adding things like CSF1R and 41IBB. And then, actually trying to get a biopsies then of the non-irradiated sites. To really say, are we really driving more T-cells in elsewhere in these humans? And finally, this is our advice trial, which is a really exciting design. And this is for patients who are then post-PD1 failure. They will undergo a screen by the ... and a true biomarker. A defined treatment will be done to choose, which of the six agents that they should go on. If you cannot find one, then the same SPRT doses are going to be used as almost a seventh agent.

01:34:52 In conclusion then, I think there's a real potential combining IO and SPRT to both improve local control, and some hint to improve the systemic control. I think the ablative doses used in the oligo metastatic trials are safe to be combined with SPRT. And I think this is really the first evidence in humans that the innate and the adaptive immunity is triggered by these ablative doses. And it's exciting now because this platform is now a testing specific hypotheses. I just want to acknowledge so many people help here, from my colleagues in phase one, to my chairman, to all the cooperative groups, it's really amazing how many people have helped to put together all of these clinical trials. Thank you.

Crittenden: 01:34:52 Do we have time for just one question here?

Speaker 3: 01:36:08 Sure, I'll ask a question. So, what would you expect in your trial that you did, I guess the I-MOSART trial, from just the pembro alone?

Chmura: 01:36:15 Yeah. So, I think if you look at all the kind of basket trails using keynote, all of those did select for at least some PD1 expression. And they ranged between 7 to about 10 percent. So maybe this on the high end and this was unselected. But I think that's all you can really say.

Crittenden: 01:36:38 Thank you. Our next speaker who is gonna speak about toxicity in combination with radiation has done a lot of work looking at this and designing trials for this. So, Dr. Jonathan Schoenfeld.

Schoenfeld: 01:36:53 So, thanks very much. It's really a privilege to be here this morning, and I want to thank the organizers and Amanda for the invitation. Well, it's been a great session so far. Here are my disclosures, and pictures of what I think Boston looked like over the last 48 hours. So, going from snow to 70 degrees, and then back to snow again. I think the same was true of DC. You know, I wasn't as smart as Marka. I didn't remove the work synergy from my slide, but I did just wanna start by pointing out that maybe I'll say potential synergy. The downside of this can be associated with increased toxicity. And I think perhaps the most clear example of this from the immunotherapy space is combination of PD1 and CTLA4, PDL1 and CTLA4 blockade. This is data from the checkmate 067 study, of course the combination of the PD1 inhibitor and nivolumab in a CTLA4 inhibitor. Ipilimumab is approved for the treatment of metastatic melanoma patients.

01:37:54 And in this trial you can see promising activity with the combination of nivolumab plus ipilimumab, both in terms of progression free survival on the top, and overall survival on the bottom. But the downside is with the combination of these two potentially synergistic treatments. You see a clear increase in adverse events. In particular I wanted to highlight the grade three to four. So, the serious adverse events. With single agent nivolumab, single agent ipilimumab, these were in the 20 to 30 percent range. But with the combined treatment used at the doses used in this particular trial, the grade three to four adverse events were at 59 percent. And this was clearly significant for these patients. The same is true, we've heard in the past few talks and in some of the talks yesterday, obviously we're all excited and want to pursue the combination of radiation and an immune therapy of all different kinds, but I think we have to be weary then in situations where we can see a potential, beneficial combination of these two agents.

01:38:52 We have to be mindful that this could also have a downside in terms of synergistic or additive toxicity at least. This morning I wanted to start by talking about, in a little bit more detail, what are some of the ...

01:39:00 I wanted to start by talking about in a little bit more detail, what are some of these toxicity concerns. Talk about some of the existing and emerging clinical data in regards to toxicity of combined radiation immunotherapy approaches, some of which we've already heard a little bit about. And then speak about how might we go forward, how might we look for combination toxicity of the combination of radiation immune therapy, and what are the inherent challenges in doing this?

01:39:28 So first to talk about the toxicity concerns. So I think this is something that's probably increasingly familiar to everybody in this room and everybody in oncology in general. The unique spectrum of side effects that are caused by immunological agents and particularly

immune checkpoint blockade was really well summarized in this review article that was published in the New England Journal of Medicine last year. And basically, from head to toe, even though the toes are cut off on this figure, they increased immunity caused by immune checkpoint blockade can lead to increase in inflammatory side effects. These most commonly involve the skin, the GI tract, the lung, the endocrine glands, and the liver, but there are these other rare, but also potentially serious, and even fatal autoimmune side effects that have been reported such as myocarditis.

01:40:21 What's interesting, from a scientific perspective is that the frequency and distribution of these autoimmune side effects highly depends on the immunologic agent use and perhaps the best example's the higher rates of autoimmune is associated with PD-1 or PD-L1 inhibitors as compared to colitis, which is more associated with CTLA-4 blockade. What's become increasingly clear as well is that the early identification and appropriate and aggressive treatment of these autoimmune side effects are important of clinical management of these patients. There have been, now, the establishment of algorithms to aggressively treat these patients and that's been very effective in limiting the morbidity and mortality that these side effects are associated with in human patients and so something that I think has been very clinically meaningful.

01:41:08 Going back to all the discussions we've had about translational models and I do think these are extremely important, preclinical models, but when it comes to toxicity, it is even more of a challenge in that even in models where we see some of the efficacy inherent in immune checkpoint blockade, you don't necessarily see the same spectrum of autoimmune toxicity, at least that you see, in human patients. Mainly for non radiation oncologists in the audience, I wanted to point out that when we think about toxicities of radiation therapy, there are particular toxicities that we think about that are highly related to the site of radiation and then in some cases overlap with the side effects that we see in patients treated with immunotherapy and specifically with immune checkpoint blockade.

01:41:54 As shown on the slide, patients that receive radiation, this is a patient that was treated with head and neck radiotherapy can get significant radiation dermatitis. Patients can get pneumonitis, you can see here in the red box, an area of a radiated lung. Radiation changes and that can be symptomatic in some patients. Patients treated to the abdomen can develop colitis and they also can develop hepatitis so you can see this hypo-density that's well demarcated within the liver, in an area of prior radiation. Another thing that's very important when we start to think about toxicity of combined radiation immunotherapy approaches is all radiation is not the same. We've heard a little bit about that in terms of efficacy, in terms of dose effects, but there's also a big effect of dose fractionation, field location in size, treatment technique, and also something that's long been appreciated is concurrent systemic therapy, obviously can affect the rate of radiation toxicity. As we move into the immunotherapy radiation space, I think those are all parameters that are important to keep in mind as we look for the toxicities with combined treatment approaches. I also just wanted to pick up on a theme that's now been mentioned in the past few talks is that obviously we're all excited about the possibility of the abscopal effect, so you radiate one legion or you radiate one place and you stimulate systemic antitumor immunity in a way that might make immunotherapy more effective, but I think we also need to keep in mind the local effects of combining immunotherapy and radiation, both in terms of efficacy and toxicity. There is now increasing amounts of both preclinical and clinical evidence that there's a potential for enhancement of local radiation effects with immunotherapy.

01:43:35 Some of the data for that has already been presented this morning so I won't go into that in too much detail, just to say that back as early as the 1970s, if not before, there's evidence that the local effects of radiation, and this was in a fibrous sarcoma model, are greater in immune competent preclinical models in an immuno suppressed preclinical model, just locally, again within the field of radiation and if you look at some of the clinical experience combining radiation combining radiation and in older immunologic agents so interferon, you did see a hint that there might be these increase local effects. Publications that were published when these two agents were given concurrently looked at some potential for increase mucositis, radiation necrosis, dermatitis, so some of these potential local toxicities of radiation.

01:44:25 What are the existing clinical data in regards to combinations of radiation in the newer types of immunotherapy and specifically immune checkpoint blockade? I wanted to start by talking about some of the data that we generated over the last few years. This was work largely done by Dr. Andrew Bang who is a visiting fellow with us and we were very interested in this potential for increased toxicity locally within the irradiated field. He very carefully performed a retrospective analysis in over 130 patients that were treated with standard of care immune checkpoint blockade and palate of radiation and looked to see whether the radiation fields overlapped the organs we were interested in, most notably the lungs, the bowels, and the brains to see if we saw any increased rates of toxicity in these areas related to the immune therapy.

01:45:10 Reassuringly, what he saw is that overall rates of immune related adverse events were similar to patients treated with immune checkpoint blockade alone. If you look in the graphs here, you can see in the blue are patients that had toxicity that received radiation to an associated site compared to red where patients received radiation to another area to try to adjust some of the retrospective bias that might be in the study. And you can see that there was a numerically greater rate of pneumonitis in patients that received lung directed radiation, this was not statistically significant, and we didn't see any increases in colitis or transaminitis in patients that received abdominal directed radiation. What was even more reassuring to us is that we saw a few severe grade 3 or higher immune related adverse events and no associations between these and the dose, site, or timing of radiotherapy. Going back to this local enhancement question, we also were interested in that in a study led by Dr. [inaudible 01:46:10] Eiser at institution and Allison Martin, we looked specifically at the patients who received stereotactic radiosurgery and the local effects, so how likely were these patients to get symptomatic radiation necrosis, or radiographic radiation necrosis. This was 480 patients, so a larger cohort, 115 whom were also treated with immune checkpoint blockade within 4 weeks of stereotactic radiosurgery. You can see on the Kaplan-Meyer curve on the right, that here we saw that the receipt of the immune checkpoint blockade was associated with an increased risk of symptomatic radiation necrosis after adjusting for tumor histology and particularly in the melanoma patients who received ipilimumab, CTLA-4 therapy, so I'll come back to this in a little bit.

01:46:54 Largely now I think we are starting to see prospective data as well so that pacific trial's already been mentioned a couple of times this morning, but just to go back to the toxicity question, again, this was to remind everybody of what this study tested, it tested adjuvant PD-L1 therapy in patients that were pretreated with chemotherapy in radiation to the lungs, so these patients received full course chemo and radiation for stage 3 non-small cell lung cancer. You can see the impressive progression free survival benefit in the Kaplan-Meyer curve here on the left and then if you look at the adverse events, what's reassuring is that,

again, if you look at pneumonitis and radiation pneumonitis, because this is a big concern with patients receiving radiation to the lung, you can see a numerical increase in any grade pneumonitis, which is not surprising considering PD-L1 inhibition is associated with a single agent risk of pneumonitis. Doesn't appear multiplicative, just additive, and if you look at grade 3 or 4 radiation pneumonitis, you see that the results are pretty consistent, 2.6 in the placebo arm and 3.4 percent in the patients that were treated with [inaudible 01:48:02].

01:48:03 So I think we're starting to see a pattern emerge here. There are, on a monthly basis, more and more published experiences, both looking retrospectively and now prospectively, a combinations of radiation and immune checkpoint blockade, both with anti CTLA-4 and anti PD-1 therapy and the majority show that the combination of the two therapies are well tolerated. I just want to highlight a few of the prospective studies. I think there are some clinically relevant situations that we all care about, we want to test in clinical trials and in standard practice, and I think there now are, at least in abstract form, a couple of studies that have shown reassuring data when we think about combining immunotherapy or immune checkpoint blockade with conventionally fractionated chemo radiation studies in the neoadjuvant setting in pancreatic cancer and in a definitive setting of head and neck cancer presented at ASCO last year and then another one recently presented just last week at the head and neck symposium.

01:49:01 I think when we start to think about higher dose stereotactic body radiotherapy treatment, and we just heard Dr. Shmore talk about his study that was recently published, also other studies as well that have either been published or presented. And then as Mark had mentioned, there's this interest in getting the sweet spot so hypo-fractionated radiation to potentially combine with immunotherapy and there's also several published studies that have used the combination of hypo-fractionated radiation and found this to be well tolerated with immune checkpoint blockade.

01:49:37 I do still think attention is needed in future studies and with longer follow up. I wanted to highlight this interesting cases that were published in the Annals of Oncology last year, so these are heat maps or isodose curves when patients that were treated with radiation to the lung. You can see on the top to the left lung and on the bottom to the right lung. These patients then went on to receive anti PD-1 therapy with nivolumab and what was very interesting is both patients developed pneumonitis eventually on nivolumab therapy, but this pneumonitis was largely localized to the areas that had received prior radiotherapy. And a recall phenomenon is certainly something that is reported with radiation and with antibiotics and with other drug therapies, but the fact that this might occur with immune checkpoint blockade I think is interesting.

01:50:23 How do we go forward? So for the last couple of minutes, I just want to talk about what are some of the challenges and how we might address those in terms of monitoring toxicity? First and foremost, I said I'd go back to the increased rates of radionecrosis that we saw in the setting of immune checkpoint blockade and I think in both in the clinical practice setting and also in the clinical trials setting, we have to always keep in mind that the concerns regarding the theoretical and observed toxicity are balances by the potential for clinical benefit and that's obviously the most important when we're thinking about this issue. So in that same group of patients, you could be concerned on the one hand about radionecrosis, and I think we should look into this further and try to find ways to mitigate this, but also we're seeing kind of impressive results in this group of patients and with the use of immune checkpoint blockade and local stereotactic radiosurgery.

01:51:16 This was a study that we did looking out outcome in this group of patients and what was very impressive is in a median overall survival in melanoma patients treated with brain radiation and PD-1 inhibitors in this series was greater than 4 years and for anybody that's treated melanoma with brain metastasis historically before the era of immune checkpoint blockade, the median survival was typically measured in months. I think these combination of treatments, while it might have toxicities, it certainly offers tremendous promise for our patients and so one thing that I've heard about is that sometimes people are concerned about toxicity and want to implement arbitrary time cutoffs between radiation and immune checkpoint blockade and I don't really think that's supported by the evidence, especially given the fact that some of these effects in the clinical activity of both radiation and immune checkpoint blockade can be long lived so holding immune checkpoint blockade for one or two weeks, I don't know is supported by any data.

01:52:18 I think some of the outstanding questions that exist is that there are fewer data still in regards to combinations in the definitive setting, for example in the definitive or larger field radiation and as we've heard already I think that's an area that's right for combination between radiation and immune checkpoint blockade and still I think there remains to be more data, more data is needed for the combination of immune checkpoint blockade and higher dose radiation or SPRT. Again, mainly for the on-radiation oncologists in the audience, you can see that all radiation is definitely not the same both in terms of dose and fractionation, but also in terms of the radiation treatment field. Here's a patient from our institution treated with lung SPRT in combination with the PD=1 inhibitor, you can see a small radiation field in another setting where we might want to incorporate immune checkpoint blockade with fractionated radiation and that's in Hodgkin's Lymphoma is shown here and you can see the radiation field is much larger. Parts of the heart and the lung are getting irradiated even with the more targeted fields that we use for Hodgkin's Lymphoma in the moderate era, you might still expect a different spectrum of toxicity. I also think that as more and more of the IO combinations and IO agents are being explored in the clinic, we need to look at potential toxicities of these combinations, so for example, CTLA-4, PD-1 inhibitors, CAR T cells, IDO inhibitors, other immuno checkpoint inhibitors and intratumoral immune therapies, I know that was mentioned yesterday as well. I think the challenges, and we can talk more about this in maybe a discussion period is that the time course of side effects can be delayed both with immunotherapy and radiation and I think that just speaks to the importance of multidisciplinary and extended follow up after initiating combined therapy with radiation immunotherapy and attribution of these side effects can be difficult. For example, pneumonitis and elevated liver function tests which can be caused by both radiation and immunotherapy. As an example of this, how might we start thinking about attributing toxicity, for example lung toxicity, which is a question that comes up? Again, I think it's important of following these patients, of integrating radiation oncology into collecting data upfront, because if you don't collect data about the radiation treatment field and the radiation dose, the fractionation, you may not have it in the context even of a prospective clinical trial so here is a patient that received focused stereotactic body radiotherapy, developed radiation induced lung injury over time and you can see it's, again, if you catch toxicity related to radiation early enough, it's generally localized within the radiation field, so if you collect this data, it goes a long way towards help attribute toxicity. In contrast, you can see the spectrum of radiographic manifestations of PD-1 inhibitor pneumonitis here, and although they can be quite variable, they're generally not localized in the same way that radiation pneumonitis is at least in the early stages.

01:55:21 To summarize, immunotherapy has unique toxicities, many of which overlap with potential radiation effects. Reassuringly initial data suggests that standard of care in experimental approaches that combine radiation immune checkpoint blockade are generally safe, but I still think more data are needed. Challenges moving forward include the lack of mechanistic understanding about why some of these autoimmune events occur, biomarkers that we can use to follow these or predict these events and the variability in time course with which side effects develop, a well as the rapid development of new drugs and therapies. How much we go about addressing some of these? Obviously I think we need to evaluate toxicity and randomize clinical trials that look at radiation immunotherapy combinations. Dr.[inaudible 01:56:10] mentions studies that we're doing, I think it's not just comparing radiation versus no radiation but also looking at the impact of radiation dose and field to try to get at the toxicities that might be increase with immunotherapy and radiation together.

01:56:24 I also think there's a big importance of collecting radiation data on these trials and also trying to use registries and databases to evaluate these sides of toxicities and rare side effects. Dr. Dickert briefly mentioned the e-ProPILOT, so we're trying to look at patient reported toxicities that we're trying to integrate on a study that I'm leading through the ETCTN, which combines Duralumin and tremeliumumab with or without low or high dose radiation and I think just from a clinical perspective, I just wanted to finish that even outside of a clinical context, I think it's more and more important for the multidisciplinary team to be educated regarding the side effects of immunotherapy and immunotherapy radiation combinations. I know that in my practice we see more and more of these patients in their early stage who have received neoadjuvant immunotherapy approaches or definitive immunotherapy approaches so it's important that not just medical oncologists, but radiation oncologists, nurses, the whole treatment team is aware of the potential of these toxicities because if we don't look for them, we're not always gonna find them. Thanks very much.

Crittenden: 01:57:36 Let's have the rest of the panel come up and if there's any specific questions for Jonathan while they're coming up, we can do that.

Sharabi: 01:57:49 For the rest of the panel discussion we have David Burman, Michael Yellin and Margaret Yu. So we're happy to have a number of industry-

Crittenden: 01:58:00 There's a chair, there's an extra one up there.

Crittenden: 01:58:02 Industry leaders. I guess we can start off with questions.

Speaker 4: 01:58:06 I have a question, I guess I'd start with Jonathan but really could be also a good question for the panel. Why should there be a local, selective, anti-cancer effect compared to a normal tissue effect? I mean we're all happy to hear there isn't toxicity but aren't all mechanisms that were discussed today, shouldn't they cause normal toxicity [inaudible 01:58:29] in the radiated field compared to the tumor?

Schoenfeld: 01:58:36 Sure, I think I can start, I don't know that I have the answer. I think that in general I would agree that some of the same mechanisms that could lead to an enhanced tumor effect could potentially lead to enhanced normal tissue toxicity. In fact, in the case of radio necrosis is that the fact that the tumor is responding better and those are the cases where you might be more prone to see radio necrosis. There are mechanisms of tolerance, obviously, and those might be more active in normal tissues in general than tumor cells. Also, as we are more and more targeted with radiation, obviously radiating less normal tissue might

partially contribute to minimizing the toxicity, but in general I think that's why it was so much of a question for us and why it's been reassuring that even though we might be seeing these enhancement of the local treatment in fact, I don't think that we can say that the evidence really shows an enhancement of a lot of the toxicities.

Speaker 5: 01:59:36 I was just gonna add, I think one of the other explanations could be, what was presented earlier by Mark about neo antigenicity versus normal antigens. Normal tissues don't have neoantigens so they're not going to induce a T Cell response. Perhaps a lot of the damage that is seen, perhaps a lot of the toxicity that's seen is due to innate immune damage, which is not affected by the checkpoint set lists.

Speaker 6: 02:00:02 I'd just like to touch on that, one important point that, the PD-1 PD-L1 agents they're not direct radio sensitizers. Obviously, in vitro if you add these agents they're not gonna directly radiosensitize due to DNA damage, they're not causing DNA damage, so they give us this paladin, which is a significant radiosensitizer and causing significant DNA damage, so recognizing that as far as safety. There's been actually thousands of patients now treated combined with palladive radiation on some prospective trials and across the board, there has not been any significant increase in high grade toxicities that we've observed. I think we have to train our residents and our trainees on the side effects, which can be serious, which can be very rapid and need to be addressed immediately, but at the same time, for us as a field I think we should really focus on efficacy and looking at the efficacy on points to see how we can best address those.

Speaker 5: 02:01:02 I'd just like to add one other point to that, in regards to immunotherapies and immunotherapy combination radiation, there's some recent evidence that stem cell compartments, maybe not so much the regenerative stem cell compartment, but the homeostatic maintenance stem cell compartment may be particularly evasive of the immune system due to down regulation of MHC, up regulation of NK inhibitory ligands so even when we ramp up some of our therapies against the cancer, it could be a few toxicities you may still stuffer, but perhaps ability to regenerate may be protected a bit due to the underlying biology.

Crittenden: 02:01:44 Okay, we'll just go in order so, when...

Speaker 7: 02:01:47 Thank you, I'd like to ask a question about the toxicities. Considering we know the radiation field, a lot of factors you just described affects the outcome and we need to collect data. How can we make sure the pharmacologists are not scared of these side effects and how to collect them knowing that they might not have the internal expertise in company? What is your advice that how they should tackle this issue and how can we help them to not get scared of radiation because of the side effects, but make sure that they do everything they can to make sure they get it, collect the right data in the right form?

Schoenfeld: 02:02:32 I can start it, I'd be curious to know that other people from industries' perspectives on this as well. I think overall in terms of not being scared, I think the existing data is very supportive that the combination now of radiation and immune checkpoint blockade is largely safe, I think that that's reassuring. In terms of toxicity I think just like on every trial and when you're combining two agents it's important to closely monitor for toxicity and I think collecting data to help us figure out why toxicity occurs is really important and I think sometimes there's a big question when you're designing these trials of what radiation dose to use, which is relevant and speaks to how you might see synergistic efficacy, but just as

important is making sure you collect data in regards to radiation, how much normal tissue is irradiated. You collect this in a prospective fashion with the ECRF forms so that they can go back and look at these questions and that you follow patients for toxicity for an extended period of time and that includes radiation toxicity and that you integrate multidisciplinary follow ups so you're looking not just for the immunologic side effects, but you're also looking for the radiation side effects and that involves continuing to have a multidisciplinary approach as these patients are followed.

