

## Oncology Dose-Finding Workshop Part 3

### Transcript: Session I, Immuno-Oncology (IO) Overview – Scope of the Problem

Liz Jaffee: If everyone could take their seats, I think we'll get started so we can stay on schedule. We have a very busy, but hopefully exciting program for you today. So I wanted to welcome everyone and of course good morning. On behalf of the American Association of Cancer Research I want to thank everyone for joining us today at this wonderful workshop. I'm Liz Jaffee and I'm the president-elect of AACR. I'm also the deputy director of the Sidney Kimmel Cancer Center at Johns Hopkins.

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[00:01:00] The AACR is proud to be co-sponsoring this workshop for the third straight year with the U.S. Food and Drug Administration and I've been thrilled to be a co-chair with Dr. Amy McKee, who's the supervisory associate director within the office of hematology and oncology products and the center for drug evaluation and research at the FDA. As the treatment paradigm for oncology shifts from monotherapy to combination therapies, a more efficient process of dose selection in the early stages of study design will be of critical importance and that's really why we're here today, to try to think about what we're going to do, how we're going to move from single agent immune oncology drugs to combinations.

[00:01:30] So the goal for this year's workshop is to explore the unique approaches that can be used by all of us to move in this direction. Specifically in this workshop we are focusing on best practices regarding patient and dose selection. We also need to focus on biomarkers for selection of those patients who will get the most benefit from combinations and ideally we'd like to begin to think about the novel endpoints that can define patient benefit. This workshop will have three sessions. The first session will be an immuno-oncology overview, looking at the scope of the problem and for different disease areas. The second session will explore key translational and design questions for immuno-oncology combinations. Finally, the third session will examine considerations to dose selection, optimization of IO combination products.

[00:02:00]

[00:02:30] One of the hallmarks of this workshop is the interdisciplinary forum with a wide range of perspectives from stakeholders throughout our immuno-oncology community and that includes academia, government, FDA industry. I'm happy to report that as of last night we have had 673 people registered for this workshop in addition to nearly 200 people registered to attend this workshop here in D.C. We have almost 500 people watching this workshop via the live webcast. So thank you all out there on the website for watching us and we hope you'll participate and if you have questions please send them to us.

[00:03:00] The AACR is continually looking for opportunities to engage on important regulatory science issues, such as dose [finding 00:03:09] for immuno-oncology combinations and the AACR looks forward to having continued productive

[00:03:30] partnerships with the FDA. So I want to thank all of you for joining us today and I will now turn this over to my fellow workshop organizer, Dr. Amy McKee who will share an update on outcomes from our two highly successful prior oncology dose finding workshops from 2015 and 2016. Thank you.

Amy: [00:04:00] Good morning. I'm Amy McKee. So why are we here and how have we gotten here? What is the FDA perspective on why would ... this is our third workshop on dose finding. So we've completed two dose finding workshops. Two years ago our workshop focused on only small molecules, if you can imagine. That's where cancer was at that point and so much has changed since then. Our second workshop focused on biologics and this third workshop is focusing on combinations of immuno-oncology agents, which could encompass all of the prior workshops plus this one.

[00:04:30] So the question is, what is FDA getting from this and how have we possibly evolved from these workshops in our regulatory work? So what I'm gonna do is give you three quick examples of what has changed in the past couple of years and how we've used our knowledge gained both at this and our expertise inside the agency. So the first example is [Ruxolitinib 00:04:36]. This was a marketing application that was submitted to FDA for treatment of patients with non-small cell lung cancer with the EGFR [T790M 00:04:42] mutation and it was discussed at an [ODAC 00:04:46] in April of 2016.

[00:05:00] So our clinical pharmacology team noted that [Ruxolitinib 00:04:52], the parent drug was responsible for the efficacy, however, two metabolites we're responsible for the safety issues of hyperglycemia and QTC prolongation.

[00:05:30] Through work with our pharmacometrics team in a population PK analysis it was noted that dose exposure was flat across all of these doses. Furthermore, the [Ruxolitinib 00:05:14] exposure efficacy relationship was also flat. So where did this take us? It meant that our clinical team pooled all the data from the various doses that we're included in the application to get a reasonable estimate of the true effect of [Ruxolitinib 00:05:29] on tumor response. So that's how it would have effected the efficacy evaluation. how did it effect the safety evaluation? So for one metabolite with hyperglycemia there was a very steep exposure safety relationship, which was also demonstrated with QTC prolongation and that metabolite.

[00:06:00] So the conclusions for this we're that we had a flat dose exposure relationship based on pooled data from across different dose levels for safety and efficacy. We had an exposure efficacy relationship that was flat and we had an exposure safety relationship that was extremely steep and the conclusion from the clinical pharmacology team was that the dose proposed by the sponsor was not adequately supported in the application.