Crittenden: 02:04:03 Does anybody from industry on the panel want to comment about that?

Yu: 02:04:07 Hi, it's Margaret Yu from Jansen. I agree with what you said. I think we collect the toxicities/radiation therapy just like we collect toxicities of other drugs that we're investigating, but I think within the industry we don't have that much expertise as far as radiation oncology goes and so we really count on our experts and academia to help us define what are the best areas to focus.

Speaker 5: 02:04:40 I would concur, I'd just take it back to the early days of Ippy when we went in the clinic, actually most physicians were afraid of using Ippy, and had trepidations about it, but there's a learning curve on both sides and I don't think industry is, at least from my limited standpoint, is put off be doing studies with radiotherapy because of toxicity and, as you said, we need to work together to understand what the potential toxicities are and how to follow them and how to manage them.

Crittenden: 02:05:19 Great, thanks. Let's go to number two.

Mason: 02:05:23 Hi, Sam Mason, reflection medical. Thank you for a really, really wonderful session; I thought it was really exciting and it's rare to have a panel like this up so I've had a million questions, but I know I can only get one. My question is about mechanisms of action. A lot of really exciting work that's been done clinically and now we're seeing proof points clinically on the abscopal effect and even the abscopal effect, and we also heard about the general concept of de bulking the disease and tumor burden and I was just curious about the panel's thoughts on which is kind of more important. Is it just removing more cancer is good and that's gonna help the systemic therapy and the patient do better? Versus how much are the immune effects are factoring in terms of the success of pacific study and the other ligo studies that Steve presented and others presented.

Speaker 5: 02:06:23 My thoughts on that, tumor de bulking is critical. Getting down to a minimal burden of disease, it actually comes down to a numbers game. You're looking at resistant clones that are emerging and clones that either lose antigen or lose MCH expression and have immune escape. Those cells would still be sensitive to DNA damaging agents and classical cancer treatments, so de bulking the disease, getting down to a small burden of disease can reduce immuno suppression and I think will increase the overall response rates as well.

Schoenfeld: 02:07:06 I think that we should separate out though that it does look like that, the patients who begin having low volumes of disease do better; however, I think it is the hypothesis that could we then convert patients into that state as almost a preconditioning one. Again, I want it to be true... I think it makes sense, not only in the IO space, but even if you look at some of the work with [inaudible 02:07:34] and EGFR, have like spot welding to actually keep people on the agents seems to be just as effective in terms of patterns of progression. Even in terms of patterns of progression on PD-1 there is a new [inaudible 02:07:51] paper out now or soon

showing that, again, in most of the lung cancer patients who progress really only progress in terms of limited sites and disease. I think it's clearly important upfront and I think it's sort of part of our model is to try to treat as much balky a disease as possible.

Crittenden: 02:08:17 Microphone 3... Sorry, oh do you-

Speaker 5: 02:08:19 I was gonna add, I think this gets to as what is the mechanism for radiation and the immune system and there are 3 hypotheses that I see. One is the tumor debalking, you can get that with chemotherapy plus IO, we know that works. The second is, what is the effect of radiation in the local tumor environment. And then the third is the boost prime. To me, the first two would really be a local tumor effect, and you wouldn't see abscopal 'cause it's mostly about what's happening to the irradiated site. The third one is about the systemic immunity, and I think we really need to understand that I was really happy to hear that there are some very good biomarket trials being done where there's going to be tumor biopsies before and after radiation so we can understand what's happening within the tumor-like environment. I would really like to try to encourage and urge that we need to study and interrogate the systemic immune system and the effect of radiation on neoantigens specific T cells to understand whether boosting priming really is an important mechanism. That's the short answer.

Crittenden: 02:09:33 Great. Microphone 3.

Speaker 8: 02:09:35 I have a very specific question, so a lot of the data present is with PD-1 and the brain radiation therapy, do you have any data for CTLA and PD-1 blockade [inaudible 02:09:45] is there... Do you see a higher signal and do you think there's a time point, whether the facts bring radiosurgery [inaudible 02:09:57]?

Schoenfeld: 02:10:00 As I pointed out, one of the limitations is more and more experience with anti PD-1 and radiation and CTLA-4 radiation, still some of the combinations is relatively less experienced. We do have more and more patients that are treated with combined checkpoint blockade and radiation to the brain and elsewhere. Certainly, I think we're all impressed by, without radiation, the high activity of the combination of CTLA-4 and the PD-1 blockade in intracranial matastacedes, that was recently presented, in terms of the toxicity, the combination with radiations. We have some patients that have received the combination and I don't think the numbers are high enough to really draw a lot of conclusions about that, at least in our experience.

Crittenden: 02:10:47 Microphone 1.

Neiha: 02:10:48 Hi, I'm Neiha, I'm a radiation oncologist from the University of Maryland. Basically just a clinician, not in the lab, but we're seeing a lot of patients on immunotherapy being offered radiation and there's so many trials out right now, some retrospective data as well, but do you guys have enough information now to create some suggested guidelines as we move forward, creating clinical trials to really define what is abscopal response? Because some of the studies are starting with radiation and immunotherapy at the same time so how are you gonna split up what is radiation related versus just immunotherapy, as well as the toxicity question, if we're talking about abscopal response, should we be worried about abscopal toxicity? Could radiating one site kind of initiate toxicity in another organ? Is there enough right now to kind of create guidelines as we analyze the results of current trials or create new trials?

Schoenfeld: 02:11:56 I think if we break your question down in terms of how should we quant itate your response, I think if we take some guided-

02:12:00 ... should we quantitate the response. I think if we take some guidance from CtIP and the NCI which is now supporting this, the idea is to use resist nonirradiated lesions and to aid prior, to define those. I think it makes sense. I think that there are other ways of quantitating and I don't think the resist response correlates well to the survival that we are seeing. But it is at least some common place to start. I think in terms of the toxicity, if you actually run these trials, the actual FDA has told us on all of these investigational agents that you have to assign the toxicity to the combined treatment. So that we are not even allowed to say, "Oh, this is probably from RT or this is probably from this." It is just to the treatment. In some ways that kind of simplifies it because you don't have to worry I think it's hard when you have these IO effects on the lung and you can have SB RT effects in the lung to then really differentiate what's causing it in the end in terms of the patient and safety, it doesn't really matter. So I think with the guidance from NCI and from the FDA, I would advocate that we should just follow that.

Crittenden: 02:13:26 Go ahead. Did you want to talk about-

Speaker 9: 02:13:27 I just wanted to comment that I think that when we're developing drugs that you look at radiation as another drug. As far as toxicities and efficacy, we're looking at what's happening to the whole patient. I think the abscopal effect is a nice explanation, but at the end of the day we need to see the responses happening overall.

Crittenden: 02:13:56 Microphone two.

Gardner: 02:13:58 Mark Gardner from OmniSeq. We're a diagnostic lab. My question is, at the end of last year, there was a publication that basically listed all the combination immune therapies that are out. It's now in the hundreds if not thousands. By far the leading candidate for combination CTLA4 and PD1 or anti PDL1, followed thereafter by chemo and so forth and so on. I guess my question is, these patients are coming in the context of having many, many many trial options. I'd be curious Dr. Chmura particularly, I like your idea of using some sort of biomarker selection to assign patients on to the various arms. Just as sort of a general question, should we be selecting patients who are more immune deserts or less immunogenic for specific cross-comparisons of chemo plus anti PD1 versus radiation therapy and anti PD1? Is that a rational hypothesis that should be tested and is that something that you're considering as part of your trial? Or others if they want to take that as well? If that was too long a question I apologize, but ...

Crittenden: 02:15:20 So, to summarize, is the biomarker that's going to distinguish who's gonna go into the radiation arm the lack of any signal, and should that be your signal.

Chmura: 02:15:30 Yes. Yes, exactly. So basically, yeah. I am really excited about the advice trial because of one, having access to these early stage agents will just encourage people to accrue quickly, which is good. And I think it really is then using SBRT as your seventh drug. It is the first time that we have done this. I think we have enough activity to actually say it is actually exciting. I think for some of the other combinations we have carved out specific areas. Like for the C4, Mozart trial, if in fact somebody has a metastases to the liver, we know that it responds poorly and the kind of major hypothesis is that it could be MTMC related. So basically all of those patients will be getting the anti CSF, which by itself seems to have some activity. I

have kind of moved past the idea of is this safe, because it seems really safe compared to just doing SBRT like 10 years ago it was far more dangerous and then far more interested into either the biomarker selection or in terms of actual patient selection, if in fact you can get that biopsy and know you have a bunch of M2 macrophages it makes a lot of sense to add a drug.

Speaker 5: 02:17:04 Could I just add to that. I completely support biomarker driven trials, but with radiation, I actually think that we need to be very cautious. The example I give is the Pacific Trial where we enrolled all comers, PL1 positive and negative prior, that's their status prior to CRT, but the benefit was seen regardless of whether they were PL1 positive or negative. I do think radiation, or CRT in this case, may be doing something to the tumor microenvironment. In fact, that's the reason I'm so excited about radiation, is because I do think it can modulate the local tumor microenvironment. So I completely support biomarkers, I just think we have to be very careful because of the promise of radiation in modulating the TME.

Sharabi: 02:17:51 I completely agree and I think we focus a lot on the antigen presentation and induction of the T cells. But recognizing that radiation can also help to complete that immune cycle by helping to induce a T-cell infiltrate. I think that's another key step, which may be a critical part in how radiation may function in this setting.

Crittenden: 02:18:12 Great. Microphone three.

Harari: 02:18:14 Paul Harari, Wisconsin. Terrific panel. Question for any of you. The capacity now of radiation to target multiple lesions. We have the ability now to selectively irradiate with pretty minimal toxicity three, four, five, six lesions in several ways. One, with directed stereotactic type body radiation, another with targeted molecular nuclides that can uptake selectively in the tumor. Any comments or thoughts about the benefit of that approach where we could actually address all the macroscopic gross tumor with radiation?

Chmura: 02:19:00 Yeah, I am actually a huge supporter of this. I think Jim Welsh would agree. I think if we really think about oligometastases we actually defined it because we could. It was something that we could treat right? But even treating for isocenters you have, like, physicists just hate me. I am just hated. So basically, our goal, and we are working on this, is to eliminate them. If in fact we could get good computer planning to actually try to do this and to use all of these data we are collecting in terms of low volume to organs and everything else. I think it is a good hypothesis to say again, could we debulk and render the patient almost to the microscopic state? Because even if you don't effect T cells, if we just know you have x amount of good T cells functioning because so many are anergic from having this bulky disease, if we could just take that and just change that ratio, it may be the true abscopal effect. It is just allowing our agents to work better. So I am excited about it, I am working on it. I think there are companies out there who are starting to see the possibilities.

Speaker 10: 02:20:30 Let's see more of those trials.

Sharabi: 02:20:30 If I could just echo that, I think also from patient perspe- it's just a lot of logistical challenges. We had one of those trials that allows up to five lesions irradiated with SBRT and then we have to start to overcome talking both from a radiation planning perspective and also a treatment perspective, it takes up-

Chmura: 02:20:50 Delivery perspective.

Sharabi: 02:20:51 ... delivery perspective it takes up a huge amount of patient time and machine time to treat these patients.

Chmura: 02:20:57 Takes hours. Just cannot take hours. It cannot take two physicists a week to actually give me this 8 isocenter plan.

Speaker 5: 02:21:07 I would also maybe comment a little bit about ... I completely agree with my colleagues although logistically it maybe difficult, there are challenges. The biology behind the potential benefit of maximal cytoreduction I think it quite striking. The reason why Alex Wong and John Wary in that Nature publication decided to look at the ratio between reactivation of T cells or reinvigoration of exhausted T cells and overall tumor burden is because fundamentally they are immunologists and also virologists and they fully appreciate that, at least in the field of virology, antigen load has a profound impact on whether or not you can mount an effective immune response versus whether or not T cells end up exhausting. The one difference between a chronic viral infection versus acute infection, the latter being cured and the former persisting is oftentimes just attributed to the initial antigen load.

02:22:08 I don't think it's necessarily true, however, that, that's all radiation is doing, debulking. There is evidence from our lab, so Vermente's lab I'm sure others as well, Sandra Demario's lab, that you can uncouple the debulking effect from the immunogenic effect of radiation. So there is a lot to the pathways that radiation is also activating in addition to a cytoreductive role. To the extent possible clinically, I think maximal cytoreducing, even in carrying some of these studies into the definitive setting I think will have, it makes a lot of sense from the biology point of view.

Sharabi: 02:22:51 I think we're running into the break. Maybe take one more question.

Walker: 02:22:55 No, we're in the break, sorry. And this is a question really targeted towards the folks from industry we have on the panel. So I think a lot of us in radiation oncology think oh, we've heard this alluded to just a moment ago, they're afraid of using radiation in a clinical trial for registration. We see a lot of these trials are investigator initiated. We also heard that well, safety is really not a concern we're aware of, this retrospective and prospective data that was presented, it's relatively safe. And now we have the Pacific Trial. My question is really, and then this is broad but take a stab at it if you want, but if there are barriers to having you think about radiation in terms of registrational trial. Can you articulate some of those or is really the time is right now and we are moving forward? If we could get your thoughts on that, that'd be great.

Speaker 11: 02:23:39 So I work in the prostate cancer area. We actually have a company sponsored phase three registration study combining hormone therapy with primary definitive radiation therapy.

Speaker 12: 02:23:51 Do you have any immunotherapy?

Speaker 11: 02:23:56 No, we are thinking about doing one, because for us, relative to the other big Pharma, I think we are relatively new to the IO area. It is certainly something that we are thinking about as well.

Sharabi: 02:24:13 Mike, go ahead.

Chmura: 02:24:15 Well, I was just gonna say that for a long time there hasn't been great evidence about the combination of radiotherapy and immunotherapy and now we're coming into that era where we are having more studies showing a benefit. So it think there's more, it's higher on the radar screen now and there's gonna be at least better rationale for moving forward in combinations within immunotherapy. I think the data is pretty clear now. It's just taken a long time to get there.

Speaker 5: 02:24:52 I would just add quickly that I think in tumors that are sensitive to immunotherapies, you are gonna see a plethora of radiation trials coming out of the Pacific. I think the major challenge as you ask, I think no one's concerned about safety. The major challenge that I've seen, so AstraZeneca and MedImmune for transparency, is that there are so many different types of chemoradiotherapies, there's sequential, and it differs whether it's U.S. or Asia, so it's dealing with that variability that can be somewhat of a limitation in it. I guess we never got to that discussion here. The other area that I wanted to touch on is, are the tumors that have historically not been sensitive to immunotherapies and the one that jumps out is colorectal cancer. If you look at the median number of tumor mutations per megabase, colorectal, which is historically insensitive to immunotherapy has the same as other tumors that are sensitive. Like, HCC is a classic one. No one knows why.

02:25:55 Colorectal is another example where if you could incorporate maybe a chemoradiation therapy approach might be helpful in a tumor like colorectal. So I think those are the two points that I'll leave you with.

Sharabi: 02:26:10 So I think that will conclude our session. Thank you all very much for the wonderful speakers and panel. We will return back in about 10 minutes, 10:35 to start the next session. Thank you all.

Crittenden: 02:26:19 Thank you.

T. Lawrence: 02:26:37 Okay everybody. I know everyone is just too excited about immunotherapy to sit still, but I think it's time for us to reconvene so to try to stay close to on time for a packed and exciting program. So I'm going to turn session four over to Esther Hammond to introduce the next speakers.

Hammond: 02:27:01 Welcome everyone back to session four where we will be talking about other targeted therapies, although I suspect immunotherapy will still creep in. We're gonna start with Kyle Cuneo from the University of Michigan.

Cuneo: 02:27:27 Good morning everyone. My name is Kyle Cuneo. I'm a radiation oncologist at the University of Michigan. First off, I'd like to thank the organizers for inviting me to speak. This has really been a fantastic workshop. I have learned quite a lot over the last day-and-a-half. Today we will be talking about combining chemoradiation with novel kinase inhibitors and I'm really gonna focus on the studies that have been performed to date. Many of these focus on EGFR inhibitors and then we'll have some discussion about why some of these studies may not have been as successful as they could have been, and different ways we can do to improve future clinical trials. Here are my disclosures.

02:28:05 So chemoradiation therapy is standard of care for most locally advanced cancers. We use it in many different settings for diseases like anal cancer or head and neck cancer. We use it as definitive therapy and it also gives us an opportunity for organ preservation. Other diseases like rectal cancer it is predominately used as a neoadjuvant or adjuvant setting. There are several potential areas for improvement. Obviously improving cure rates of our patients should be the number one goal. But secondary areas could include organ preservation. This is very important for diseases like rectal cancer where nonoperative approaches are becoming more prevalent. And also, novel therapies can be combined with chemoradiation in order to reduce toxicity through potentially de-escalating either the concurrent chemotherapy or the radiation dose.

02:28:51 This is a timeline from a review article that Ted published with others and JCO four years ago showing the development of chemoradiation regimens. I find this very fascinating because the two first agents developed are still the predominant agents that we use with radiation therapy to treat most locally advanced cancers. And very little advances have happened over the past two to three decades. The one exception is cetuximab, the only targeted therapy that's been approved for combination with radiation therapy. So there is really a great opportunity for us to use all these advances in biomedical sciences and all in these drugs that have been shown to be effective in the metastatic setting to combine with chemoradiation to improve outcomes for our patients with locally advanced disease.

02:29:38 5-FU is the backbone of chemoradiation regimens for most gastrointestinal cancers. This drug was first synthesized in the 1950's and the mechanism of radiation sensitization is fairly well understood. 5-FU is converted to a number of metabolites within the cell. FDUMP inhibits thymidylate synthase and this is its main mechanism of action and has several downstream affects including decreased TTP levels leading to inhibition of DNA synthesis and accumulation in early S phase. This is the predominate metabolite felt to be responsible for radiation sensitization. 5-FU also is converted to FDUTP which misincorporates into DNA and initiates a futile repair cycle.

02:30:27 Cisplatin has been around for well over a century and was first licensed for medical use in the 1970's. This drug interferes with DNA replication, it cross-links DNA. However, the mechanism of radiation sensitization is not fully understood despite us using this drug in combination with radiation for over 20 years.

02:30:48 So there are several strategies that are being investigated to improve chemoradiation therapy using targeted therapies. As mentioned before the predominant focus in many of these studies, at least the studies that have gone to stage three, have been with EGFR inhibitors, and a lot of this was based off the original work in head and neck cancer. But obviously there are several other signal transduction pathways that are very important and this is by no means an inclusive list.

02:31:13 Cell cycle checkpoints also are very attractive targets, Meredith Morgan will talk about this more in the talk following mine. We've heard several great talks this morning and yesterday in immunotherapy and it's potential to alter the microenvironment and work with radiation to improve patient outcomes. And also VEGF and VEGFR inhibitors have also been extensively studied in combination with chemoradiation for locally advanced disease.

02:31:40 So, we've seen a slide like this several times over the last two days. Obviously this is a very important study. This is a study by Dr. Bonner et. Al., looking at the use of cetuximab adding to standard radiation therapy for patients with locally advanced head and neck cancer. Cetuximab is the only agent that's been approved with radiation, or the only novel targeted agent. This study showed a survival benefit from The Lancet Oncology, this is the 10-year update. So with time the survival benefit persisted and this was obviously a very effective therapy for patients. Around the time this study was published, the standard of care for head and neck cancers were switched from radiation therapy alone to chemoradiation, so the next logical step was to combine cetuximab with chemoradiation therapy in head and neck cancer patients. This was done in RTOG 0522.

02:32:36 Unfortunately, this study was a negative trial with no benefits seen in terms of overall survival in the patients receiving cetuximab and these patients had increased toxicity. A number of other phase two studies, here I list some of the randomized phase two trials, have looked at combining EGFR inhibitors, either cetuximab or panitumumab with radiation and chemotherapy. These studies have largely showed the same results that were found in RTOG 0522 with minimal impact on patient outcomes. None of these studies had a significant improvement or progression in overall survival. Many of these studies also showed increased toxicity with the combination. So really the question is, why is this the case and are there things that we can do to incorporate these agents better using better preclinical models or investigating these more rigorously in early phase testing? Moving on to nonsmall cell lung cancer. This is another disease site where target therapies have been investigated in a number of clinical trials, the most notable one being R2G0617. This study is probably better known for its dose question, which showed no benefit for dose escalation, actually a detriment but the study also looked at incorporating cetuximab and standard chemoradiation therapy for patients with nonsmall cell lung cancer. When they analyzed all patients on the study, there was no benefit at all with the addition of cetuximab similar to what we saw in R2GO522 but interestingly, in about a quarter of patients, they had tumor tissue unable to determine EGFR expression. And what they found in this limited subset was that patients with high EGFR expression appeared to have an overall survival benefit with the addition of cetuximab to standard chemoradiation suggesting that patient selection is potentially very important in designing these studies and selecting patients for clinical trials.

A few other phase two studies have looked at combining EGFR inhibitors with chemoradiation in nonsmall cell lung cancer and similar to R2GO617, these studies have shown no improvement in overall survival or long terms outcomes in patients, and many of these studies have shown increased toxicity with the combination therapy.

02:34:53 So rectal cancer is a very interesting, very attractive disease to study target therapies in. In this disease we treat most patients prior to surgery, so we can get very early readouts in terms of their complete response rates as a surrogate end point. Additionally, nonoperative approaches are now actively being studied. If we could develop therapies that could improve the complete response rates, many more patients might be eligible for this approach.

02:35:18 Here I'm just gonna highlight a couple of phase two studies looking at using EGFR inhibition with chemoradiation in rectal cancer. These are both randomized trials. The study by U.S. Oncology was about 100 patient study. This used standard chemoradiation with 5-FU plus or minus cetuximab. What they found was that there was no improvement in complete response rate, response rates, or overall survival. Additionally, the addition of cetuximab with chemoradiation resulted in increased toxicity including diarrhea and rash formation.

02:35:51 The X proC trial was a little bit different in that they specifically looked at patients with KRAS, BRAF wild type rectal cancers. We know that mutations in these pathways are associated with resistance to EGFR inhibition, and it should be noted that this trial technically was a negative study. Their primary end point was negative. But their secondary end points of radiographic response and overall survival were positive in patients receiving cetuximab versus standard therapy with capsaicin radiation alone. So again highlighting the need for patient selection when designing future clinical trials testing targeted agents, especially ones where we have a good idea of what could predict resistance and response.

02:36:33 This is a table from a review article we wrote a couple of years ago looking at EGFR response and different factors associated with sensitivity and resistance in head and neck cancer, lung cancer and colorectal cancer. What's very fascinating when putting this table together was that there was quite a wide variety of factors. It's very much disease specific in what predicts response. So probably these are best characterized in nonsmall cell lung cancer where we know there is a number of specific EGFR mutations that confer both sensitivity and resistance to small molecule inhibitors. A number of drugs have been developed based off this concept. Additionally, we know that KRAS mutations in addition to a number of other single transduction pathways, are associated with resistance to EGFR inhibitors. Using this information for future clinical trial design will be vital in order to have successful trials and identify patients who are going to most likely benefit from these therapies.

02:37:33 Next, I wanted to shift over to the importance of scheduling of chemoradiation with targeting therapies. Anyone who's tested novel agents in a laboratory setting is well aware that the scheduling effects radiosensitivity quite a bit. This is one of the first things we look at when we are testing a new agent. Once we find out the appropriate dose to use for radiosensitization, then we have to figure out how to give it, in what sequence. This is just an unpublished piece of data I just am currently working on that I just pulled. I've seen the same effect in many other drugs I've looked at. This is looking at Crizotinib in three different colorectal cancer cell lines. This is the exact same dose of Crizotinib given at three different schedules. And these are the Clonogenic survival curves. We can see that our dose enhancement ratios with certain schedules are very minimal. Whereas if we give the drug

differently with different schedules, we can see very strong sensitization with this single agent alone. This is very important to keep in mind when designing clinical trials.

02:38:35 It's quite difficult to model scheduling what we give in patients in animal models. Obviously in patients, routine is most of the patients get five to seven weeks of daily radiation, often with daily chemotherapy. And that is just not feasible to do in a mouse study. But there is definitely a need of having a proved preclinical models so that we have a better understanding of the optimal scheduling and sequencing of drugs. In that way, we could potentially avoid a suboptimal sequencing, which may lead to missed opportunities for patients and may lead to drugs, which otherwise may be very effective being shown to not be effective and not receiving approval.

02:39:18 This is a figure from a review article we published a couple of years ago, specifically looking at sequencing cetuximab and chemoradiation. This is very theoretical, but this is following the schema on R2OG0522. Many of these studies with cetuximab have used this loading dose and then gave cetuximab weekly during radiation and then cisplatin given every three weeks. There are several positive effects from EGFR inhibition. It blocks repopulation, it can inhibit radiation induced signaling pathways. It can attenuate DNA repair. But there are also negative effects.

02:39:52 One of the more important ones, and this has been shown in multiple preclinical models is that EGFR inhibition can actually antagonize cytotoxic chemotherapy based on the way it is scheduled. Part of this is related to it induced a G1 arrest. So certain chemotherapy agents that are reliant on certain phases of cell cycle like 5-FU, if the cell is arrested in G1, then it may not be as effective. It may not be able to reach its full potential. Also EGFR inhibition can block cell cycle redistribution. This can prevent cells from reaching the more sensitive phases of the cell cycle. There is a number of complicated resistant mechanisms that are just being elucidated currently.

02:40:34 So we came up with some potential thoughts about how potentially we could improve the scheduling issues with EGFR inhibition with chemoradiation. One thing would be simply, what if we got rid of the loading dose and gave cetuximab after chemotherapy. Again, this would have to be tested in patients to confirm whether or not this would be effective but perhaps, this could avoid some of the negative effects that we had seen before.

02:41:01 Also drugs like cetuximab have a relatively long half life. And perhaps using EGFR inhibitors with shorter half lives that are dosed multiple times a day or have dosing that we can better control with radiation might be more beneficial in order to optimize chemoradiation combinations with novel targeted agents.

02:41:21 I just briefly have one quick slide on VEGF inhibition. VEGF inhibitors have been combined with radiation in a number of studies. In rectal cancers there's been a least 14 phase two studies reporting rectal cancer, and these have been mainly underwhelming in terms of their complete response rate. It just really hasn't seemed to be any better than what we were just having with standard therapy. Additionally, many of these studies are showing concern for increased postoperative complications. The main reason why I wanted to talk about the VEGF is because there was this very interesting study that was published from Italy. Probably many people aren't familiar with this. This was published in Oncotarget 2015. This is one of the few examples that I know of where investigators actually have looked at

the effect of scheduling on an outcome in patients receiving chemoradiation with a novel targeted agent.

02:42:07 In this scenario, these are patients with rectal receiving chemoradiation regimen. What these investigators found was that with schedule A where they gave Bevacizumab prior to radiation and then on day 1, 1529, they only had a complete response rate of 12% versus schedule B where they moved it up 10 days. They had a complete response rate of 50%. Again, it is a small study but this shows the point that scheduling potentially has a huge impact on the overall success of a trial. There is definitely a need for improved preclinical testing to optimize scheduling of targeted therapies with chemoradiation. Additionally, there's a need, a potential need, for running early phase trials where we look at different scheduling regimens based off preclinical data to try and optimize these regimens prior to moving into the larger phase two and three confirmatory studies.

02:43:01 So in conclusion, chemoradiation regimens have evolved very slowly since they have been introduced. Novel targeted therapies give us a great opportunity to really improve patient care, specifically patients with locally advanced cancers. Our previous studies have been limited by potentially by scheduling issues, but also by patient selection. Obviously, optimizing these is going to be essentially for success, but we need improved preclinical models and understanding of how chemotherapy interacts with targeted therapy and radiation. And also, we need continued biomarker development, and we need to use this information to select patients for studies in the future.

Cuneo: 02:43:43 Thank you.

Hammond: 02:43:43 Do you have any questions?

Speaker 1: 02:43:56 So thank you. Based on the work that Quynh Le has led as head of the Head and Neck Group at NRG Oncology, Joanne Weidhass of UCLA has been looking at germ line mutations of a KRAS variant and has shown in 0522 that if you have that KRAS variant, so that trial didn't show a benefit to cetuximab and the chemoradiation space randomized trial, but once you segregated those patients who had the KRAS variant versus those who didn't, it was a significant difference in outcome. So, we have a couple of other stories that are coming out in NRG Oncology on that KRAS variant. 0617 which you, the slide you showed, so there's gonna be a similar story that we are putting together. Also that it shows that this KRAS variant really trumps everything else in terms of response to cetuximab.

02:44:57 I think there's both tumor issues and then there's these germ line issues that can impact on response

02:45:00 ... There's these germ line issues that can impact on response to these core targeted therapies.

Cuneo: 02:45:06 Right, that's great point and its very exciting that we have opportunities now to take information from these studies that maybe weren't successful and now find out which patients may benefit and then potentially design new studies specifically enrich our patient population.

02:45:23 Obviously, with targeted therapies each tumor is different and we know from the metastatic setting that not all tumors respond the same and as we obtain more and more information

on biomarkers, really the feel is gonna change quite a bit in the way that drugs are approved with radiation, is gonna be dramatically ultra cultured because of these information that is coming out.

Speaker 2: 02:45:44 I have a question about your hypothesis regarding Cetuximab and Cisplatin sequencing because there's actually phase three minimized trial and patient in metastatic setting. The extreme trial when Cetuximab is adding to a Cisplatin based regimen there was an improved survival. That's why it moved us into an earlier setting with chemo-radiation and that didn't work. The question is, is that the radiation? Is it the Cisplatin, is it the combination of both?

Cuneo: 02:46:10 I don't think we fully know. I think the radiation, obviously, plays very big role in that and we know that Cetuximab potentially by inducing cell cycle arrest may make the effects of radiation, what would affect redistribution, which would make cells less sensitive to radiation. These are really questions that need to be investigated more rigorously in pre-clinical models and in potentially in early phase studies to see if we can optimize the proper sequencing and figure out why these prior studies, when we combine a targedation with chemo therapy are successful in a metastatic setting, but why we're not seeing that benefit in radiation.

02:46:54 It seems like we don't really have that information yet. Obviously, that's a huge area where we need to improve upon.

Hammond: 02:47:02 Okay, thank you.

02:47:13 Next up we have Meredith Morgan from the University of Michigan.

Morgan: 02:47:30 Good morning. So, first I'll begin by disclosing that I'm a biologist. So the main mission of mine ... Not alone ... The main mission of my laboratory is really to develop experimental strategies for sensitizing tumors to standard of care chemo-radiation therapy.

02:47:59 My real disclosure is I have research funding from AstraZeneca and I will not discuss any off label uses. So, what I'd like to cover today is to begin by explaining the rational for our almost exclusive focus on DNA damage response inhibitors and then to go through three different promising strategies that we're currently pursuing in the laboratory as concepts for combining DNA damage response inhibitors with radiation. Giving you both clinical and pre-clinical examples of each of these.

02:48:37 The first of all will be sharing our clinical experience in pancreatic cancer combining DNA damage response inhibitors with chemo-radiation therapy. Then the strategy of combining DNA damage response inhibitors with each other and radiation, with the idea that we might be able to to replace standard cytotoxic chemo therapy with strategic combinations of these agents.

02:49:07 Finally, a less mature and newer idea for a DNA damage response laboratory, is the concept of using DNA damage response pharmacological inhibitors with radiation to convert poorly immunogenic tumors that are not responsive to immunotherapy to more immunogenic and potential responsive therapies.

02:49:34 This doesn't really need much of an introduction, radiation is the most prescribed of any single cancer treatment modality and as David mentioned in his talk, it's responsible for

contributing to approximately 40% of all cancer cures. In the last 20 years we've seen major technological advancements in our ability to deliver high dose radiation to tumors while sparing normal tissues and this radiation is given, as Kyle mentioned with concurrent, in many cases, with concurrent full dose chemo therapy.

02:50:12 Chemo-radiation is generally already escalated to maximum tolerated doses and in order to further improve upon this, what we need is tumor cell selective agents that can enhance chemo-radiation therapy efficacy. Why the DNA damage response? It has a lot to do with the biology of chemo-radiation. DNA is the principle target of the radiation and we know radiation induced cell death is caused by un-repaired DNA damage, DNA double strand breaks.

02:50:45 We know pre-clinically if we inhibit the DNA damage response we can enhance the efficacy of radiation and chemo-radiation therapy and that this suggests great promise clinically in targeting this to improve locally advanced cancers.

02:51:02 The DNA damage response refers to a collection of related but distinct cellular processes, so in response to DNA damage cells will stop proliferating so this allows time for DNA repair. They pause DNA synthesis temporarily, blocking origin firing so as not to replicate on a damaged DNA template and they initiate the physical DNA repair process, which repairs thousands of single strand breaks and fewer, but the more critical double strand breaks.

02:51:40 The proteins that modulate these pathways have become very important drug targets in the last five to ten years and there's been this explosion of agents. Many agents for a given target and agents targeting a variety of these proteins. This is not an inclusive list, but simply the ones that are in clinical development or in the case of PARP inhibitors already approved now.

02:52:08 Treatment with these agents in combination with radiation causes cells to keep proliferating in the cell cycle, despite having DNA damage, causes cells to get elevated levels of replication stress and not be able to properly manage those and to have persistent DNA damage. All of which leads to tumor cell killing in response to radiation.

02:52:37 One of the common concerns for these agents ... Looks different than it did this morning. Is what effect they have on normal cells. The tumor cell selectivity is really based on the mutations in tumor cells that cause them to have elevated levels of replication, stress, and DNA damage, which are vulnerabilities that can be exploited with agents that target other DNA damage response pathways. So this is clinically validated with PARP inhibitors and BRCA mutant cancers.

02:53:13 Now we see a merging ... Many other combinations of specific mutations, like APOBEC mutational signatures conferring sensitivity to ATR inhibitors. These are emerging. The interesting thing about radiation in this context is that it can induce DNA damage, specifically in tumor cells. Conferring sensitivity to DNA damage response inhibitors in tumor cells that may not have well defined, BRCA or APOBEC mutational signatures.

02:53:48 The inclusion of radiation can really broaden the applicability of this important class of agents. The first strategy that I want to talk about is incorporating DNA damage response inhibitors with standard of care chemo-radiation therapy.

02:54:06 One of the features of this strategy is that many of these inhibitors are able to simultaneously sensitize to chemo therapy as well as the radiation therapy, which translated to a patient, means that we may be able to improve both systemic and local disease control.

02:54:28 In contrast to monotherapy, as sensitizers, these agents are often effective at lower doses and somewhat surprising, given the maturity of PARP inhibitors, one of the inhibitors that we're seeing most extensively studied in early clinical trials is the Wee1 kinase inhibitor, AZD1775. There are a number of clinical trials ongoing now with chemo-radiation and I'll share our experience in pancreatic cancer.

02:54:59 The median survival in locally advanced pancreatic cancer is approximately one year and Gemcitabine radiation is a standard therapy and this is a disease, despite being called locally advanced, the consensus is the majority of these patients have microscopic metastatic disease. Both systemic and local disease control are equally important in this patient population.

02:55:27 I'm skipping over years and years of preclinical data that were generated to support this clinical trial in which we integrated a Wee1 kinase inhibitor with Gemcitabine and radiation in locally advanced pancreatic cancer patients. This trial was led by Ted Lawrence and Kyle Cuneo. It's a 36 patient trial. It's a dose escalation study. The primary objective is to determine the dose and the toxicity of AZD1775. It's been begin given on a standard backbone of Gemcitabine radiation and using a time to event continual reassessment model to assign patients to one of five dose levels.

02:56:13 This is an example of one of our patients. A patient that responded very well to the therapy. Over on the left this is the patient being presented at our pancreatic tumor board with a surgically un-receptable but not metastatic locally advanced adenocarcinoma of the pancreas. The patient was eligible for our trial, was treated and six months later had a radically reduced tumor, which allowed this patient to go on and have a surgical resection. This patient is still alive two and a half years later after treatment. That's a single patient.

02:56:54 These data are representing the median overall survival of the first 25 patients with follow up data in this trial. The median overall survival for the patients is approximately 23 months and that's compared to historical controls and these historical controls our patients that were treated at our institution with the same gemcitabine radiation that we're using in the experimental treatment group where the median overall survival is 11 months. So these data are still preliminary, but very promising in pancreatic cancer, where the last two FDA approved strategies for metastatic pancreatic cancer were approved on the basis of median overall survival improvements of two to four months.

02:57:44 As a biologist it's great to see your data go to a clinical trial, but then you have to figure out what to do next. One of the things that we became interested in was strategic combinations of DNA damage response inhibitors with radiation. It's true and not surprising that when we combine multiple DNA damage response inhibitors that we can induce profound radiosensitization in tumor cells.

02:58:11 What's more interesting is that it's really only certain combinations in the absence of radiation that are able to produce synergistic cyto toxicity in tumor cells. In an effort to try to develop a strategy where we could alleviate the need for cytotoxic chemotherapy and chemoradiation regimens, we really are looking for combinations of DNA damage response

inhibitors that house that synergistic cyto toxicity as well as radio- sensitizing activity that might confer when translated to patients both systemic and local disease control benefits.

02:58:53 Some of these combinations are actually antagonistic, so not advisable. The first combination that we became interested in was a combination of the Wee1 kinase inhibitor and the PARP inhibitor. And PARP related to mechanistic studies that showed Wee1 kinase inhibitors could also inhibit homologous recombination repair and thus, we reason, potentially would be able to sensitize otherwise resistant cells to alapropisty therapy.

02:59:28 Over on the right, the combination is no surprise, induces a lot of radiosensitization. That's the purple line down here, so it's a big radiation enhancement ratio with the combination that's more than either agent alone. What was somewhat disappointing is that if we just look at cyto toxicity in the absence of radiation, this combination was not particularly effective. The cells were very resistant to alapropive and combining with the Wee1 inhibitor didn't have any real synergistic activity there.

03:00:08 In other mechanistic studies we identified replication stress as being a very important target of this category of agents and so we reasoned that ATR inhibitors which have a much more direct effect on DNA replication, than a Wee1 kinase inhibitor, might be advantageous in terms of being able, not just to run radio-sensitize, but also to overcome primary resistance to PARP inhibitors in HR proficient pancreatic cancer cells which are shown over on the left hand side.

03:00:45 These cells are very resistant to alapopive, micromolar concentrations here really have no effect. When given in combination with ATR inhibitors, we see dramatic sensitization to the PARP inhibitors, and I'll point out, this is on a long scale here, so the magnitude of this is pretty impressive, suggesting that ATR inhibitors can overcome PARP inhibitor resistance in the absence of radiation therapy.

03:01:17 This is also true in HR deficient pancreatic cancers.

03:01:25 Likewise, if we look at radiosensitization by this combination, it's no surprise that there's a lot of radiosensitization in either homologous recombination repair, proficient or deficient pancreatic cancers. Based on the synergistic cyto toxicity and the radio- sensitizing potential of this combination, we think this is a strategy that might be useful to carry forward into pancreatic cancer patients, where we're trying to treat both local and systemic disease. There are a number of clinical trials under way now in the absence of radiation. Looking at combinations of these agents. ATR with PARP inhibitors, even the Wee1 with the PARP inhibitor and I think that these trials will set us, once they're mature, will set us up for future studies to be able to learn from these early clinical trials and integrate radiation.

03:02:27 Last strategy that I want to cover is, using DNA damage response inhibitors in combination with radiation as sensitizers to immune checkpoint therapy. It's already been mentioned during this meeting that radiation, by inducing DNA damage can cause the release of DNA, either in the form of single stranded DNA or double stranded DNA, or even micro-nuclei into the cytoplasm of cells, activating this innate immune pathway, which is developmentally a pathway that exists to fight off viral infections, but also in tumor cells can recognize DNA as foreign.

03:03:17 The idea is that inhibitors of the DNA damage response may be able to enhance this damage DNA in the cytoplasm and increase immunity in tumor cells and potentially synergize with immune checkpoint therapy. This is early work from my laboratory, not published and still ongoing, where we looked at the ability of DNA damage response inhibitors to activate this innate immune pathway and interfere on response. Measured by phosphorylation of TBK 1, which is a readout of the Cgas sting pathway, and by phosphorylation of stat 1.

03:04:01 DNA damage response inhibition causes a little effect, likewise radiation only combined DNA damage response inhibitor with radiation. We see enhanced activation of these pathways. This is not just true for this example of HR defective pancreatic cells, but is also true of HR proficient pancreatic cancer cells and mirroring pancreatic tumor models. The DNA damage response checkpoint therapies are being investigated clinically in the absence of radiation. There are ongoing trials looking at PDL1 inhibitors with ATR inhibitors, PARP inhibitors, Wee1 inhibitors ... I would point out that I don't think all DNA damage response inhibitors will be equal here. Some of them actually may be antagonistic.

03:04:54 For example, the DNA PK inhibitor that came from the work of the PEN group that was already mentioned today, DNA PK inhibitors may be antagonistic because even though they cause an increase in DNA damage, they lead to self cycle arrest and can prevent the formation of these immunogenic micro nuclei.

03:05:15 Again, integration of radiation will be important in future studies. Looking to the future, I first think it's important to consider where we've been. When I first started in this field, it was almost impossible to get pharma to give me a experimental agent to use as a radio-sensitizer, even pre clinically. That is changing now. Partly attributable to DNA damage response inhibitors but also immuno-oncology agents. Now, we have pharma companies coming to use for collaborations.

03:05:50 I think that the advancement of these DNA damage response inhibitor combinations with radiation, it's gonna happen naturally as treatment for metastatic cancer improves.

03:06:05 The next most important issue is how do we better control the local tumor? These strategies will be important. Then I have to mention the biology. I just think it makes perfect sense to combine DNA damage response inhibitors with radiation or chemoradiation and so I think the biology demands these combinations.

03:06:25 Finally, I think the most potentially ... The greatest potential for success in getting a DNA damage response inhibitor approved in combination with radiation lies in combining with standard of care, like the clinical data that I showed you from our experience, but still, there are a lot of obstacles to face there in getting to later stage clinical trials. Even when we have promising early clinical data.

03:06:56 With that, I'll end. I'd like to acknowledge Ted and Kyle who ran the clinical trial and AstraZeneca who've been great collaborators to us and the NCI, we are now a U01 site charged with the task I described here, of developing Cgas DNA damage response inhibitors to sensitize to chemoradiation for next generation clinical trials.

03:07:23 Thank you.

Speaker 3: 03:07:29 So, I'm sorry, I'm gonna ask an immunologic question.

Morgan: 03:07:32 Oh no.

Speaker 3: 03:07:34 Your sim works very nice and obviously you have an interest in pancreatic cancer. We looked at Sting expression and pancreatic tumors it wasn't very high. Now Cgas and signaling can go through other pathways than Sting as a activator of cytokines, have you looked at whether or not most of the tumors you'd be looking at or are you gonna use Sting as a prerequisite or do you think other pathways may be involved?

Morgan: 03:08:05 No, one of the very first things we did was we actually started out with the wrong models because they didn't have Sting intact. In contrast to some of the colorectal cancer models, we looked at where Sting was not expressed in any of them. Not every pancreatic cancer, but a majority of the pancreatic cancer models we looked at had Cgas expressions and had Sting expression and another criteria that we used was to look for those models where radiation could activate the pathway.

Speaker 3: 03:08:43 Thanks.

Lacha: 03:08:46 Benjamin Lacha, Princess Marvin, Dr. Morgan, thank you so much for that talk and the overview and all the exciting work that's happening in your laboratory. I'm gonna ask a PARP inhibitor question.

Morgan: 03:08:54 Okay, easier, I hope.

Lacha: 03:08:57 Particularly in combination with radiation, as we know there's a couple mechanisms at play here in just inhibiting the catalytic function of it, but also the PARP trapping mechanism, poison, and polar race as described by Youth Premier just a few blocks north of here.