[00:06:30] So my second example, which has been discussed previously is Nivolumab, which received approval in 2014 for metastatic melanoma at a weight-based dose. This approval was based on analysis of ORR in duration of response of the Nivolumab [arm 00:06:30] in a randomized trial and the clinical pharmacology data included

[00:07:00] [pharmacometric 00:06:34] data from over 1,000 patients in the application. The exposure response relationship for efficacy was flat. The exposure response relationship for safety was flat. In September 2016 based on a population PK model we approved a change from flat dose to solid tumor indications and this was based on all the work that both the company and our team did internally to validate that there would be a small difference in exposure that would be unlikely to have a clinically meaningful impact on efficacy and safety in the solid tumor indications and that is the dose that is labeled today.

[00:07:30] My third example is [Lenvatanib 00:07:20]. This was approved in May of 2016 for renal cell carcinoma at an 18 mg. daily dose in combination with [Everolimus 00:07:27] and it was based on the efficacy demonstrated in a randomized trial versus [Everolimus 00:07:32] alone with the progression free survival and overall survival [curves 00:07:36] here that supported the application. The issue with this application from a dosing perspective was that almost all of the patients required a dose interruption or reduction, however, in light of the extremely game changing efficacy we approved this product with a PMR for dose optimization. The issue was, what is the dose that should be studied? So our clinical pharmacology team and [pharmacometric 00:08:03] team used exposure response modeling to recommend a dose of the post marketing requirement.

[00:08:00] Now this had ... the modeling has also been presented at previous meetings, but the challenge of building this model for the pharmacometrics team was that the exposure was not constant over time with the frequent dose interruptions and reductions because that led to a bias exposure [inaudible 00:08:22] response relationships, so they had to build a new model to recommend a dose for the post marketing requirement. The conclusion was that we recommended [Lenvatinib 00:08:30] 14 mg. dose with the option for up-titration and to compare it to the [Lenvatanib 00:08:36] approved dose of 18 mg. in combination with [Everolimus 00:08:39] with the primary objective to evaluate the instance of intolerable, grade 2 and grade 3 to 5 adverse reactions.

[00:08:30] So these are the three examples of how we have been evolving from a regulatory perspective and making regulatory decisions based on modeling and other methods within our clinical pharmacology and clinical divisions. You will hear more about some of these novel regulatory approaches to initial combination trials, in particular from one of our FDA reviewers, [Tiffany Ricks 00:09:07] that have been submitted to the FDA. Our hope is to continue this relationship with all of our partners to further evolve how we evaluate these combinations because there are so many combinations we could examine, about which we'll hear in the next session that I'm not sure how well do it all in a reasonable amount of time for the patients who really need these products.

[00:09:00] So that is the end of my ... what I was going to start with and so as the moderator for the first panel I'll just note that I'm gonna introduce all the speakers at the start. If you have a burning question that cannot wait for the moderated panel discussion we may have time for one or two questions at the end of each speaker, but if it can wait until the moderated panel discussion there

[00:10:00] will be time for questions from the audience, both in person and online, but I will introduce all the speakers at the start and then they will come and give their presentations. So our speakers for this session are Dr. Robert [Vonderheide 00:10:03], Dr. David-

Speaker 1: And our doctors Robert Vonderheide, Dr. David [McDermott 00:10:04], Dr. [Leisha Emens 00:10:04], and Dr. [Joaquim Bellmunt 00:10:07]. They're going to give us a perspective of what are the challenges for immuno oncology combinations within their respective disease expertise. Thank you very much for coming and I'll welcome Dr. Vonderheide to the podium.

[00:10:30]  
Dr. Vonderheide: Good morning everybody. Good morning to those listening in, all 614 of you. We're glad you're here. Thank you Amy, thank you very much and Liz for the very kind invitation. Today, what I would like to discuss is the immuno oncology perspective looking at pancreas cancer and what issues there are there that might lead us the way forward.

[00:11:00] We're sitting in the middle of the cancer immunotherapy revolution. We're all aware. We've learned many things over the past few years in particular the power of T-lymphocytes to make tumors regress and potentially go away. We've also learned that this is not a 100% winning activity in that there's a bitter sweet quality to what we're doing and we hope to do quite a bit more. Last week some FDA panel unanimous recommendation of the cart 19 T cell program is just yet another amazing development in this field yet we're mindful of how can we do better. That's I think why we're here today.

[00:11:30]  
[00:12:00] From my perspective within academics at the University of Pennsylvania and the Abramson Cancer Center, and also discussing with many colleagues and industry, my impression is that this is the paradigm we're living in with the exception of the cart 19 experience, we're in the PD-1 plus X experience. The future of cancer immunotherapy very often is PD-1 plus your pipeline and that's it. There's an argument to be why that's wise. I want to talk today about how perhaps, particularly in pancreas cancer we need to switch that around and I'll go through that.

[00:12:30] Pancreatic ductal adenocarcinoma is notorious, in fact among tumors being resistant to the currently available immune therapies, in particular checkpoint blockade where with the exception of MSI high patients there really are no reported responses. Pancreas cancer is now the third leading cause of death in this country. As of January of this year, more individuals will die of pancreas cancer than breast cancer and that's the bad news. The good news is that combination chemotherapy is actually starting to have an impact. Combinations such as gem and [napacotexol 00:12:43] which we'll talk about.