03:09:13 I guess, have you observed any differences on terms of radiosensitization between the different agents in respect to how they function in these various mechanisms, cuz that's something of interest of mine. I'm a pliant lung cancer rep, we've been seeing some differences. Just seeing what's been observed in pancreas or other terms that you've been investigating and your thoughts on that in general as a field of how we should think about this.

Morgan: 03:09:37 Definitely of interest. And I would say in the context of radiosensitization, that we just recently had a paper published. It was actually related to lung cancer, but catalytic inhibitions seems to be sufficient for, what I would call modest radiosensitization. The interaction between PARP inhibitors and Wee1 kinase inhibitors or ATR inhibitors, I do think that the trapping is important and that there's some interplay between the trapped PARP, inducing DNA replication stalling and the need, for example, for ATR inhibitors to be able to stabilize those stalled replication forks.

03:10:23 When you put both of those together, that's detrimental and I do think that it's an important mechanism of radio-sensitization as well for cyto toxicity.

T. Lawrence: 03:10:36 Thanks Meredith.

03:10:41 Next speaker will be the co-chair Esther Hammond and she is gonna revisit the theme of hypoxia success and failure.

Hammond: 03:10:51 First of all, thank you very much to Ted and all the organizers for inviting me to attend this meeting and also sending me the challenge of this title.

03:11:01 This is not a talk I normally give, and I must admit I have enjoyed, I have enjoyed putting it together.

03:11:06 So obviously hypoxia got a mention yesterday. I still think it's important to start off with some introductions just to make sure we're all on the same page. So, hypoxia, technically defined, just means insufficient oxygen. It's not just the one thing. It's not a black and white situation. Tissues are not hypoxic or normoxic. An actual fact, so normaxic, what we refer to as normaxia is actually what we see in tissue culture. This is the oxygen concentration that's in the air, and that we've routinely exposed our tissue culture to.

03:11:43 There's no real accepted word for this. Physioxia, is my sort of favorite, but this is the oxygen concentration that tissues actually experience. It's important to note that this, again, this is not the same. This varies between different tissues and I've given you a few examples there. Then we get on to hypoxia. This is a situation where it is indeed insufficient and this is usually associated with hyph-stabilization. And then we have radiobiological hypoxia. This is a really severe level of hypoxia where we see those oxygen enhancement ratios and that radiation resistance that we used to studying.

03:12:22 Why do we care about hypoxia? I'm assuming everybody does, but, the reason we care, is that it affects ... It doesn't matter how you treat your patients, it has an effect. So if you're giving them chemotherapy, it's gonna be harder to deliver those agents. If the tumor is very hypoxic, then even if you remove it, by that the time the cells have probably started to spread. Of course, for the reasons I just said, the cells can be very radiation resistant.

03:12:52 I've just put two examples here, but I could have picked any number of examples, from over many, many years, showing that the more hypoxic the tumors are, the worst patients do. Again, this is independent of how the patients are treated.

03:13:11 Should we target tumor hypoxia? You'll see I deliberately put my arrow at the edge rather than in the middle. That's not an alignment issue. I think we should. Many studies have shown that hypoxia correlates with poor prognosis. We know that these ones in radiobiological hypoxia are radiation resistant. We know the hypoxic cells are some of the most motile and invasive. We also know that hypoxia is one of the most significant differences between normal and tumor tissues, and this is obviously what we're ... The definition of an ideal target.

03:13:45 Something that's not in the normal parts of the body and is in the tumor. So even if you're not convinced, I would argue, though, at the very least we should be checking that at the preclinical testing stage, that our therapies, and particularly novel therapies actually work in hypoxic conditions.

03:14:04 What strategies have we already come up with for targeting hypoxia? And this is not an exhaustive list, but we have the hypobaric oxygen chambers, which are not used routinely now, they were associated with some toxicity. And they're obviously extremely difficult to provide to our patients. There are the oxygen mimics. I think we heard about those. We saw instructions yesterday for some of these.

03:14:32 These work by being electronofinic, so they work exactly like oxygen but of course, the cell has no use for these compounds, and so they're not metabolized and are able to diffuse through the whole tumor. Of these, Nimorazole is the most well tolerated and is actually used in the treatment of head and neck in Denmark, but that is the only place it's used.

03:14:55 However, there is a clinical trial running at the moment, called Nimrad in the UK, which is again testing Nimorazole with radiation in head and neck. Carbogen is another strategy that people have come up with, again, not routinely used, despite some positive results in clinical trial. Also, there are hypoxia activated pro-drugs or cytotaxin. The two most famous of which, you'll agree, are Tirapazamine and the more recent Evofosfamide, which I've had to learn how to say.

03:15:31 So this is a beautifully simple concept. This is again, the very core of this is taking advantage of the difference between normal and tumor. These drugs, in theory, have no effect when the oxygen levels are normal. They undergo this futile cycling and to remain in the pro-drug form and have no effect. However when oxygen is limited, this reaction is complete and you end up with your effector. Which traditionally have been DNA damaging agents. Both Tirapazamine and Evofosfamide are DNA damaging agents.

03:16:10 It's worth noting that there is a more recent movement away from the DNA damaging hypoxia activated products towards making molecularly targeted products. This is something that we're pursuing in my own lab and also the groups in New Zealand are very actively pursuing this approach.

03:16:29 The rush now there is that potentially these will have les overlapping toxicity issues when combined with chemo-rad. Obviously, it's a lovely concept, there are clear challenges. I'm not gonna try and pretend there aren't. We're talking about delivering drugs to the regions of the tumor where you can't get oxygen. Delivery is clearly gonna be a problem.

03:16:50 I told you at the very beginning, hypoxia is not one thing. So what happens if this reaction requires an exact level of oxygen or absence of oxygen, and you don't actually get to that level in the tumor. Is this drug gonna work?

03:17:05 It's also reliant on the expression of reductors so we'll see if they're not there, the drugs not gonna work. Unfortunately, the one place these reductors are expressed is very much in the liver, which can lead to toxicity problems. Of course, this strategy should only work in hypoxic tumors. If they drug is designed as it's supposed to be, it should have no effect unless the tumor is hypoxic.

03:17:34 Here, just a very brief summary of the, where we're at with the Tirapazamine and Evofosfamide. Tirapazamine has been through clinical trial and has shown no evidence of benefit of adding TPZ for head and neck in combination with radiation. This has been attributed to many reasons, one of which includes the radiotherapy quality. There was serious concerns about the radiotherapy that some of these patients received and how that may ...

03:18:00 The radiotherapy that some of these patients received and how that may have affected the outcome. But it was also given to every patient who walked through the door, so there was no selection of the patients based on tumor hypoxia. Now a lot more recently, evofosfamide was trialed in pancreatic and soft-tissue sarcoma. This was not obviously in combination

with radiation, but I think it's worth pointing out that again there was no selection of patients based on tumor hypoxia. So what these people effectively did was rolled the dice and hoped to win, because these drugs shouldn't work unless there is tumor hypoxia. So I think the sense in giving it to patients without knowing they have a hypoxic tumor is challenging to understand.

03:18:53 Okay. So I think you need to know whether your tumor is hypoxic and obviously that's hard, but we have less and less excuse now for not doing that because we have multiple methods of measuring tumor hypoxia. Obviously the needle electrodes, the Eppendorf machines, they're barely used these days. These were obviously instrumental in those first studies linking hypoxia with patient prognosis, so we're grateful for that. But these are not really used now. The serological markers, so we're talking about agents like osteopontin or miR-210. Things that can be measured very easily and most importantly, repeatedly, I think have great promise. I don't think they've been fully validated yet, but I think this is gonna be an interesting one to watch, because really, as was mentioned yesterday, what we really want to be able to do is not only determine which patient has got a hypoxic tumor to start with, but also monitor that hypoxia throughout the treatment. So something that's repeatable is very advantageous.

03:20:03 The hypoxia signatures and the tissue based biomarkers have both been well validated at this stage. There are a number of hypoxia signatures for various disease sites. One thing to note is that I think that these are sometimes very reflective of HIF signaling pathways, certainly the hypoxia signatures. So you have to ask yourself, "Is HIF expression what you're trying to measure?" And if you remember my first slide, you know HIF expression doesn't necessarily mean radio-biological hypoxia. So it's not necessarily gonna pull out those ones that are really radiation sensitive. And again, the tissue based biomarkers, I think it's important to know whether you're measuring CA9 or using pimonidazole to think about what exactly is it telling you. Is it ... You know for some of these studies, unfortunately, we're going need to know exactly what level of oxygen we're measuring, and some of these markers don't actually tell us that. And course there's imaging and there's a huge amount of work going into the various types of imaging. The PET using FMISO, for example, is probably the most well established, although extremely expensive and therefore not routinely used. I don't think the oxygen enhanced MRI is obviously ... Is showing great promise for the future and has the advantage of being much cheaper. So hopefully we're gonna soon lose this excuse of not being able to measure hypoxia routinely.

03:21:34 So where else do I think we may have gone wrong in testing hypoxia modification? And I think I want to be very clear that I'm not saying that pre-clinical testing is not warranted, okay? Going back to our discussion yesterday, I'm a firm believer in pre-clinical testing. But I think we have to be a bit more honest with ourselves. I think we have to stop stacking the deck in our favor. So for example these sections that you're looking at here, these are all non-small cell lung cancer cell lines grown in centigrams. They're all grown to the exact same size. The brown staining you're looking at is CA9, so it's a HIF target, it's reflecting hypoxia, and look at how different these are. So you can think of these as eight patients, for example, just look at the different levels of hypoxia in these sections. And yet, if I was gonna test a brand new hypoxia activated prodrug, you can be sure I'd be picking one of these. I think I'd go for that one, because I think that there's some hypoxia, it's not completely hypoxic so maybe I'll have some chance of getting the drug in and hopefully see an effect. I certainly wouldn't pick this one, or maybe that one.

03:22:50 So I think we have to be really careful. And obviously when we're doing this pre-clinical testing, we have to be very strict with ourselves. We have to check the pharmacology. When we're thinking about going from mouse to human, we have to be sure that the drug is working the same way, that the biology is the same, and that of course we're hitting the target and using reliable biomarkers. So quite simply, is the drug in the right place, at the right time, and at the right concentration? And we have to be sure that we're translating from mouse to human in order to see these agents work.

03:23:27 So does hypoxia modification work? And this paper was referred to yesterday. This is the metro analysis by [Yenz Overguaard 03:23:36] who took all of the trials over a, I think it's 35 year period, that have used hypoxia modification and did a metro analysis to try and sort of tell us whether this is a strategy was going to work. And the answer is yes. This is ... I'm showing you local regional failure here. The overall survival is less impressive, to be honest, which obviously gives us some real concerns. There are numerous trials here, admittedly they're all quite small trials. There are many different ... I think there are nine different strategies here, and all lumped together, the answer is still not overwhelming.

03:24:19 So I think we have this problem. This has been lost in translation. I mean, I am not a clinician. No one is ever going to let me make this decision, but I can imagine that faced with this, then what would you pick? What would you choose? Which one of these strategies would you take forward?

03:24:40 So now I'm just gonna briefly talk about one of the newest strategies that has yet to be really tested in clinical trial, and that is still by targeting hypoxia, but through reducing oxygen consumption. So it's very simple and this is our standard hypoxia model. These are the nicely oxygenated cells. If we can persuade these cells here, these sort of blue ones, to not use as much oxygen then these one become lighter blue, they can receive more oxygen and therefore should become more radiation sensitive. It's a simple strategy.

03:25:12 So Geoff Higgins and Gillies McKenna back in Oxford did a High-throughput Screen using FDA approved agents to look for compounds that effected oxygen consumption and the compound that they quickly narrowed in on is atovaquone. Atovaquone is an FDA approved antimalarial and importantly, it's an antimalarial without all the significant side effects that are associated with those drugs. So it's very well tolerated.

03:25:40 And this is a 3D-spheroid model so these are cells grown in balls big enough so that the middle becomes hypoxic. In this example, stained with EF5, and you can see as the drug is added, this hypoxia reduces. And it's important to know that these cells are not dying and when you actually take the drug away that hypoxic middle comes back. And there are other examples of this. Formin has a similar action, although the dose required here is a concern. Phenformin also has a similar action but is also ... Oh sorry. No. How do I get back? Oh there we go ... But is now actually not FDA approved.

03:26:19 They then took this into an in-vivo xenograft model. So again, these are the tumors, EF5 marking the hypoxic regions, and you can see after atovaquone treatment the hypoxia is significantly reduced. And most importantly, they measured the level of the drug in both the plasma and the tumor so they can see how much drug are they getting in there, what's achievable. And obviously we have the ... You know, we can translate to the human situation because this is a repurposing situation so we have all that data for atovaquone.

03:26:51 And perhaps not surprising, given the difference between the level of hypoxia when they added radiation in, they saw a significant effect. So there was no effect of atovaquone on its own, this is not an intrinsic ... I should've mentioned, this is not an intrinsic radio-sensitizer but when you added them both you see this significant effect. And the way they did this was they gave atovaquone for 10 days and the radiation as a single dose on day 7.

03:27:17 So what's next for this? So what's not gonna happen is an efficacy study in unselected patients. Instead of that, what they've designed is this window of opportunity trial, where they're going to give atovaquone to lung cancer patients just prior to surgery and they're gonna ask a very simple question: Does atovaquone reduce tumor hypoxia in patients? And they're gonna ask that question and then see what happens. And hopefully with a name to stratifying patients who will respond and identifying a biomarker that's gonna predict response. So this is what the trail looks like. And really, I just want to highlight that part of this trial, or a lot of the things that I've already talked about today, said they'll be measuring hypoxia up front. They'll be doing this in a number of ways including the serological markers, the scans. They'll start the atovaquone and then repeat those hypoxia measurements to see if there's been a change.

03:28:21 They will also, obviously, eventually then have the advantage of being able to get these tumors, so we can see what has happened. This trial is ongoing but Geoff has shared one scan with me, which I'm allowed to share with you. On this side is pre-atovaquone and over here is post. And this is an FMISO-PET, and you can see this is a hypoxic region in this tumor which is significantly reduced after treatment with atovaquone. So fingers crossed.

03:28:53 Okay so finally, my last slide. Ted asked me to address why don't we have a hypoxia cell sensitizer for use with radiation, and I'm a little bit worried about disappointing him. I sort of made a bet with my self that this slide, this trial result would've been shown several times during the day and so I'm quietly pleased with myself over that. I don't think one of the reasons is that look at this effect. I mean I'm not a clinician, but this looks like a big effect to me and I can understand why this is now already FDA approved. If you see a big effect like this, people are gonna be enthusiastic about this compared to those effects that I was showing you in the metro analysis, which certainly didn't persuade anyone to take on that therapy.

03:29:43 And I think that's for several reasons. I think we need better drugs, we absolutely need to confirm the activity in patients, and maybe we just haven't good enough drugs to do this to date. We need better trials, and by that I mean we need to be putting the right patients in these trials. We need to stop testing these agents in patients that don't have hypoxic tumors. And maybe that means letting go a little of "all tumors are hypoxic", because you know, I'm sure they are to some degree, but maybe that's not what's important here. We need to know if they are hypoxic enough to benefit. I think we also need trials that we can walk away from as well. We need to test these things, and if they don't work, move on. So for example, if atovaquone doesn't reduce tumor hypoxia, then let's forget it. That's certainly not then combine with chemo-rad.

03:30:37 I think unfortunately, we need to overcome negative perceptions associated with this and I think the recent failure of evofosfamide, it is gonna make that a struggle. And to do that, we're gonna need clinical champions. We need people in this room to get on board and drive this forward. And of course, we're gonna need people to pay for it.

03:30:57 So with that, I'd just like to thank a few people who helped me put this talk together and also ask you to save the date for the International Congress of Radiation Research, which will be in Manchester next year. Thank you.

T. Lawrence: 03:31:14 Think we have time for one, well actually, for one quick question. I have one of ... Go ahead. Yeah. Sorry. Microphone-

Speaker 4: 03:31:22 Especially patient selection, it assumes that hypoxia is very static condition and I saw evidence to otherwise. Can you comment on that?

Hammond: 03:31:33 Yeah, no. I absolutely agree. And I think that ... I mean that's why I have a little bit of a soft spot for the serological markers, because it's cheap and I think that you would be able to monitor throughout treatment, because I think it's absolutely not static. I mean I think, even on any given day, it's fluctuating and then throughout therapy for sure. And I think that's almost like a biomarker. You know, those that are changing versus those that aren't changing, could well be telling you how patients are gonna respond. Yeah.

T. Lawrence: 03:32:05 Very good, thank you. Our next speaker who is working his way up to the podium, is Andrew Wang. You don't have to run, but it's amusing to see you run. He's from the University of North Carolina Chapel Hill, he's gonna talk to us about nano-therapeutics and radiotherapy. So I hope you see, we've tried to cover a spectrum here of different things that aren't immunotherapy.

Wang: 03:32:29 Well actually, there's gonna be immunoncology so thank you for the opportunity to speak.

T. Lawrence: 03:32:29 Everybody has to be immunoncology or else they're just-

Wang: 03:32:34 No, you know, I'll tickle your brain with this one. So quickly, this is my disclosure. For those of you who are not familiar with nanotechnology, basically the field ... We work with particles that are about 100 nanometers in size or smaller. Why do we care? Why is there excitement over it? Well, nanoparticles give you some unique particles that doesn't exist on the small molecule scale nor in bulk scale. So for example, iron oxide nanoparticles are super paramagnetic. Also, we're gonna talk about is nanoparticles are intrinsically immunogenic, so these properties can be taken advantage of. Also, we can engineer these particles in a pretty precise way. And we can use them for drug delivery for a slew of things.

03:33:25 Within the radiation oncology context, there are a few things to like. One is their unique biodistribution. So they are macromolecules so they penetrate the tumor because of the leaky vasculature, but they have a very low distribution in normal organs because they're big, they can't get out of the capillary. So that unique distribution is really good for radio-sensitization. Another aspect is that many of the nanoparticle drugs have a controlled drug release profile, so they release their drug in a slow way. As radiation oncologists, we know that the slower the release, the more the synergy, so that can be an advantage.

03:34:05 So just to give you a diagram, we think nanoparticles works is ... You know, here's a small molecule with radiation in rectal cancer and with nano-therapeutics the idea is that they go to the tumor more, there's less normal tissue distribution, and therefore we enhance the therapeutic racial. So my group has done a number of preclinical studies in comparing nano-therapeutics with non-nano and each time it wins. And then we did pre-clinical evaluation with this therapeutic, this is a nanoparticle camptothecin, so the parent drug for irinotecan.

And in pre-clinical colorectal cancer models, we show that adding 101 to 5-FU under radiation significantly improved the tumor growth delay.

03:35:00 What's also interesting is when we compared it to oxaliplatin, which many of you know, that didn't really offer any benefit to 5-FU plus radiation in rectal cancer. Low and behold, the oxaliplatin didn't move the curve down, but 101 did. And so based on that, this pre-clinical data, we launched a clinical trial. It was phase 1B2, essentially adding 101 to standard 5-FU and radiation, and we were able to complete the initial phase 1B2 with every other week and then we found out we could actually give it weekly because it's a very low toxicity profile. We found that the MTD is actually 50 milligrams per week.

03:35:55 So long story short, the signal seems to be good but the company put most of the ... Because of registration issues that we discussed yesterday, the company put all their eggs in the renal cell basket and that didn't work out well with the immunoncology stories, so we're somewhat in limbo with this. That said, there are other nano-therapeutics that's coming down the pipeline. For example, there's liposomal mitomycin C that I'm quit enthusiastic about. So I think that story is just the beginning, we hope to see a lot more.

03:36:28 By now, many of you probably know about Nanobiotix. I saw it in an earlier slide. So this is a company that's very interesting. It's a French company. They have a nanoparticle that's made of hafnium oxide. What it does, is basically boost the electron production from radiation. It's very interesting, good pre-clinical data and as you can see they're in clinical trials in a number of different diseases and different sites. It's got issues. You know, you need to be injected intratumorally and there are a number of other things we can talk about.

03:37:11 With that said, I think it's very encouraging. Here you got a nano company that's entirely devoted to radio-sensitization, there's no other indication. So I think there's enthusiasm for this interface. As I promised, there's gonna be immunoncology stories, but that said, it's gonna be very different. So I'm glad that somebody else ... Marcus said, "Radiation is a terrible vaccine." So I don't have to say that first time to offend everyone, but I agree. So here's our one story that we have to improve radiation and immuno-response.

03:37:51 As I mentioned, nanoparticles are the size of viruses and they're actually very intrinsically immunogenic, unless you coat them polyethylene glycol or hide them from the immune system. So on the reverse is we want to take advantage of that immunogenicity so we generated, what I call sticky nanoparticles or surface chemistries where they can grab onto protein antigens that's coming out when you give radiation. We hypothesize that because now they look like viruses, they would do a much better job at antigen presentation and elicit a more robust immune response. I can't go into all the details, but here we basically show that by changing the surface chemistry of nanoparticles we can indeed grab onto different proteins including neoantigens and then in a abscopal set up experiment, we show that we can improve the therapeutic outcome from PD-1 plus radiation. A couple of nanoparticles did really well. One of them cured 20% of the mice, and then also you can do adoptive transfer and rechallenge and so it's true immunity.

03:39:05 This is actually just a bare minimum particle, we didn't give any STING agonists, we didn't give any TLR agonists, so there's a lot that we can improve upon this. But this is one area that nanoparticle can improve immunotherapy and also in the context of radiation.

03:39:21 Another story that will come up very soon is that the next generation ... Or at least my biased opinion, is that the next generation of immunotherapy is combination and less toxic combination than [epinevo 03:39:37]. One of the combinations that's coming down the pipes is the PD-1 plus OX40. I think some of you have seen it in the previous slides. So we had a hypothesis which is when you deliver two signaling molecules separately they engage a T-cell in a statistically random way. So we hypothesize that if you can present both of these to a T-cell at the same time, you can potentially have a more robust signal, because we're nanoparticle people so we put them all on nanoparticle. And the other thing that helps is that OX40 is in the TNF-alpha family and the signaling is boosted when you have a clustering effect and so it's hard to cluster but with nanoparticles you achieve that. So we show that basically ... So I'm skipping a lot of the other in-vitro studies, go straight to mouse models so in B16-F10 we basically show that the nanoparticle with both therapeutic is way more effective than the free mix. And we also actually compared ... So it's not here ... But in a different tumor model, we actually compared it to nanoparticles containing a single one and we mixed the nanoparticles. So it's not a nanoparticle effect only, it's the fact that ... Our hypothesis is that it's the fact that you can present both to the T-cell at the same time eliciting a much more robust signal.

03:41:13 But this is just another flavor or something that nano can offer to immunoncology and the little bit of radiation here is that, as you heard earlier, is that OX40 doesn't really work well unless you give a priming does of radiation or else really nothing works. When we give the immunotherapy nanoparticle we determined that ... We showed that there is more immuno-cells infiltrated in the tumor. Last but not least, we also have ... You know, nanotechnology can also offer, not just on the therapeutic side, but also on the diagnostic side. So here is a story, as I showed I do want to say that as you've seen in the disclosure, this is something that we confounded a company on commercializing. That said, I'm not gonna give you any ... Hopefully you don't think this is a biased opinion.

03:42:18 The CTC technology has been around for a long time and everybody knows about CellSearch. The biggest limitation with CellSearch is that it doesn't capture enough cells. So if you're only working with three to five cells there's very little can do with that, and for the longest time in the field we wanted to prove that sensitivity and specificity of capture. And here, the innovations are that we ... So one is that we induce a surface where the tumor cells will roll on the microfluidic channel instead of just flowing rapidly through it. So the slowing down of the tumor cells help us capture it. And the nano part is that we anchor a flexible dendrimer, which is a nanoparticle but it's very flexible, it's like a tree-like structure and you can conjugate about several hundred antibodies per dendrimer. So the surface, instead of a single antibody anchored onto the surface, we use dendrimers and this allows multivalent binding.

03:43:25 So in patients ... These are patients undergoing chemo-radiation, most of them are head/neck patients, but there are several other diseases. We basically showed that we can capture a lot of cells from curative patients. These are non-metastatic. In fact, T2N0 patients have several hundred CTC's per milliliter. And the nice thing, for the most part, is that you see this nice correlation with chemoradiation treatment and at the end of the treatment, when the tumor is gone, the CTC goes down. The couple lines that are going up, unfortunately those patients actually had progression. So it also helps ... The biomarker is complementary to clinical practice because both of these patients were actually on [inaudible 03:44:15] dose de-escalation study and the PET/CT caught the residual disease in both of these patients. When we looked at the CTC ... So this one, is really like base line or

normal and this one was going up, and low and behold when the patient had neck dissection there is residual disease here and there is just inflammation here. So that's another area where nanotechnology offers advantages to diagnostics.

03:44:48 I flew through that and I know everybody wants to go to lunch. And then the last thing that I want to say is that all the hard work is done by my lab, so I have to acknowledge them. I just do the all the talking, they do all the good work. And then I want to thank the funding agencies and all the collaborators. Thank you.

T. Lawrence: 03:45:11 So we have time for a couple of questions. I think while we're waiting for a question, Andrew or Andy if I can ask, one of the themes of today has been enriching the patient population ... Or and yesterday, to get patients who are gonna respond to the chosen therapy. Are there mechanisms for looking at whose tumors are the leakiest and so who might be the best candidates for this?

Wang: 03:45:36 Yeah so I think that's a great question. We don't have that level of data yet, but I would say that most of the studies looking at vasculature shows that most of the tumor vasculature have holes that's about at least a couple hundred nanometers in size. But the other aspect is does it penetrate thoroughly, uniformly? And it doesn't. But that said, with several sites ... So it penetrates the periphery of tumor very well and then the heart of it is always challenging with chemo with everything.

T. Lawrence: 03:46:20 Right.

Wang: 03:46:20 But the idea is that if we have a better radio-sensitization then we peel that off and we go to the next layer, peel that off.

T. Lawrence: 03:46:27 Then one more thing I wanted to ask along those lines is can you use these as a theranostic? Can you actually see them? Image them? So that you can look at a tumor and see if they've been deposited?

Wang: 03:46:38 Yeah so you can. You can radio label these. So [Meramec 03:46:43] I think has always talked about labeling their ... So they have liposomal drugs, not coming into the radiation arena yet, but you can always label them. The challenge has always been that the minute you label them, it changes their property a little bit, you do change the surface chemistry most of the time. So there's a little bit of concerns to whether that's true distribution. That said, I think that's ... Pretty sure Meramec is developing that.

T. Lawrence: 03:47:12 Okay. Thanks very much. Actually don't go. Don't go. Andrew come back. I can't let you go. We'd like to thank our panel here, our speakers from this morning and we have a couple of additional people who did not speak this morning. Dr. Blumenthal and Dr. Ataman, we're bringing you back and I thought your voice sounded ever so slightly better today than it did yesterday, so you can croak more authoritatively for us. I wanted to start the conversation but trying again to focus back on the theme that Amanda has charged us with about how can we get radiation earlier into the life cycle of the drugs that are developing? It seems to me that ... I'm gonna throw out an idea, and then I'd like to hear reactions, especially from the FDA and from industry but from the other panelists as well. Actually, Zelanna you're still here right? I may call you to the microphone too because you're the one yesterday who hit so hard on quality of course, always quality, but speed. You talked a lot about speed. How do you get to your indication, right?

03:48:28 We have seen this slide that you and many others have shown that it is possible with durvalumab to get an indication for a primary disease. That is most of what we see in drug development is someones two months away from death and if your new drug can push that off another month, in a randomized trial, you get your indication, right? The question then is, can radiation therapy become part of the life cycle of the drug earlier using for definitive ... I'll say definitive bad diseases. Maybe I'll pick like bad head/neck, GBM, locally advanced lung. Can we get it earlier and what do we need to do to do that?

Blumenthal: 03:49:17 Hi everyone I'm Gideon Blumenthal from the FDA, so I can take the first swing at that. First of all, great to be here and thanks to Amanda and all the organizers for inviting me. I think it's a great question, I think the Pacific trial was a great recent case study of sort of maintenance, anti PDL-1 following chemoradiation and locally advanced non-small lung cancer. As mentioned the effect sizes were huge so wasn't a big leap of faith, from a FDA review stand point, to go ahead and approve that indication. But great for the field.

03:50:11 I think one thing that's gonna be critical is the development of intermediate endpoints. We have more and more therapies, which is great for certain therapeutic indications like lung cancer and renal cell cancer, melanoma, etc. Some other areas are still therapeutic deserts like pancreas and GBM. But to sort of speed the development, we're gonna need intermediate endpoints, overall survival and I'm sure you've heard a lot from Paul and Tatiana yesterday ... While obviously the gold standard, not always gonna be feasible, particularly as we molecularly subset patients into smaller and smaller subgroups, we have cross over issues, we have-

03:51:00 Then to smaller and smaller subgroups, we have cross over issues we have equipoise issues, so we're going to need to look at intermediate endpoints. We've done a lot of work to start to look at endpoints. We actually have a workshop next week, in lung cancer, talking about that neoadjuvant lung cancer trials, we have a radiation, oncology component to that as well borrowing from the breast cancer experience. So, can we look at for example pathologic complete response, or major pathologic response. We've also done a lot of work on blood based biomarkers, you mentioned a CTC, so we've done a number of workshops with ACR in terms of liquid biopsy, you know, the field is starting to evolve, particularly in some settings, CTCs but also circulating tumor DNA looks very exciting in certain contexts.

03:52:06 So can we start to qualify changes in circulating tumor DNA both to enrich your trial, for higher risk patients, as well as a potential surrogate endpoint for an accelerated approval, and then looking at novel imagine modalities as well. So, I think we're poised to really be one of the stake holders, it has to be sort of a group effort with industry and other government entities and academia and patients to come up with these endpoints. It's very painstaking work, requires a lot of collaboration, a lot of cooperation and sharing of data but its certainly ... We're poised to help out.

T. Lawrence: 03:52:58 Yeah, Ozlem was kind enough to list four questions for us to focus the panel, and you've actually touched on two of them already but on the surrogate endpoints if I could, again, turn back to you and ask, one of the big areas that we think about in radiation oncology is working preservation. We think if we can develop something that improves the ability to avoid a colostomy and anal cancer, or avoid laryngectomy and head and neck cancer, we think we've done something very good for that patient. Can you see a path forward for those being endpoints that could lead to registration?

Blumenthal: 03:53:32 Absolutely, and those could actually be direct clinical benefit endpoints. So not even surrogates, but if you can preserve critical organs that could be benefit in and of itself.

T. Lawrence: 03:53:48 So, that was a yes, right? I didn't even hear, "Yes, but." That was just yes. Well maybe I can ask the other panelists to respond to this but, before I let go of that, what do you see as the impediments for laryngectomy free survival or colostomy free survival? What are the impediments to developing that as a direct patient benefit endpoint?

Blumenthal: 03:54:12 Yeah, I mean I think it'll require a lot of discussion with patient groups, experts out in the field. You know, obviously, overall survival is easy, you know, you're either alive or you're dead.

T. Lawrence: 03:54:26 We get that.

Blumenthal: 03:54:26 Progression free survival, easier, you know, you're looking at changes in radiographs. You know, there are certain biases inherent in deciding who should or should not get a colostomy, or should get a laryngectomy, so not insurmountable but I think technically the designs of those trials can be more challenging.

T. Lawrence: 03:54:55 I'll let go of this after this last question, because I think this is an important one for us, so how would we move that ahead? What would be the pathway for us to overcome the obstacles for those kinds of endpoints?

Blumenthal: 03:55:06 Yeah, I think it's very disease specific. So, we've sort of restructured our organization within FDA to have disease specific expertise. So, you know, if it's head and neck, if it's GI, I think it makes sense, first of all, to get patient advocates on board that's critical.

T. Lawrence: 03:55:31 I think most patient advocates will say that it's better to be able to speak than not to speak, and it's better not to have a colostomy than to have a colostomy, right? You go ahead.

Speaker 5: 03:55:43 [inaudible 03:55:39] said before the [inaudible 03:55:44] patient advocate, but I think it is disease specific as well, and bladder cancer would be a great place to start. I think that's where it's really critical, and there's a lot going on in that area as well in all of these different technologies. So, if you could start there maybe and do something like that and another endpoints that patients have talked about is time to the next treatment. Especially when you're talking about metastatic disease. You know, even if there's staple disease or minimal progression sometimes you stay on a treatment longer than you get off the trial, but patients really go from treatment to treatment. That's their stage, their kind of trajectory so that's another option.

Blumenthal: 03:56:28 Great point and actually we have an ASCO abstract, that we've started to look in lung cancer because you have these different response phenotypes where you know, you have ... You guys know this better than anyone, sort of these slow progressors who might have one unique site that needs to be spot-welded, versus rip-roaring progression. So, we've actually looked at time to treatment discontinuation as sort of a pragmatic, real world endpoint could be abstracted from EHRs and, you know, it seems to actually correlate quite well with PFS for those drugs that are given continuously. Obviously if you have a plan stopping, or one cycle or something like that, that could be a bias, but for continuously administered drugs time to treatment discontinuation could be a very pragmatic endpoint and could be, you know, has real world implications and very beneficial.

T. Lawrence: 03:57:30 So I ... Zelanna, do you wanna address that point?

Goldberg: 03:57:33 No, actually I want to ask a further question about endpoints that you might consider, which is, is there any movements on accepting landmark timed endpoints? So, events at two years.

Blumenthal: 03:57:45 Yeah, so we've also looked at that ... Consulting with our statisticians we call them milestones, but they're also called landmarks because a landmark analysis from statistical standpoint is like censoring the rapid progressors. So, landmark analysis are milestones looking at like one year OS, or two year OS. We've explored that, you know, you're looking at a single point in time versus the log rank, hazard ratio sort of measures, sort of the totality of the experience so you have to be careful in choosing your landmark analysis. But certainly with IO where you're having delayed separation beyond the medians there could be some advantages to that.

T. Lawrence: 03:58:37 So, Zelanna while you're still there, and Ozlem, I wanted to ask both of you to address the question that you posed for us, the second question. What would it take ... what kinds of data would you want to see from people like Meredith, to start to think that you could get the first registration of a novel agent to be in combination with radiotherapy. What would it take to see that pathway, because it's obviously going to start with some late preclinical data, phase one, two type data, so it's a pathway. So, what would you need to see from us as a field to say, "We want to launch on that pathway." So, maybe Ozlem you go first and then we'll, pick on Zelanna since she's standing there.

Ataman: 03:59:21 I hope I sound a little bit today, but I think the most important will be ... We talk about endpoints and guidance, but there is nothing written as a guideline with radiation combinations, so if there was a compound that really, there is a potential and the questions will come. And I was wondering when we had the UK workshop, in London, we had a UK agency representative there and the reason he said that there wasn't any guidelines was because the companies or they didn't ask enough questions. So, I think, do you expect more companies to come with this kind of registration questions to FDA so that you would start thinking of putting a guideline together. Is there any hope that this is there, because really this is what I get all the time, that they constantly say so, you're talking about pathologic CR but is that registrable? Yes, we have to go and ask early questions, interaction but if there was some guidelines out there I think that would be amazing. I don't know if there is any support on that from others but, yeah.

Goldberg: 04:00:34 I would certainly echo that is, the things that we really need are guidelines from the agency more so than research. You know, let us know, in writing that yes, pathologic CR will be an accepted endpoint because that's an early endpoint so that's a very attractive place to move. I would note that as much as the Pacific trial was fabulous and landmark, it was not an original. It was a not a first approval in the same way that the Javelin study for head and neck, well it's very much a radiation study in fact, in a sense more so than the Pacific because we're using it with radiation, it's not a sequential trial like Pacific was so they ... From a clinical trial perspective they avoided all the issues around giving radiation and being responsible for it, is part of a registrational study they just randomized after.

04:01:33 Javelin and also, of course, Keynote O42 are involved with the radiation delivery as part of the therapy and that has a whole bunch of implications. We certainly had to negotiate a lot the FDA when we went to them in terms of our endpoint and the FDA was very, very responsive. I mean we had very good and positive interactions, but Pfizer and of course

Merck, are very big companies, we can afford to be doing this, again not as a primary registration. So, if you want the first registration to be radiation related, that requires of course the early data, which is not a requirement for filing an IND, so it's something that people do not necessarily think about doing early on and therefore in those original dose finding studies they are not being done with radiation.

04:02:26 And that's, I think, where the biggest lag is, and we need early endpoints for an ability to have an accelerated approval pathway that is understood and we can point to for our colleagues who have never thought about radiation as a modality to use in their early registrational thinking. And they don't have experience with, and it's not easy to run trials with in combined modality setting because of some of the things we talked about yesterday, in terms of the dominance of medical oncologists in these trials.

Wang: 04:03:03 [crosstalk 04:03:01] I was just gonna share my experience with the Cerulean Company and how that worked out. So, basically it's a financial argument, as you said, so the company was very clear that the most likely clinical study to succeed in their portfolio was their one with the radiation. The data was great. But that said is, they were very upfront in saying if survival was the endpoint that's never gonna work out for them, especially for a company that's not Pfizer, Merck size. And then I guess the timing was bad so, you know when they had to ... Obviously I'm not part of the company so I wasn't at the discussion so when they approached the agency it was right around when the breast cancer past ER story came out and I guess that poisoned the water, so what they got was that PCR was no go and that pretty much just shifted all their focus away from it.

04:04:02 And so, I think again ... As I said this yesterday ... I think what I'm hearing is a much more open dialogue about these surrogate endpoints and if so then I think that's really great for us because if it's always gonna be survival then I don't see another way to come for rectal cancer, for example.

Goldberg: 04:04:22 I would agree on one more point before I give it over, which is also, the FDA to their credit are much, much better to deal with than the EMA ... They're much more responsive, they're much more data driven, they're not as rigid and so I hope that as you guys do your work you also can help your European colleagues in understanding the evolving landscape and the need for earlier endpoints.

Speaker 5: 04:04:51 So maybe this is a thing that radiation oncologists have a confusion but, you know we're very familiar with not making overall survival impacts, and it takes meta-analysis often to see our local control rates equate to overall survival benefit. But, we get indications as radiation oncologists all the time for enhancing local control and preventing further surgeries and things like that. So it's very difficult for me to understand, particularly the agents just discussed, which really in a lot of cases are about enhancing radiation efficacy. Why would you not consider local control enhancement as a direct clinical benefit when we have a long history showing it's a direct clinical benefit and why is that never even discussed as this is the indication we're gonna go after with radiation, we're enhancing local control? So, just curious about comments about that.

Blumenthal: 04:05:48 Yeah, again, I mean it could be a direct clinical benefit I think ... To my initial point ... I think it requires sort of, discussion amongst the thought leaders, the academics, the patient groups, et cetera, to come to that determination. You know, frankly I'm a little surprised that this company was told that PCR was a no go, because we have a whole guidance in

breast cancer, you know, on this very topic we even have an example of approval with Perjeta in early breast cancer. [crosstalk 04:06:32]

Wang: 04:06:32 I don't know how that conversation went but that's what the feedback to me was.

Blumenthal: 04:06:33 Yeah, so to answer your question, I mean I don't think that's off the table you know. I think it requires sort of discussion across stakeholder ... I think there are also ... The other thing that I would say is we're trying to fix our guidance generation process and it's gotten better so you'll be seeing more guidance from the agency in general but there are also opportunities for professional organizations like ASTRO, AACR, to actually take a first stab at writing the guidance and then, because obviously, we have limited resources. We have, right now we have one radiation oncologist and it's very hard to recruit radiation oncologists so we're resource constrained.

04:07:32 But there are opportunities for patient groups, et cetera to actually present the agency with guidance to help us with the process.

Speaker 6: 04:07:46 My question is out of the discussion but I'd like to mention just for the record, and for your consideration, there is a whole group of drugs that has not been discussed here, which is radio-pharmaceuticals, especially therapeutic radio-pharmaceuticals that are now, as you know, getting more and more popular and sooner or later I hope that it would become by the radiation as something worth considering.

Speaker 7: 04:08:12 [inaudible 04:08:11] and it really potentiates radiation but Boyd potentiates normal stuff to, so having said that I think in conjunction with the comment that was made, it has to be two pronged and that's why I'm a big fan of Andy's. I was involved in his nano-particle because I think it's gonna be a local control advantage, which is important in lots of diseases, but I think you gotta couple it with, here's a normal tissue elements that were also not enhanced. So now you're telling people, "We're gonna control your tumor longer and better, but you're not gonna pay a price for it in terms of normal toxicity." I think harped the FDA to sort of push it back and given the IMRT, I'm talking radiation for the folks in the room who know radiation, but the IMRT data for head and neck, and anal canal, I mean that's really compelling data to say, "You get to the same point in terms of survival, but boy you have a whole lot better quality of life when we're done with you."

T. Lawrence: 04:09:03 Can I go back to our two industry people and ask another question? So, for locally advanced cancers, and I think that was Kyle Cuneo's first slide, for locally advanced cancers I would say essentially everything is treated with a combination of some chemo therapy and radiation therapy. For locally advanced disease I think that's the [inaudible 04:09:22] pretty much from head to toe. So what are the complexities of getting an indication for a new agent if you're looking at locally advanced disease that is not metastatic disease, what are the complications of getting indication on top of chemo radiation?

Ataman: 04:09:45 So, I think first of all, it has to come early enough in the discussion, and we've been discussing this for a couple of different sessions that ... The company has to think about radiotherapy early enough to start a combination study. You need preclinical evidence to move into the field and then the relevant endpoints, so once these come together, probably there is some way to do this. But you then, I think, internally bump into some kind of CRF issues like the case report forms are never really tailored for radiotherapy studies and what

to collect, and you start really working with the data management, the statistician because everything is based on continuation of a drug til the progression.

04:10:37 And here they have difficulty in understanding that this is gonna be given for seven weeks or ... You have to do everything from scratch basically, designing the case report forms, the data base, everything. And it's not that straightforward while you're in there and there's no others that actually know and understand and I found myself going in circles and circles many time's til I get there. And then the toxicity, what do you collect ... Basic forms are really very basic, it's just those and fractionation. So, I don't know if others said the same.

Goldberg: 04:11:16 So, to share when I first went to Pfizer, and it wasn't a registrational study for radiation. I had multiple rounds of engagement with our data collection folks and the people ... We call them our CRF police ... And I could not get them to change how they collected radiation data at all. I kept going back around, and around and they just were completely intransigent. In fact, I can tell you for our registrational study we sort of gave that one up, we're doing all our radiation data collection through Quark and then we're gonna import the database. So. that's a very real issue is that nobody outside of radiation understands what a radiation prescription is. So that's a very basic problem, but in terms of local control ... I mean it is, you're designing every single step almost of the clinical trial paradigm that the pharmaceutical industry has used. The CROs are also extremely unfamiliar, in fact totally unfamiliar with radiation, and they don't have existing relationships with radiation oncologists or dosimetrists to get the radiation quality assurance up and running if you build that into your study as we certainly did. And we didn't even go into the material that was covered with IROC in terms of verifying the machine output. We sort of took that as a given.

04:12:46 One of the other main challenges, and you can kind of go every step of the way there's challenges, but one of the big discussions we had with the agency was around how we were going to verify this issue of local control because the standard in metastatic standings is people use resist through a blind independent radiology review. Well, once you've radiated your area your scans are ... Technically those are not lesions you can ever follow using resist, so it's only the presentation of metastatic disease that can be done that way. You have post radiation change, which we're all used to looking at in the field but if you then send it to a blind reviewer you can't distinguish well radiation impact from potential recurrence. And you need to therefor address that in your endpoint.

04:13:39 And that was actually a big negotiation and, as I said, it was a very productive one and we got really good interaction and feedback from the agency. Never the less, again, the size of Pfizer allowed us to do what the agency demanded, which was to parallel collect a full second set of data on resist outcome. A smaller company would not be able to do that, would not be able to finance it so that is actually a significant barrier. This could not be done as a first approval, it would never be done as a first approval, because it's too complicated, it's too expensive, and the endpoint is still very long. So, we're going, you know, is a progression free survival endpoint in locally advanced diseases is very long, in metastatic it's not. And that has significant financial implications on every aspect of how the opportunity is evaluated relative to the metastatic opportunities.

T. Lawrence: 04:14:42 Okay, I'm not giving up. I have another try. How about locally recurrent disease, like in GBM or in head and neck, locally recurrent, where we know these patients have very short survival, and we know they die of local progression using survival outcome. Does that sound like a registration approach?

Goldberg: 04:15:02 GBM could be, certainly from a company perspective, it meets the criterion for timeline. There's no question that those patients do very poorly and therefore there's an opportunity to impact them and to see that impact quickly. Again, we've never, I don't think, done that as a registrational study certainly at Pfizer I've not been involved in any. I think it's a tough situation ...

T. Lawrence: 04:15:28 Zelana that's all you ever say, "It's a tough situation." Do you say anything else?

Goldberg: 04:15:38 I can't see reason it couldn't be done, let me put it that way, off the top of my head.

Wang: 04:15:43 So looking at what nano biotech is doing, I think that's what they're aiming for is the recurrent head and neck as indication. But that said even if you get registration it's a tiny population so it's not gonna do anything to the financial outlook for the company I don't think. I don't know where their game is, but to me it's not a game changer it's not like upfront you can apply your agent to a wide range of patients.

Goldberg: 04:16:15 And why would you not add recurrent metastatic and then do what companies are used to doing. That's a very real thing so, we have radiation, it's a recurrent disease, we treat it locally but then why not just add in the recurrent population in the metastatic population. And that's often done, and it's done in a way that allows a larger potential patient pool so it's easier to recruit and then there's a greater pool of potential patients to market to as well later on.

T. Lawrence: 04:16:52 Okay, any other comments from the audience or any questions, anything else our panel would like to add to the session as I see we're 53 seconds away from lunch so maybe ... Unless, anyone has a 53 second question maybe we'll call our panel. Thank you very much everybody for being here and for your contributions.

T. Lawrence: 04:17:10 Ah, before you walk away one second, Michael Powell, could you just stand up and wave to the group? Michael is our lead AACR representative and anyone who has any interest in AACR and science should wanna meet Michael because he's been a tremendous advocate for us in the radiation informing, the radiation sciences and medicine working group, and all the great things that ACR now is doing for radiation sciences and medicine. So, he's your man. Thank you Michael.

FDA-AACR-ASTRO Clinical Development of Drug-Radiotherapy Combinations Workshop
Transcript: The Debate

Tran: 00:01:14 Okay folks, just so we keep on time, and the many hundreds of people that are following the webcast can catch the lectures they want, we need to start on time.

00:01:27 So, it's my pleasure to introduce Dr. Daniel Spratt from the University of Michigan. Dr. Spratt is an Associate Chair in the department for clinical research. As I had said before, even though he's only a few years into his career, he's already been able to contribute quite a bit to the field of GU Oncology; not even just GU Radiation Oncology, but GU Oncology.

00:01:59 He's gonna be giving us a lecture on prognostic and predictive biomarkers. I am sure he will not disappoint.

Spratt: 00:02:14 Alright.

00:02:15 First, thank you so much Amanda and everyone for inviting me to speak today. Alright, so I have no relevant disclosures to this, and I will not be talking about IO on this talk. Just so you know.The objectives of the talk is really to understand the difference in the prognostic and predictive biomarkers, and really understand methods to use these biomarkers for drug approval for combinations with radiation therapy.

00:02:43 So when people hear the word biomarker, they think of things, genomics, transcriptomics, metabolomics, but really a biomarker could simply be checking someone's blood pressure, or their BMI or their tumor stage. But, in reality how we're using these in these trials, and I'll mainly discuss, and where most of the biomarkers are really relate to genetic and transcriptomic changes.

00:03:04 So what is a prognostic biomarker? Many of us know this, but just to make sure we're on the same page, essentially, this is real world personalized medicine. This is what AJCC staging is, is that they can tell you if you have a worse or better prognosis, but if you're treated or not treated, the hazard ratio would essentially be the same. It doesn't discern who should or should not be treated. Predictive biomarkers is the ultimate form of personalized medicine, and obviously this patient, these patients here on the left that are biomarker negative derived no benefit, and those that are positive have a very large benefit. So, the benefit is treatment specific.

00:03:47 And how do you prove a biomarker is predictive and not just prognostic? Obviously if you look at those curves, we can all tell, but formally, you do a test for an interaction between the biomarker and treatment group, and this needs to be performed. And so really what you're testing is an interaction between the treatment group, the biomarker, and the outcome of interest. And this, of course, should be statistically significant.

00:04:11 So, examples of prognostic biomarkers. There are thousands, if you just look at actually how many have been published. I mean, there might even be tens of thousands. I'll be talking mainly about prostate cancer today, these are just gene expression classifiers that are prognostic biomarkers, KI-67 in breast cancer. And some here are looking at me and they'll say MGMT is a predictive biomarker, but it's interaction test is p equals 0.29, it is not a

predictive biomarker. It is prognostic. Examples of predictive biomarkers, there's actually very few, just some of them are listed here.

00:04:48 So, this is data just for a publication we're putting out soon looking at the MolDX, so this is sort of they discuss and consult with CMS for approved gene expressions, so RNA based biomarkers. Many of you will not be familiar with probably many of these. I wasn't. But you'll see things that you are familiar with, like MammaPrint and other things in breast cancer. There's about forty of these on the market, ranging from whole transcriptome panels, to custom arrays, to just multi-gene PCR tests. And most of these are just prognostic biomarkers. MammaPrint is one of the select few that is a predictive gene expression classifier.But, predictive biomarkers that you're probably more familiar with is in colorectal cancer you look at RAS status, the wild type versus mutant, and of course, testing matters here for the benefit of Cetuximab.

00:05:38 And so here's a laundry list from just came out in Nature's scientific reports in 2017, that you hopefully, it's slightly large enough, that you can just see it. But these are most of the drugs that have gained approval with their companion biomarker listed here, and kind of how they were approved. Again, there's radiation is obviously not listed up here. And how were these approved? This is a Sankey plot here, or diagram, and so there's two points I want to make about this.

00:06:10 First, a number of the trials, they're actually not enriched trials. You know, they test all comers, and they often eventually then test an enriched population to prove that there is a significant interaction, and you can see here that some of the trials end up having a significant interaction, some obviously do not. But, what's very fascinating is that the majority of trials actually were only enriched. And what does that mean? That means that there was such strong mechanistic work, like BRAF, that you went into it just only taking the biomarker positive patients and putting them on trial. I think a purist might say, it'd be nice if you proved that, cause some of these may actually be prognostic biomarkers, but I think the mechanism for a lot of these are strong enough that it's safe to say they are predictive biomarkers.

00:06:57 So what you see from a lot of these trials here is they give you these tests of interaction, and you can see that some of these, and these are the companions, so you see the drug and the companion biomarker. Some of the interaction tests are borderline significant, some are clearly significant, and some are clearly not significant. But yet, that's the companion. So you can see here, with your biomarker positive or negative, for Exemastane and ESR1, it didn't actually seem to matter.

00:07:24 So, what about in radiation oncology? Well, prognostic biomarkers are prognostic, regardless of treatment. I just put the same list up, it doesn't matter if you get radiation or chemo. There is not, and I mean this and I have published upon predictive biomarkers so I'm negating my own work, there is not a validated CLIA certified predictive biomarker to predict dose or use of radiation therapy. Now, why is this? Well, as people have covered for the past two days, this is very complex. Immune cells, tumor cells, microenvironment, the circulating disease which can then reseed the primary site, the actual host factors, limitations of our pre-clinical models, this is a, safe to say, formidable opponent.

00:08:10 What I would push back on is that tumor cell radiosensitivity, and there is great work, some out of U of M but a lot out towards [inaudible 00:08:19] has done this work, where he took

a panel about forty-eight cell lines, and has a very good method of determining pre-clinical radiosensitivity, but this really ended up just being prognostic and not predictive, and so if all we focus on is the tumor cell, radiation as you've heard does a lot more than just affect tumor cells, so to get a true predictive biomarker, we're going to need to actually be looking at this whole microenvironment as well.

00:08:44 So, what about a different way? Rather than me going into the work, the failed work into this, what's another way that we can use biomarkers in an oncology, for drug approval? And you can use prognostic biomarkers, and obviously you could develop predictive biomarkers for combination agents. They may have unique, biological, and I added this in, synergy, with radiation therapy. So I said synergy, and in prostate cancer, I think we have probably the best example, which has not been discussed during this meeting, of a radiosensitizer that actually provides synergy.

00:09:18 If you look at patients who have hormone therapy, and then they go have surgery, 100% of them have viable disease. Patients who have radiation therapy, 40% will have viable disease. And if you combine them, only 20%. I'm not a mathematician, but that looks like synergy to me. But you can even show this for long term outcomes, like prostate cancer specific mortality. ADT in localized prostate cancer alone does not improve survival. In fact, it can hurt overall survival. In randomized trials, it almost cuts the rate of death by half when you add radiation to hormone therapy, and that when you compare surgery versus surgery and hormone therapy, or radiation versus radiation and hormone therapy, again, there's no impact of getting ADT with surgical patients, and there's a profound impact here, all with GI induced side effects are not increased. This is probably the best example, I'd argue, in radiation oncology, where chemotherapy, we've talking about where you're enhancing toxicity quite a bit.

00:10:21 But, so using prostate cancer and hormone therapy in an example, for drug approval, these are three of the common treatments for prostate cancer. I've left surgery off of here. But, radiation, hormone therapy, and taxane chemotherapy, and of course, we have no predictive biomarkers that are validated to guide their use. There's a lot of interplay, and that's why the results I showed you previously, the clinical outcomes that we've been working out, the the androgen receptor is almost like a master regulator. There's about thirty DNA repair genes that are regulated by the androgen receptor. And functional assays in patients and pre-clinical models, shown here, ARN509 is Apalutimide, shows that you can nicely inhibit DNA repair from the use of hormone therapy.

00:11:07 In addition, a very complex interaction is that when you radiate various cell lines with increasing dosage, you actually upregulate the androgen receptor, and then activate these DNA repair pathways. So, kind of the working model in prostate cancer is it's this cyclical, circular mechanism that AR is essentially, through DNA repair pathways, is promoting radiation resistance. So to start with, this will come into play a little bit later, is prognostic biomarkers and how they can be used with the radiation for drug approval. So, this is on label, this is approved. The deciphered test is a twenty-two gene gene expression classifier. About fifty papers have been published on this work. It's an Affymetrix high density microarray. They capture about 46,000 coding and non-coding genes. And so, early in 2017, we looked at, can we use this gene expression classifier across all of the published studies to actually infer if it has prognostic value? And so, the important point of this figure that I want to show you on the left, is this is ignoring a mans PSA, their Gleason score, any factor that we would normally use in clinic just using the biomarker, and you can already stratify

patients very nicely into those that'll have a high event rate versus a low event rate. And this is consistent, obviously, across all of the trials included in this meta-analysis. And because, like in any paper, you have to have a multi-variate analysis, the biomarker significantly still predicts, despite putting all of those clinical factors back in.

00:12:40 Now, clinically, none of us are just going to use a biomarker and ignore clinical factors. You're going to always use your staging factors when you're interpreting the biomarker. And so we then later, in 2017, published this much larger study in JCO, about 7,000 patients with retrospective and prospective cohorts, to integrate the clinical and pathologic characteristics we use daily with the genomic characteristics. And just to show you, this is what our clinical pathologic staging, this is what we use today in clinic, performs very poorly in terms of predicting which men will metastasize, where this is our new model that we've developed by integrating this biomarker into our clinical staging, and you can't really see these low risk guys, they're right here. And these are patients treated with radiation and hormone therapy.

00:13:28 So, hopefully, your mind is already working, if you wanted to do a clinical trial, to say, well if you're including a lot of these low risk guys and you're trying to add a drug, your trial will fail. You want to be trying to pre-select these patients here. And this is exactly, although not some interesting new therapy, but this is what's going on in NRGGU002. These are men that get surgery. They then have a persistently elevated PSA, so they have not been cured. And they get post-operative radiation therapy and hormone therapy. It's a randomization to plus or minus chemotherapy.

00:14:02 They are stratified by that decipher score, so this is a biomarker stratified trial, and what's interesting is that we published off of pooled data from that analysis last year, that this stratification, the low and intermediate risk patients, this is without chemo, have almost no events. Those with a high decipher score have a lot of events. So, you may say, should this trial have been designed to only be an enhanced trial, but you'd want prospective validation. So this is a phase two, if this signal is here in the phase two, their phase three will likely only include the decipher high patients, again, to capture an event rate to shorten the time for the trial to complete.

00:14:44 Now, what about predictive biomarkers in prostate cancer? Well, in 2017, Dr. Felix Feng, our resident, superstar resident, Dr. George Zhao, and myself presented at GASCO, this predictive biomarker to subtype luminal and basal subtypes of prostate cancer. For those unfamiliar with prostate cancer, it's kind of similar to breast cancer, even bladder cancer. There's a luminal and a basal cell cancer, typically we think comes from the luminal cells, with potential cross-talk with the basal cells. And in breast cancer, you may be familiar with the PAM50 classifier test, and so we essentially, which predicts potential hormone therapy benefit. We applied this breast cancer classifier to prostate cancer patients. And so taking a big step back, this is the paper published by Parker et al., about 200 patients who have breast cancer. You can see their luminal A, B, and basal subtypes. This is a heat map of their gene expression profiles from the genes listed here. And this is the prostate cohort from the cohort we assembled on about 1500 men. And remember, these are breast cancer, sort of genes so to speak in the sense that these were not, we didn't remove the genes that do nothing in prostate cancer. We didn't optimize this at all, and you can already kind of see a recapitulation of these subtypes. What's very interesting, although retrospective, when you do a kind of propensity matching by all of your clinical factors, policing score, PSA, receipt of radiation, et cetera, and you see who benefits essentially from post-operative ADT, what we

found is that luminal B patients have a significant benefit from the use of hormone therapy, whereas the non-luminal B patients had no benefit from hormone therapy, again going back to this interaction test that's highly significant.

00:16:33 So, we then, to kind of expand upon this, I just gave this talk a few weeks ago at GASCO, diving more into these molecular subtypes. Looking at androgen receptor signaling in prostate cancer, and what we've identified is actually, there's a small subset of prostate cancer, I call this the low AR active subclass of prostate cancer, and what we show here is that again these are those subtypes, basal, luminal B, luminal A, that when you have low AR activity, you essentially have a basal like phenotype. When you have high AR activity, you have a luminal like phenotype. And we would think that these patients over here would be the ones that respond best to hormone therapy.

00:17:15 And to validate this, I took the NCI60 cell lines, so these are not all prostate cancer, and we generated drug response quarters for eighty-nine oncology drugs that have drug response data available, and what you'll again, you're not supposed to be able to read these drugs just so you know, is that by AR activity, you can see low AR active tumors have a different drug response than high AR active tumors, and just kind of zooming in on the drugs that are most relevant or interesting right now in prostate cancer, let's take hormone therapy and taxane chemotherapy, the standards of care. This modeling would predict that those with higher AR activity, so the more luminal patients, would have increased drug sensitivity, whereas PARP inhibitors or platinum chemotherapy, is the low AR active may have improved drug response.

00:18:05 So this is a trial that I'm co-leading through the NRG with Dr. Felix Feng. It's NRGGU006, it's a phase two double blinded placebo-controlled randomized trial of Salvage radiation therapy, so radiation after surgery in men that have recurred with or without enhanced anti-androgen therapy, Apalutimide, the drug that recently just got FDA approved, I think it was last week or the week before, in a different setting. And so the unique aspect, this is the first potentially predictive biomarker stratified that NRG has run with radiation therapy. Let me go back. And what we're stratifying by is those molecular subtypes, and we're powering it also, not only for the primary endpoint of the overall cohort, but these luminal B patients. And this is a phase two, so if this actually proves to be true, our phase three trial would be a biomarker enhanced trial in those luminal B patients to see if we can finally have a predictive biomarker to decide who to give hormone therapy to.

00:19:05 In addition, a concept that I've been developing with Arul Chinnaiyan, and talking with various pharma companies, is we're going to be starting a trial in high risk prostate cancer, where we're going to be the TOPAR trial, many of you may be familiar with Johann de Bono, where in prostate cancer they showed similar with breast cancer, DNA damage repair alterations predicted a lap benefit, but we'll be getting basically germ line, somatic, DNA information.

00:19:36 We'll be getting that AR activity score on these patients, and we'll be combining a PARP inhibitor, and there's a lot of interest, because actually there's a Nature communications paper showing that when you combine ADT with PARP, you can almost induce a semi-synthetically lethal approach. And as Ted sort of has talked quite a bit about this, we'll be leveraging this tight serum design to make it a much more rapid, a cool way to find the right dose level. And again, if we see a signal here, because we'll be getting post-treatment biopsies on these patients, you can then envision once we deem this to be safe, you can do

a phase two again enhanced if either of these actually predict the patients to have improved response to therapy.

00:20:18 So, in conclusion, I think there has been a lot of success in developing CLIO grade prognostic tests for many malignancies. There's been isolated success stories for developing predictive biomarkers for systemic therapies, and there have been no success stories, despite my own work, yet for prospectively validated predictive biomarkers for the use of radiation or radiation therapy dose. I think that often we forget that both prognostic and predictive biomarkers can be used to personalize treatment and to design trials to select a patient subset, most likely to derive benefit from combination therapy, and these biomarkers would be ideal candidates to be used in combination therapy trials to increase the success of the trial and speed drug approval.

00:21:03 A lot of people to thank from across the nation, especially Dr. Lawrence, everyone at the University of Michigan, funding support, and I'll take any questions.

Speaker 1: 00:21:12 Hi, really, really nice talk. Can the disease state change from basal type to luminal type in prostate cancer? Is that known? [crosstalk 00:21:34]

Spratt: 00:21:34 Potentially, yes. So, in metastatic CRPC, so we have cell line models, not patient data, but in cell lines, you can take a link act derived cell, you can make it resistant to first generation hormone therapy, and link FAR is sort of a modified version of that. And you can even create an Enzalutamide resistant cell line, and you can switch it's subtype. In patients, it hasn't been looked at.

Speaker 2: 00:22:01 Hey, great talk. Quick question about what the field is thinking right now, going back to the idea of adjuvant end points and intermediate endpoints, because this is a really tough space. As you know, adjuvant prostate cancer. What's the data on looking at PSA? One of the issues with organ preservation and things like that, it's very location specific so it makes sense in brain, it makes sense in, you know, head and neck. Prostate, we need to figure out what's the local progression clinical significance, so I guess what's the field been doing? I know there's a nice CaP initiative, et cetera, but maybe you can...

Spratt: 00:22:36 So, I'm involved with that ICECaP initiative, and so we have a paper that just came out this year looking at intermediate endpoints for post-operative patients, so Salvage, demonstrating the five year distant metastasis appears to be potentially a surrogate endpoint, and we have access, I just got approval with Dr. Shipley to use the ART DOG9601 data to then validate, cause the ICECaP publication, as you're familiar with, didn't include almost any surgical trials, very few. So this is probably the best trial with very long-term outcome, and if we validate in that trial that it's a surrogate endpoint, I think that that will be what, at least through NRG, we're gonna be trying to push as a distant meds.

00:23:22 I have a lot of caution about using just a PSA endpoint until we can define the patients that are healthy enough, that will live long enough to where that is a surrogate endpoint, be it biochemical failure in isolation. At least in prostate cancer, I have a lot of concerns about because the competing risk of just death from any cause. But, distant metastasis, even if you looked from a quality of life, I think it is going to be, I'll be very surprised if it's not a surrogate endpoint, just like the ICECaP study showed for localized disease.

Speaker 3: 00:23:54 With respect to distant metastases, I mean that's a metastasis free survival, I guess endpoint which has already been used for registration with apalutimide, so.

Spratt: 00:24:04 Yeah, which is, well you probably have heard more than I have. There's been a lot of criticism of that decision because this is castration resistant prostate cancer, the FDA approved it for. But, absolutely. I think that's where we'll be trying to move our phase three trials because the R2G9601 trial that started in 1996 just got published effectively last year. That's twenty years. If they use distant meds, they could have published it about six, seven years earlier. That's a lot of money and a lot of time that could have been saved, and so I think that's gonna be the push going forward.

00:24:49 Alright, thank you guys.

Walker: 00:25:05 Okay, thanks Dan, that was a great talk. So we're gonna switch gears a little bit. First of all, I just wanna thank everyone for the phenomenal panelists this morning. I think everyone was really pleased with the conversations and the presentations, they were all very excellent. What we're gonna do now is a debate. So I've been talking to a lot of people in radiation oncology over the past few years about what's really gonna take off this field in terms of radiation drug combinations, and what I've found is interesting, is that a lot of the discussions are very polarized. It almost reminds me of the phrase, believers and non-believers with low-grade glioma trials in terms of, is it immunotherapy, or is it gonna be something else?

00:25:44 So that really gets us ready for this debate, that really is posing the question, what is going to be the next drug approved in combination with radiation? And what do I even mean by that, first of all. So, I mean the indication in the label that the FDA grants is the drug is for use in combination with radiation, so the PACIFIC trial and the Durvalumab approval was great, radiation is in the statement, but the drugs not given with radiation concurrently. So, we're close, but we're not quite there yet. So what we're gonna do is Jim Welsh and Ted Lawrence are gonna each present one side, so Jim Welsh is gonna try to convince us that the next drug approved with radiation is going to be an IO agent or an immunotherapy agent, and then Ted Lawrence is gonna try to convince us that the next drug approved with radiation will be something else, another targeted agent. And so they're gonna each give ten to twelve minutes, and then we have a few more minutes for rebuttal, and then you get to decide who wins. So, with that, I guess I'll hand it over to Jim.

Welsh: 00:26:50 Well, thank you for having me here, and a topic I'm happy to debate any time and take on with my worthy opponent. So, first I have to touch on Ted's amazing ripple effect, I bet everyone in this audience has a similar story on how Ted has really affected their lives. I never had the pleasure of training with Ted, but my background is I came from Genentech, I went into radiation oncology, I was passionate about biology and no one really did much, and Ted started the astrotranslational conference, which was amazing when I saw this go out. And I actually had nothing ready for it, and I wrote him kind of a pathetic email saying I really am passionate about this, I wanna be there. I know my abstracts not good, but next year, it'll be good, so please give me a travel grant, and he did. And it literally was one of these life changing events, cause I met physician-scientist there, Keith Cengle at Penn, many of you may know him, and what he was doing is he got resources to run his lab while he went back in the clinic, and this light bulb just went off, I'm like, that's exactly what I'm gonna do, as a first year resident.

00:27:46 So, I ended up developing a drug during my residency, licensed that out, took that revenue to keep running my lab. That drug ended up getting me involved in Steve Job's case because he had the similar mutation, so I worked on his case, which lead to a company I created called Molecular Match, which now does real time decision support for EMR's and for pairs. And we do that for genomics in immuno. This obviously led to my job too at MD Anderson. So, at MD Anderson, we have several strategic initiatives. I'm head of immunoradiation, which is a great position, I enjoy that. And then recently I started MD Anderson's first immuno-oncology company, Onco-Response. So, Ted is now tainted by some immune stuff that has happened since his conference started. But I just wanted to reassure everyone that you might be worried that I'll take it easy on Ted, because he's done so much for all of us, but don't worry. For a scientific integrity, I'm going after it, and no hold disbarred here. I'm gonna take him out.

00:28:41 Okay, so I've got three pillars for my argument. The first one is the radiation turns the tumor into an ensitu vaccine, you've heard a ton about that. The prior speakers today really did a beautiful job. Then I'm gonna talk about [inaudible 00:28:54] disease, and letting the immune address the microscopic, you've heard a little less on that. And then I'll tell you about using radiation to pull in T-cells, which I don't think you've heard too much about at all.

00:29:00 Using radiation to pull in T Cells, which I don't think you've heard much about, at all. So there's a very strong rational, here. The immuno cycle is a cycle, right? And, so, what do a lot of our Med/On colleagues do? You know they're doing step four with step six, without antigen release, but the beauty of radiation is we can start the cycle, cause this antigen release, and really drive it and use immunotherapy ,selectively, around that. So can radiation turn the tumor into an in situ vaccine? This is a nice piece of data out of Stanford, where the green cells, here, are the CD3 cells you see pre and post radiation. It certainly does. And then they showed if you were to radiate the tumor in the mouse, versus radiating the tumor outside, and then injecting it, it's much better in terms of vaccination. So, better to kill it inside.

00:29:45 So, what about clinical data? So, now I'm presenting more of this clinical data is getting ready. This is a 100 patient trial with ippian radiation, with five different arms. We're looking at sequencing. Is it better to do ippi before radiation? Lung versus liver in different doses? So, what we found it's better to sequence it. We get a better response with CTLA-4, beforehand, probably depleting the tregs, and our best group in lung, we get a clinical benefit of up to 42% in the non-irradiated tumors. And, again, this is no melanoma in here. So they're not typically going to respond. This is the waterfall plot. This is with the irradiated lesions, included. So, kind of cheating a little bit, if you will. This is without the radiated lesions, overall 51% clinical benefit, in non-irradiated lesions.

00:30:29 So, similar thing with OX40. You heard Marca did a beautiful job talking about this. We have similar data. And what we found, is radiation increases the OX40 on the CD4 cells. And then, it works. So we did this data, literally a week later, the very first patient at MD Anderson got treated on an OX40 drug, didn't work. Here's the tumor, it's progressing on OX40. They asked me to irradiate it, and I irradiated this spot, totally went away. Really nice abscopal on the first patient at Anderson, treated with OX40.

00:30:57 But we need to get beyond PD1, right? I mean, these were studies we were designing five, six years ago. We gotta go beyond PD1 and CTLA-4. So this is the PD1 resistant model that

my group published awhile ago. Now we're testing many new agents and PD1 resistance for abscopal. This is PD1. This is CTLA-4. These are a lot of the hotter, new immuno agents and here is a beautiful one. Where the tumor actually grows, and then just completely flat-lines, and gets a great response. So this will be in clinic, in a combo, in about two months. So that's the first argument.

00:31:26 Now this other concept of, if you can ... Abscopal's hard to do, okay? But if you can block out and irradiate all the gross disease, and let the immune system address the microscopic, without stroma, it really does work. And, so, this just shows you the T cells. So here you see them in the stroma, they're not in the tumor, this is graphed here. They don't get in. This is why I think the Pacific Study was so strong and so positive. Even though I think everything they did wrong ... from a radiation stand-point was wrong. The fractionation was wrong, they had concurrent chemo, they had steroids, yet it's still a massively positive study, because the immune jug only had to address microscopic disease. So this is close to winning the debate. It was approved after. And we know if the drug was given within 14 days, these people actually did a lot better than the people who had the PD1 drug after ... for that duration. But it's not concurrently [inaudible 00:32:16] moving there.

00:32:17 So a whole new concept now, that I'm working on, is using radiation in very different doses to pull in T cells. So when I was running that ippi trial, I've had this really interesting case. And this is a spot I treated with radiation, here. Went away. Very big tumor. Not treated. But got scatter, which you can see, here. Totally went away. And then the tumors below it did not go away at all. So, it's not an ippi response, otherwise everything would have. So, I started looking at this more and more, and I find tons of examples of it. I took every patient on that 100 patient ippi trial, I took every tumor, and we looked at the response. If it had no low-dose, or it got low-dose scatter radiation. If there was no low-dose, the response rate was 10%, if it got low-dose, it was 40%. So, it's pretty dramatic. I have many cases of it. I've only seen people, for the last four years, on my trials with immuno radiation.

00:33:06 And, so, it's really fun going to clinic, because I never know what I'm going to see. I just saw this patient Wednesday. This is a patient treated with this tumor, right here, with ippian radiation. And this is all the other tumor, here, that's now knocked out on PET. The reason I wanted to show this is because, what do we use for criteria? RI resist criteria. This patient's progressing, based on resist criteria, right? This tumor is bigger, based on a CT scan, but these are the tumors that got low-dose, on PET now, they look biologically dead. So, something interesting to pay attention to.

00:33:39 So, Ted may talk about some other things, too. Parp inhibitors, other things, but a lot of these other pathways actually have immunologic complications. So this is nice data that shows that parp inhibitors actually can up-regulate PDL1. P53, we all know P53; the guardian of the genome. My first boss at GenenTech actually cloned P53, and we had this paper that came out that showed P53 loss leads to loss of [inaudible 00:34:03], which actually up-regulates PDL1. Implicating PDL1 into the P53 access. So a lot of biologics met EGFR, right? Went actually have immuno aspects that we actually just ignored, or weren't smart enough to figure out, back in the day.

00:34:19 So with that, I'm going to stop with one closing comment. So Michigan is not actually a name of ... it's actually an acronym, right? We use a lot of acronyms in radiation oncology. And Ted may not want me to share this acronym with you, but I'm going to. So Michigan actually means, miraculously immunotherapy can help improve grays, and the "A-N" is for?

Approve now. So every time you see Michigan on his slide, I want you to think about this, and I want you to remember what it stands for. So with that, I'll turn it over to my worthy opponent.

T. Lawrence: 00:34:59 I didn't guess the acronym. That's great. Okay. Okay, so again, I want to return to our actual ... Charge to us. This house believes that the next agent to be FDA approved with radiation therapy ... that's why the Pacific Trial does not count, right ... with radiation therapy ... will be immuno therapeutic, and I am against. So, sadly, I have no financial disclosures. They're irrelevant to this talk. And I will mention the off-label use, or investigation use of [inaudible 00:35:32] inhibitor, and the views expressed in this talk, do not represent those of ASCR, ASTER, or the FDA, or, frankly, the speaker, himself. They should be received in the spirit of stimulating discussion, and hopefully a few smiles from the audience.

00:35:49 So, I have to pause for a second. Abbreviated immunotherapy is IT, rather than IO. I picked IT, because it is immunotherapy, and secondly, it's just like our IT departments, which is very expensive and partially effective. But the path to approval is filled with obsticals. Immunotherapy can be found to cure every problem of mankind in the coming years. I am convinced of it. But, I don't think it has a strong approval pathway in combination with radiation. The fundamental problems for IT are the focuses on radiation therapy stimulating, where I will continue to call the "illusive" ... I should have said the "antidotal" ... "Illusive Antidotal Abscopal Effect." Getting your response, where we actually are not even pointing the beam. And the big question is, how to differentiate the abscopal effect from the systemic effect of IT? Next responses are rare. These abscopal effects, when they do occur, and we have heard some examples from [inaudible 00:36:43], but they tend to be rare. And because the mechanisms are very mysterious, there are going to be too many approaches for all of the IT group to come together and figure out how to run the key study.

00:36:57 The approval path of radiation [inaudible 00:36:59] drugs is slow, but it is straightforward. Drugs work by increasing the response, or producing protection from radiation, where we point the beam. The responses can be easily measured. The responses are common. And because the mechanisms are clearer, it's easier to get agreement on dosing schedule. So our side has the successes, and we have more in the wings.

00:37:21 So, immunotherapy is going to cure everything. It's going to be better than sex, drugs, and rock and roll. We know that already. Immunotherapy with bad breath, immunotherapy is going to take care of it. I'm sure there's some form of immunotherapy will eliminate bad breath from the world. Immunotherapy with bad hair, bad hair's a problem. Even this guy had it. Immunotherapy's going to cure it. I'm sure of it. No problem. Bad taste? I don't know if anyone ... you ever seen Warner dressed like that? But I think immunotherapy even has the potential to get rid of bad taste. So I look at a tremendous future for immunotherapy and all of its various forms. But to get FDA approval, with radiation therapy, IT is counting on the illusive abscopal effect. And this is the definition I got from one of the papers describing this. The abscopal effect is a phenomenon, in which local radiotherapy is associated with regression of metastatic cancer at a distance from the irradiated site. That's our basic definition, right?

00:38:26 I've taken chunks of text from two of the earlier papers in this area. "The patient was treated with two cycles of Avelumab, followed by stereotactic radiotherapy, to two to eight metastasis, two additional cycles of ippi, remarkably ... " When everyone says, "remarkably", put your hand on your wallet ... "remarkably, the subsequent positron emission

tomography, computed tomography, showed that all metastases had completely resolved." That's one paper.

00:38:52 Second, "He was treated with intercranial stereotactic radiosurgery, and immunotherapy with Avelumab, the patient received palliative radiation to his primary melanoma, it delayed, but rebilshed response in all the treated cutaneous metastasis. Then this type of response and distant tumors, after local radiotherapy, is known as the abscopal effect." It does not, the abscopal effect, it's likely a systemic effect of immunotherapy. The patient was treated with two cycles of Avelumab, and two additional cycles of Avelumab, in that first paper. He was treated with stereotactic radiotherapy and immunotherapy with Avelumab. So we have to take some care in distinguishing what could be the direct response to immunotherapy, which does work in melanoma, from just hoping that, somehow, it was related to the fact that we gave radiation therapy. And I think, actually, Dr. Sprat had a question about that, earlier, on one of the talks. Or was about to ask that question if he ... well, I didn't give him the chance to.

00:39:51 So, I want to go back to the original brief report. This was the father of all abscopal effects in melanoma. And this is the paper from Memorial, and I think everybody must have read it, but the key factor I want to point out to you that presents to us a very obvious problem with doing immunotherapy, is the following. 22 authors, one response. A ratio of 22 authors per response. So what's this going to mean for future trials? So I work carefully with a statistician in our department, Matt Skipper, and he plotted for me, the number of responses, versus the number of authors that need to be involved in a study. And so for any reasonable study, it's probably going to have to take, at least, 50 responses to get some sort of statistically significant difference between the two arms. And, so, Dr. Skipper, with his PHD in biostatistics, was able to plot out for me, and show, that this is going to require over 1,000 authors, just to publish this paper. Over 1,000. And Matt is preparing, by the way, a manuscript on this general topic, of how do you plot a graph that shows you a slope of 22, when there's 22 authors per one response. So this is a room filled with 1,000 unhappy radiation oncologists, who all have had to participate in this trial, just to try to get that number of responses.

00:41:23 Now, finally, IT trials are incredibly disorganized. I pulled this paper out of a recent Red Journal paper from 2016. So we have some studies with vaccination approaches, CTLA floor approaches, PD1 approaches, other approaches. We have different cancer types, we have different doses per fraction, we have different fractionation schemes, we have different timings of all these things. How are we ever going to make sense of any of this to pull together the definitive study? It's a mess. So, I think this is a desperate situation for immunotherapy.

00:41:58 Now, we actually have some successes with drugs. I know a lot of people aren't using Amifostine anymore, because we have intentionally modulated radiation therapy, but this was a successful study, ran by Dr. Brazell and his colleagues, comparison of mean scores, a xerostomia score during the post-treatment follow-up period, and patients receiving Amifostine, showing up here on this line. Plus, radiotherapy, has significantly higher a means score. So this was a radio-protection approach, and the result of this was, Amifostine with radiation, FDA approved. We have an example that's been mentioned in several other of the talks, earlier. I'll just spend a moment on it, but you know this. With radiation therapy, combined with [inaudible 00:42:38] versus radiation therapy alone. For patients with head and neck cancer, overall survival by treatment, five year median update with a strongly

statistical significant approval in survival. And what was the result of this? [inaudible 00:42:51] with radiation therapy, FDA approved.

00:42:53 So we actually have the examples, although it's been difficult, of drugs that have made it through, and actually made it all the way to FDA approval. We have some things in the wings, and Meredith showed you this slide, and I'll just make a very brief mention of it. ACD1775, just as a quick example from her own work, which [inaudible 00:43:13] radiation, producing an overall median survival of 22.6 months, essentially equal to the median overall survival of resected patients with pancreatic cancer. And these were all desperately un-resected patients. I just give this as one example of many. Kyle mentioned some, Meredith mentioned some, there are other studies that are going on that are showing that drugs are making progress. So we have a lot in the wings in addition to the successes.

00:43:38 So I think we're all going to agree that immunotherapy is better than sliced bread. It's just the most amazing thing. But this summarizes that maybe immunotherapy is cool, but drugs will rule. And we look at the ease of assessing response in immunotherapy, it's hard, it's a systemic response, it's an elusive abscopal effect, which is it? With drugs, it's easy. Just look inside where the beam was. You'll see the responses. As far as response rates are concerned, rare. You need 1,000 physicians to carry out the study. With response rates, and with drugs, are common. Getting an agreement on the right trial, is hard. Every citacin and every T cell has it's own fan club. So we're all working toward ... it's gotta be my T cell. And in the case of drugs, targeted therapies are, wait for it, targeted. So, it's usually much easier to come up with a conclusion. And successes, so far, are none in the case of immunotherapy, but in the case of drugs, drugs are already FDA approved with radiation. So, the next agent with be FDA approved, combined with radiation therapy will be, a drug. I rest my case.

Welsh: 00:44:52 Alright, well Ted made some good points, I have to admit. But I have another pilar of support that I'm going to bring out, which is hardware. You know, I live on the biology side. I only really only focus on biologics. But there's actually a couple hardware tricks that actually might make this doable for us. So I'm going to tell you about that. Proton dosimetry, proton biology, and autonomous stereotactic. Okay, so this is a paper we wrote after O617, showed higher dose had worse local control. How can that be? We hypothesized that it's killing their immune cells. So, if you look at the start of radiation, these are the immune cells, the neutrophils, and this is how they precipitously decrease with radiation. It's only the neutrophils that are very sensitive, and this drop in neutrophil on multi [inaudible 00:45:35] analysis, was more prognostic than any other factor, including lymph nodes. So, immune cells are important.

00:45:41 So the biggest factor for killing these immune cells, is the low-dose radiation. So when we do IMRT, and we bathe the lung in that low-dose, this is what kills it. The V5 was the most prognostic factor. Well, protons is beautiful for this. So here's a proton lung plan, versus an IMRT plan, and that V5 is dramatically different. So protons is actually ... could be a hope for us to improve immune response.

00:46:03 What about the biology of protons? You know, the vision that we have now at Anderson, is we will be tailoring immunotherapies to photons, protons, and now, carbon, because they all have different biological properties. So here's an example. Apoptosis is no good. When we kill a cell, and it dies through apoptosis, it does not stimulate a T cell response. It gets cleared away, and there's no immune priming. Not good. We actually now have a drug now

that will block that mechanism from happening, so any apoptotic cell you get, can only activate a T cell. Which is great for radiation oncology. Now protons, ironically, cause more apoptosis than photons. So, here, you can see dose-per-dose of [inaudible 00:46:43] of radiation afterwards. You're getting more apoptosis, which traditionally, is not good. But you could fix that now, with the potential drug that addresses that mechanism. So one thing we'll be looking at.

00:46:53 So as you guys heard, in my ASTRO talk that I've given, I have a self-driving car. And once you have a self-driving car, it literally changes your outlook on everything. Why can't everything be autonomous, and every time I'm doc of the day, and I'm covering all the stereotactic in the morning, I'm like, "Why can't we just automate this?" So, you know, self-driving cars, a heavy lift. A lot of calculations to think about, a VMAT plan is simple. It's a circle. Right? Just automate it. So the vision we have is, could we make stereotactic autonomous? So one of the machines that we're working with is the Reflection Company has a biologically guided radiation machine. So this is three pieces of hardware in one tube. A PET, a LINAK, and a CT. And it uses the PET emission to then fire at the tumor in real time, without motion or uncertainty. So a neat concept, but what this now potentially gives you is the potential to really automate the whole process.

00:47:46 So with that, could we put that ... As we do in the brain why ... We'll do 15 stereotactic in the brain, and we don't think about it. But in the body, we can only do one or two. So we're working on concepts, now, where we can do autonomous stereotactic to multiple sites. And what was great with Steve Chmura, at ... Chicago's also working on similar concepts with them, and we came up with exactly the same design, but mine was written horizontally, and his was vertically. But we're thinking exactly the same about this concept. So we're going to take patients with stage four disease, up to 10 sites, we're going to randomize them to PD1, or PD1 with radiation to every site, ale the Pacific Study because it worked. Because you knocked out all of the gross disease, and now the immune system addresses the microscopics. We can't do this with our current technology, but it just shows how technology could actually help win the debate that the next drug will be with immuno.

00:48:33 So with that, since we're close to Washington, I wanted to bring in some Washington politics. Some of you may not know this, but Stormy Daniels, she was actually into radiobiology, and actually worked in our field, but with the hard RO1 funding era, she wasn't able to get her R1 renewed, and she had to change professions, and that's how she got involved with Donald Trump. So, I told her I was coming to town to have this debate, and this is what she said to me. She said, "You know, I may not have voted for Donald Trump, but you definitely have my vote, Jim, that immunotherapy will be the next drug approved with radiation." So, let Stormy have the final word.

T. Lawrence: 00:49:15 Well, I knew my learned colleague would come up and try to baffle you with more anecdotes, and more promises of what's going to happen in the future. But I still think that when it ... and I do have to confess that we don't have an auto ... I don't drive an automated vehicle. I still have a fountain pen that I use to make my notes with. But I still think that the classic approaches of using targeted therapies that ... where the target is known, where the beam is known, are still going to win the day. That's my rebuttable to your anecdote.

Walker: 00:50:00 What are we doing?

T. Lawrence: 00:50:00 You take a vote. And-

Walker: 00:50:03 We're going to vote via applause-

T. Lawrence: 00:50:03 ... and we announce that it's a tie.

Walker: 00:50:08 Poor folks on the webcast can't see the hands. So we're going to take a vote. Those who think that Jim won this debate, and the next drug approved with radiation is going to be an immunotherapy drug, raise your hand. Alright. About half. Those who think that Dr. Lawrence won this debate, and the next drug approved with radiation, will be a drug that is not an immunotherapy agent, raise your hand. About half. Fantastic. It's a tie. Time will tell.

T. Lawrence: 00:50:42 I did forget. And thank you, Jim, for those nice comments about me. I did write that down, and forget to say that, thank you.

Walker: 00:50:57 Okay, great. So, next, we'll have the final panelists come up and we have a 30 minute panel, and then we'll be finished with the workshop.

Goldberg: 00:51:06 I'm not on your slide. Am I supposed to be here?

Walker: 00:51:15 Or shoot, yes, you're supposed to be here.

Goldberg: 00:51:20 That's okay.

Walker: 00:51:27 Excellent, so yeah. I just want to reiterate, thank you everyone for a phenomenal job on all the presentations and the panels. I think this has been an excellent workshop. So what we're going to do now, is just sort of close it out with some additional discussion. So we have an excellent panel, right here, and what I'm going to do is just allow each panelist to introduce themselves, briefly, and then, really since the goal is to have some sort of output from this meeting; where are we headed? I think Ricky Sharma's ... the CT Read Conference really put out wonderful consensus statements, which will be ultimately a goal of this workshop, as well. So I wanted to get all the panelists' thoughts on, really, what are some action items that we can leave here, today, with. So, we'll start with you, Zelanna, if you want.

Goldberg: 00:52:12 I'm Zelenna Goldberg, I work for Pfizer. I'm sure nobody's heard my voice this whole conference. I'm talking without the mic on. So no one did hear that. I am Zelanna Goldberg. I work for Pfizer. I'm sure everybody knows that by now. What do I think we can do? I think I hammered on the FDA a lot, during these last couple of days. I think there a couple other things we haven't really even mentioned, as yet, and I'd like to bring up one that I think is within our power to address. And that is the academic pressures to do independent research for each person.

00:52:53 Investigator initiated research gets over valued in academic promotion, and in the designation of the NCI designated cancer centers. Inconsequentially, the investigators who are participating in the large, randomized studies that take hundreds of sites to be successful, are not given full academic credit for the amount of time they spend, and the hard work that they do. And the fact that these larger studies are the ones that genuinely change treatment. They improve cancer care and cure. That is a problem across all disciplines, I think. But I think it impacts radiation oncology more so, because we don't have as strong a network of people working the community who still want to be involved in

studies. So the burden of registrational studies fall heavier on academics sites. So I think that's within our power to fix.

00:54:03 One of the questions I was asked earlier, that I didn't really address fully, what do we need, really, to start a radiation study from industry? We need to know if we give the drug before, during, or after. The doses are not ... We're not going to know doses before we put them in people. But we do need to know schedules, and that very simple mouse experiment that was done with giving the PDL1, PD1 inhibitors a concurrent, versus sequential, was the entire under-pinning of the Javelin 100 Study in Havenic. Wasn't a big experiment, but it was very influential.

Iannone: 00:54:48 Hi, I'm Rob Iannone, I head the late stage Immuno Oncology Development Group at AstraZeneca. I did make some notes from the excellent talks I was listening to, earlier today. Before I do so, though, I wanted to just make a comment on Ted's speculation that immunotherapies could cure gray hair, and actually may have seen the publication by Rivera in JAMA Dermatology of a series of 14 patients who had re- pigmentation-

T. Lawrence: 00:55:17 Oh my gosh!

Iannone: 00:55:17 ... after a PD1 inhibitor. So, I think it's actually possible.

00:55:26 So there's so much, but let me see if I can distill it down to the three key actions that I think will be most critical. One is around the safety. I think we heard about a lot of data suggesting that radiation and immunotherapies can be given safely together. But I think it will be important to be systematic and careful about how we do those safety experiments. I'm expecting that there may be differences between disease sites, such as head/neck, or lung, and I think that, depending on the combination agents, whether we're talking about combining just with immunotherapies, or other things like DDR agents, the safety profiles might be quite different.

00:56:08 And one big lesson learned from me, from the Pacific Trial, is the value of a placebo controlled arm in such a study, because it was clear that there were immune-like toxicities occurring on the placebo arm. Even things like, myocarditis. That would be hard to distinguish if it weren't randomized and placebo controlled. So I think they'll need to be some careful work to sort that out. The next, and I'm thinking about Annie Min's presentation, in particular. More to understand. So we see results like Pacific, but more to understand why that was such a positive trial. Does it have to do with some of the interesting potential radiation synergies, or does it have something to do with tumor burden, as Annie was pointing out. And I think trying to parse that out, is going to be very helpful, because it will drive how we select the patient population. Should we be looking at earlier stage disease? What about oligomets, versus how we might approach metastatic disease.

00:57:10 If, on the other hand, the radiation synergy is critical, then we need to carefully parse how best to deliver that. Things like dose, the type of radiation given, and what the fields would be. I was trained as a bone marrow transplanter, so the best way to get in and out an unrelated allogeneic graph, was to radiate lymph nodes. So, clearly, there must be some optimization around how to deliver the radiation.

00:57:40 And then lastly, I was thinking quite a bit around sequencing and timing. You said, "Before, during, or after, or possibly-

Goldberg: 00:57:48 Or all of the above.

Iannone: 00:57:48 ... all of the above."

Goldberg: 00:57:50 Yeah.

Iannone: 00:57:50 So, thank you.

Kluetz: 00:57:54 So, again, my name is Paul Kluetz. I'm with the Oncology Center of Excellence. And I wanted to thank Amanda, and all of her colleagues for putting this together. I think it's been a very good workshop, and I've learned a lot, and

00:58:00 Putting this together. I think it's been very ... A very good workshop and I've learned a lot, and I also just wanted to mention personally that Amanda's been just an amazing person to be able to work with and have some radiation oncology expertise with an oncology and the FDA, so I think it was to your benefit, actually your entire field's benefit to have her 'cause I think she's done some amazing things.

00:58:18 As I listened to the last couple days, I just wanted to talk briefly about the three main things that I think FDA can help a little bit with and that is, trial objectives, trial design issues and endpoint issues 'cause I think that came up over and over and over again.

00:58:32 As far as trial objectives, I think I heard that there was ... there's an ethicacy objective and there's even some subtly in there. Is radiation going to used as the backbone? Is radiation going to be used as the drug? I think that's very interesting and you should parse that out carefully. But, there's a big safety tolerability part of this too and I know when I used to do the systemic therapy part of the head and neck cancer back in fellowship, it's a really challenging regimen to get through, so I think looking at that comparative tolerability is something that will be really interesting and that may be where we can use some of these complimentary PRO and other tools.

00:59:10 In fact, the Friends of Cancer Research and FTM and several other people are involved in a work group looking at comparative tolerability and how ... what would be the measures that would be able to define a regulatory path for an indication such as that.

00:59:23 For trial design issues, I think things to think about are the heterogeneity of the delivery of your therapy and I think that's come up a couple now. There's so many different ways to deliver radiation therapy and when we have a trial, we try to reduce as many of the variables as possible, and so you'll have to be very careful with that.

00:59:40 The quality control, I was kind of ... It opened my eyes a little bit to the quality of control of interventions, like surgery ... We knew surgery is a key satisfaction factor for surgical trials because the quality of the surgery means everything in many oncologist settings, equally important is the quality of the radiation ... the curative radiation being administered and that was really eye opening from Jessica Lowenstein's talk, so that's going to have be considered and then radiation as drug or radiation as backbone, as I mentioned.

01:00:06 Endpoint issues. I think it's important if you come out with anything, to out with the idea that the FDA is open to different endpoints. We are not married to overall survival as the only endpoint in the clinical trial. We understand it is a gold standard and has a lot of great strengths, but we know its limitations as well. We will almost also get radiographic endpoints. We would like to see what survival does regardless of its primary endpoint and the standard safety complement these with clinical outcomes that you can find and one of those clinical outcomes is organ preservation or morbid procedures and as Skidon talked about and as I've talked about, that's an endpoint like any other with strengths and limitations. The limitation is basis associated with investigator decision making and you have to cover yourself for that.

01:00:50 Moving forward, I'd say action item number one would be define your priority trial contexts and make sure that you attack context by context 'cause it'll be different, including disease. Within those contexts, look at your available endpoints. If it's specifically head and neck, that's going to have some different endpoint stuff then would be prostate, then would be others, and then I would hold disease specific working groups to look at organ preservation specifically as an endpoint to try to understand what the strengths and limitations are of that endpoint in the different contexts.

Sharma: 01:01:26 Good afternoon. My name is Ricky Sharma. I'm the chair of radiation oncology at UCL in London and I led the CT Rad working group that published the consensus statements that have been referred to several times during this meeting, so thank you for your acknowledgement of that work.

01:01:45 I think this has been an absolutely fantastic meeting. It's been like a celebration of some of the most exciting areas in radiation oncology and I'm just amazed at how AACR pulled it together in just three months, basically, which is just amazing. If we get it right, I suppose we'll be looking back on this meeting in 10 years and saying, "Well, what was all the fuss about? Look at all these combined registrations and drug radiotherapy registrations", but it was interesting to hear how people thought that in 2006 was going to open the flood gates of all these new drugs plus radiotherapy and there have been zero since then, so I think we do have to get it right.

01:02:26 In terms of distilling it down to three points, that's tricky. Firstly, with the preclinical package, bringing together some of points made by Tom Palmby and Tim Illidge, it brought home to me how important it is to concentrate on safety in that preclinical package and we don't always do that as academics 'cause it's difficult to publish that work, but in fact, it's really critical for moving that drug radiotherapy combination through to the next stage, so I think we need to think about that in terms of the preclinical labs and RadCom, for example, in the UK and maybe a network of labs in the US, which would be very nice.

01:03:10 Secondly, with regard to clinical trials from Paul's talk and from that whole session about endpoints, I was ... I learned a lot about endpoints I'd never even thought about and it's great to hear how flexible the regulators can be about endpoints, and so we need to think about that with regard to the endpoints, but also with regard to patient selection, 'cause that was a point that kept coming out through the meeting. Patient selection is really critical to the success of these trials.

01:03:40 Thirdly, in terms of immuno oncology, it's just amazing how much activity's going on there and how diverse that activity is, so I think there the issue is really identifying the key

questions, so pharma said that they need the key opinion leaders for that, and I think those academics also need to talk to consumers and patients and really define those key clinical questions, so that we can harness the resources in the right way.

01:04:12 Ultimately, what we're trying to do, not just for immuno oncology, but for all of us is to bring together the academics, pharma and the regulators for patient benefit, so we have to keep track of that. Thank you.

Le: 01:04:27 My name is Quynh Le and I'm a chair of radiation oncology at Stanford. I do run a lab in looking at repurposing a drug for xerostomia prevention, but my hat in clinical trial is I run the head and neck committee for energy oncology and within the committee we run a gamut of trials. We have GAT trials that look at mile marker, EBB DNA for enrichment for patient for advin therapy. We're looking at developing a phrase three trial for patient reported outcome for very good risk patient population, and then we have the pile on study where we add more drugs to patient would ... high risk patient, so we think quite a bit and in head and neck cancer, I think we've reached to the point where we at the level of toxicity, we cannot add more to many of these patients, so the question is, how we best select the patient?

01:05:17 We have also developing ... It used to be everybody was treated the same way, but now we're learning larynx cancer patients are different from hypopharynx cancer patient, from oral pharynx patients, so we're sub setting patients quite a bit and so, one of the thing that we think quite a bit ... a lot about is endpoints, so that's why I keep harping on the endpoints here, and as an international group, we've actually put ... get together what we ... through NCI Global to form this head and neck inter group with all the corporate groups internationally, as well as big center together and we are looking to harmonize things because I think endpoints an endpoint as you mentioned overall survival is something that you can measure ... easily measure, but definition of other things, such as progression fee survival or cost specific survival, etc cetera can be depend on you define ... define it.

01:06:09 For example, if you have surgery immediately after radiation is it considered part of your initial package or is it salbit surgery or is it an event? Some of these things, we're really working together and we hope to be able to get inputs from the FDA and the European agency to say how the definition we get together how acceptable they are.

01:06:29 The other thing we also trying to do is harmonize a few things that I think safety is really important from a radiation standpoint. I get out of that here, as well. The problem that we're doing now with clinical trials, when we had drugs or new drugs to radiation is that we really can do a three by three because toxicity is different pattern, and we can't really run a large study, wait four years for toxicity to enter, so then we do these eight to 10 patient run in study, and we think that's feasible and move onto a big phrase three study.

01:07:03 I think something like platform study would actually allow us to get more drugs into earlier chemo radiation setting with a little bit larger patient population to get more confidence enable around toxicity and get more time to look at toxicity then what we're doing right now with early run in type of situation, and I think the platform study's really crucial from many of us to get in at least in the head neck setting. I think the last thing that I ... the radiation quality is important, and I don't know if you know, but EIAE does have a way to look at radiation benchmarking for a lot of developing country and when you do this studies with large phase three trial, you bring in patients with two to ... it's into the ... enroll two to

three patients in each of these study, and we've got data that've shown before from the RTOD is large occurrence do better, a 10% survival in it.

01:08:01 We also have data that quality control for both concurring as to symmetry improve local regional control in these patient, so that's one ... the thing we hope to do with the inter group is to collaborate together with IEAE as well as the IROC, which is the center set up by NCI to come out with some sort of benchmark baseline quality. Obviously, when you do something like this, you can't really get a lot of patients ... if the bar's set so high, nobody can get there, but we have to have a common denominator and a common bar and I think those are really the three main points I want to bring up is really the quality control for radiation, the endpoints and also get ... also the question for the FDA is also, if you accept the endpoint of survival, what bar do we have to get to for that endpoint to be acceptable? I think that I would love to have that coming out part of the manuscript if that's possible and hopefully, a figuration that that form trials.

Bulbeck: 01:09:07 My name's Helen Bulbeck. I'm here as the patient advocate. I steer, probably about 90 consumers for the National Cancer Research Institute, which is the equivalent of the American NCI and proactively CT RAD and I think CT RAD has been a phenomenal experience for me because I've grown with it and I think we've all learned through that experience about what good consumer involvement looks like, so thank you for inviting me here. I've been stunned by the eloquence and the clarity of the talks and I know that's true because normally in scientific talks I last three slides and then lose interest.

01:09:47 The whole thing around the abscopal effect, for me I think is the message that we can take out to the community, so the shift from using radiotherapy for local control to using radiotherapy to stimulate a response to systemic therapies is going to be a really big message for our community.

01:10:08 Patient first had head and neck cancer, but also a caregiver. My daughter's had a brain tumor and my husband has advanced prostate cancer, so I'm quite well versed and we've all agreed that actually it's harder to be the caregiver then it is the patient 'cause a lot of the time you're projecting what you think the patient's going to be thinking and most of time we're not thinking about it, we just to get on with having a good life and enjoying ourselves. I have two takeouts for ... so view from the balcony to take back to the community. What I've learned, I think is that research is very clean and tidy and focused, but as soon as you bring a patient into the room, it becomes messy, broad and chaotic and it's really lovely to hear you, Paul say that endpoints ... that the FDA's open to looking at endpoints other than overall survival and what I think is you've got toxicity, health related quality of life versus survival and I thought Paul, Tatiana's, Patty's and Adam's talks yesterday were very insightful.

01:11:12 It sets a high bar for clinical trials when you've clinical and symptom benefit as primary outcomes and we know and understand so much about the science of cancer now, the biology of cancer, but I think as patient related outcomes as endpoints is still very much in its infancy and I think hearing the messages in this room over the last two days, that's where I felt people were still feeling their way.You're confident when you stand up and you talk about cells and biology, but patient reported outcomes, no. There's a big piece of work to be done there.

01:11:55 I think too, my second takeout is that there's opportunity and scope to create supportive and educative materials that will develop agency in the communities and the patients that we work with, so that they can become co-pilots in their decision, in their care and on their pathway, particularly where it comes to clinical research. I think we need to demystify the sophistication of the biology of cancer.

01:12:17 I think we need to work very hard on helping the community to understand the complexity of design and everything that comes into play with it and also the different modalities of treatment that are out there. We've got a big agenda, which I'm dealing with in the UK. As soon as proton beam hits the Christie later this year, every patient's going to want to have proton beam and it's about managing expectations, so I think to develop some resources that particularly deal with the complexity of these radiotherapy in combination trials would be really good because we can then build resilience in the community, so that patients feel comfortable with uncertainty.

01:12:57 They need to understand that you too are uncertain about what you're doing. It was the biggest lesson for me on my daughter's journey. It took me 12 months. When I walked in to see the consultant, I suddenly realized, it was a light bulb, and I went, "He didn't have the answers," and as soon as I understood that, the consultations become less adversely. I didn't have the expectations and that comes from living in a paternalistic NHS system where we go along to a paid professional expecting them to fix us, but that's something we can't deal with here. That's something that's going to change overtime.

01:13:32 I think building resilience in the patient community, so that they're comfortable with uncertainty, which is not the same as feeling unsafe. It's about building levels of trust. Patients want to be informed, they want to be involved and they want to be engaged.

01:13:47 Millennials, they're all digitally native. 49% of millennials will go online the day they are told they have a cancer diagnosis, so there's a message there too about getting the patient information sheets in some sort of digital format and not handing them 16 pages to read through before they sign on the dotted line and 89% of patients will Google their illness at some point on their journey.

01:14:19 I think there's a lot of work to be done, but I think working together, we'll have a lot of fun doing it.

Walker: 01:14:27 Thank you so much everyone. Now we'll talk a few minutes if we want to ask questions among the panelists, we can do that.

Goldberg: 01:14:35 My question actually is straight down to the other end because Robert made a very important point about exempting placebo controlled studies and we struggle with that and clearly some of investigators do because patients do and we know that patients respond to what information they receive, but it's so critically important. How can we best engage with patients to very generally educate about the importance of placebo controls and then how would that ... I guess the second piece is, does that enable us to use some of these ... I don't want to call them softer, but shorter endpoints, does that make the regulators feel happier and then if so, how do you then engage the patients with that, so we can get the endpoints you want by putting in a placebo control?

Bulbeck: 01:15:25 It's about engaging patients even before the question has been defined. You need to have questions on board right at the beginning of the trial. What tends to happen in the UK is that we are invited to participate right at the end and the patient information sheet, that's way too late. We've had a very similar thing recently, it doesn't involve radiotherapy, but it's about using an anti-epilepsia medication prior to brain surgery for brain tumor, so it's a really tricky one because we're asking not only some patients to have to go on the placebo arm, but also for some patients to be taking a drug for a condition, which they don't have.

01:16:02 The way we've managed that is by running focus groups really explaining why this trial is needed and it is about engaging that limbic bit of the brain. If they can understand why and what the benefits will be, then they're usually comfortable with the what and the how, but it's engaging patients even before the question is being designed ... designed so you have an idea that you need to get them in room and talk to them.

01:16:26 Sometimes you have to accept that it's not acceptable and it's not going run. It won't have legs.

Speaker 4: 01:16:36 I definitely agree with that, totally. I think it's about the equipoise 'cause patients think, "Oh they think this drug is good and yet I'm not getting it," type of thing, so it is about educating about how trials are a test and we don't know if it's better and so, I think that the immuno therapy and problem with immuno radiation therapy, there's a lot of hype out there right now and so, you're struggling about the hype versus the realty of what it is. As long as it's eqapose and a lot of time I push for, if it is something like that, do the two to one versus the one to one and they get a better chance or there's pushes now to do more real world data thing where you open it up for broadly, but you do have your defined set in there. Those type of things, but I think randomization will always be a problem with patients and so, I think the more education that you give patients, the better.

Walker: 01:17:37 Thanks so much. Actually, we're running short of time. I think those are excellent take home points and action items. I'm happy that we have a transcript, so we can read over them carefully later. I did take a few notes and I'll just give some final thoughts before we depart.

01:17:54 I kept being reminded of Alcove and Paul, the first two talks saying, "We need to keep throwing more darts at the dart board." I think everyone here can agree that that's the case, but the things that I heard throughout this final panel discussion is really that when we throw these darts, we have to be very thoughtful in how we do that, and it requires collaboration to think about the way to move forward.

01:18:19 In terms of being thoughtful, there are a ton of trials ongoing right now. We really need to be cognizant that we have to learn from the data that we have already. Patients on a clinical trail, this data should be used in the best way possible and we should really learn from ... learn from what is ongoing and get the read out as soon as we can and take that information when we develop clinical trials moving forward.

01:18:43 Then the other piece about collaboration, I keep hearing that over and over. I think when we first started this workshop two days ago, there was a sense that we're never going to align our interests. I loved your talk Yaacov, by the way. It was fantastic and I actually love this concept of game theory and if we could just say, "We need a personalized incentive structure to get everybody on the same page," it would be phenomenal, but what I, over the past two days have realized, we do have a lot of our interests aligned at the moment and it's

really finding ways to best collaborate and to determine a path forward where all the stakeholders have a voice and everyone will some mutual benefit from the conclusion.

01:19:25 Those specifically what I'm talking about really in terms of this endpoint discussion. This earlier ... an earlier readout from a trial such that these trials are not going to be so expensive to run for many, many years to get your survival endpoint, for example. It's a difficult thing. I think the agency can't say we want ... this endpoint's acceptable, this endpoint's acceptable because it depends. The disease site you're treating, the agents that you're talking about, it's really ... the radiation therapy is such a heterogenesis field and we treat so many different diseases. I think the recommendation about disease specific working groups is fantastic and that should be relevant to really defining a path forward.

01:20:04 Let's say, this looks like a promising earlier endpoint. Well, how do we really get the data we need to justify that so that we can come to the agency and say, "This demonstrates clinical benefit."

01:20:13 The other piece was in terms of collaboration. I think radiation oncologists and are colleagues in the industry really, I think, should communicate more in terms of best defining the information that needs to be collected in any radiation trial. I understand quality assurance, the full IROC quality assurance is ideal, but in an area where you have limited resources and in a disease site where the treatment varies so significantly from different countries, it's difficult in realty to mandate that or say that this is the new standard, but I think what we can do collectively as a field is to develop consensus guidelines in terms of, what is the minimum data that does need to be collected and that may just be in the form of every company that is incorporating radiation therapy in their trial needs to have a radiation oncologist really involved from the beginning, just like we need patient advocates involved from the very beginning. Radiation oncologists in these trials should be involved from the very beginning.

01:21:16 I love that ... just the possible opportunities for collaboration with the patient advocates, I think is something, as a field, we should definitely work together more on and it will be, I think, an exciting, exciting future. I don't know. I feel like, at the end of the day, I feel very optimistic about the path forward and that really it's all on us. We're in this together to really define the path forward, but there are many opportunities to getting drugs to market, as we've learned.

01:21:48 Yeah.

Kluetz: 01:21:50 Just two other things as I heard Amanda talk that I think could be really, really helpful. There was a ... so, one thing is about standardizing radiation within your trial and having the protocol elements very well spelled out. There's a group called Spirit from Europe who had done this for protocols. What to put in protocols and they just did an extension for patient boarded outcomes. Similar situation, PRO has just ... sometimes it's in the protocol, sometimes it's not. Sometimes it was very heterogenesis and if we're going to make it scientific, they said, "Let's make it very clear," so maybe a radiation type of project where you go, say what are the key protocol elements that must be in there.

01:22:26 The second thing is, with respect to these working groups, these disease specific working groups, it doesn't have to a formal situation, but you could reach out to the FDA disease specific teams and make sure you have an FDA person or an MEA person even to talk with

your disease specific groups and as you hash it out can get feedback real time rather than coming up with something and then it being a non starter.

Walker: 01:22:50 Thanks, Paul. That's great. I just have to say thank you to everybody and I have a list, but there have been so many people who have been so critical in putting this all together, so I don't want to forget anybody, but of course, all of my co-chairs, all the speakers, all the panelists, phenomenal job. You guys all deserve a huge congratulations.

01:23:07 AACR, again, really, this wouldn't have happened without the ... all the logistics behind the scenes work that Sarah Martin and Anna Sadusky did throughout the last three months, so we should just give them a round of applause right now.

01:23:24 Also, from AACR, of course, Josh Britton who's our local AACR liaison and then Jon Retzlaff and of course, Marge Foti. None of this would have happened without the support from AACR. ASTRO, Judy Keenan, Tyler Beck, you guys have been amazing, as well, and then FDA, obviously. My colleagues who are here, this has been really incredible. Thank you so much.

01:23:45 Then [Uravi Asaylis 01:23:46] has also helped me. I think we were just talking about how this workshop really started ... I started bugging her about this about a year and a half ago actually, so she's been with me the whole time.

01:23:56 On a personal note, I just feel like I have to say thank you to these people. David Raben, he can't make it here today, but he's always been supportive of more collaboration with FDA and radiation oncology and also Adam Dicker, who's here and he's been with me also from the very beginning and Vic Vikram who's not here today, but I wanted to say thank you to those people too.

01:24:19 Thank you.