As we thought about pancreas ductal adenocarcinoma and how can we use the immune system to attack, which I'm showing here this [desnoplasic 00:12:53] stroma, along the way I met this person named Liz [Jaffy 00:12:59]. Literally over

[00:13:00] the last ten years have become her wing man as we try to put together some national efforts, along with many other folks to take this problem on. I do think that pancreas cancer is a window to understanding the immunology behind so called cold tumors, those that have a scant effector T cell infiltration in the tumor, which is the typical, not 100% situation in pancreas cancer. It's dominated actually in its leukocytic infiltration with myeloid cells, which we think are there because of the special oncogenic signaling processes of KRAS. We've noted now many others that there are few missense mutations not [indels 00:13:38] that are seen in other tumors. It doesn't create a high burden of neo epitopes as we understand it today.

[00:13:30]

As I said, this tumor is resistant to the currently available immune therapies and three recent studies, vaccine only studies, randomized study in this disease were negative causing us to think a lot. I should point out that in the setting of resected patients, those who go to surgery with the intent of cure, the higher the expression and the higher the CD 8 infiltration into those tumors, the longer the patients live. The experiment of nature has been done. CD 8 T cells can make a difference.

[00:14:00]

We had the opportunity of looking at the data provided by the TCGA working group a few months ago and analyzed 134 primary pancreas cancers, these are humans, for the expression of acytolytic signature, which was comprised of [gramzine 00:14:33] A and perforin 1 shown on the left. You can see this S shaped curve indicating that in fact most tumors show a low cytolytic index but there are some in the orange box there that have a higher cytolytic index. If one removes those two genes from the rest of the transcriptome and looks at by principal component analysis, you can see that cytolytic high tumors and cytolytic low tumors are completely different even in pancreas cancer.

[00:14:30]

[00:15:00] We wanted to understand, is this on the basis of tumor intrinsic qualities so we looked for the burden of neo epitopes and plotted on the bottom right cytolytic activity versus neo epitopes defined in a classical way. You can see that there's not a correlation. In fact, it's a little bit inversed. Those patients with the high cytolytic index are the ones with the lowest predicted neo epitopes for class one and vice versa.

[00:15:30] Looking further at TCGA transcriptome data, you can see in the upper panel, the massive heterogeneity of primary pancreas cancers with regard to the expression of a number of immune checkpoints shown here and scaled in the heat map as indicated. Certain vulnerabilities highlight themselves such as potentially vista but I wanted to point out PD-L1 and how it's a rather lowly molecule in this disease although it's a dynamic one it's perhaps something to keep our eye on. You can see where pancreas cancer fits across the rest of TCGA.

[00:16:00] There are unique qualities of pancreas cancer when compared to other tumors, particularly melanoma and lung cancer.

To understand whether T cells have a role in this disease and can be exploited, we turn to a genetically engineered mouse model of pancreas cancer, the KPC

[00:16:30] model, which is generated by mutated KRAS and mutated P53 into the pancreas of these animals and watching by serial ultrasonography the growth of tumors in the pancreas as identified here. That allowed us to observe these tumors growing in wild type animals but also compare it to animals in which we had pharmacologically depleted the CD 8 and CD 4 subset.

[00:17:00] And this data's been published so I'll summarize the key points that we found. KPC tumors, like human pancreas cancer, exhibit a low mutational burden, an absence of predicted neo epitopes derived from these, a scant T cell infiltration, and resistance to checkpoint therapy such as PD-1 and CTLA 4. Spontaneous tumor progression in this model is identical whether or not there are T cells. This is much different than the models upon which the immuno editing hypothesis was based in which there was a huge difference in the phenotype whether or not T cells were there. Here, no. T cells furthermore rising in T cell depleted mice grow unchecked, never rejected in immune competent hosts. Again, in contrast to the immuno editing hypothesis.

[00:17:30] We introduced hypothesizing that the problem was antigenic burden. We introduced the strongest [senich 00:17:29] that we can think of which was full length ova. When we did that in this tumor model, it leads to the rejection of the tumor and T cell memory and this doesn't happen in ova tolerant animals indicating the special quality of ova in this experiment was it's neo quality.

[00:18:00] Is there a way forward? As Liz and I have talked many times and with our colleagues, we speculate there is. That this is a glass half full example. Maybe, in the absence of strong antigens, there actually is no darwinian like pressure from T cells in this tumor and that the underlying pancreas tumor cells remain highly susceptible to T cells because they've never had to escape. There is a role, perhaps of T cells if and only if we can provoke these T cells into the tumor micro environment.

[00:18:30] This is our paradigm, I think currently in the cancer immunity cycle and this now famous paper in immunity in 2013. In 2017, I think largely we're over here with most of the FDA approved drugs over here, checkpoint blockade where success is based on the preexisting infiltration of T cells in these tumors. But if that's not the case such as in most patients with pancreas cancer, I think we have to go to the left here and trigger a response.

[00:19:00] An observation that we made in the KPC animal is that even in those ova expressing tumors, if the animal does not have CD 40, or does not have BATF 3, so there is no dendritic cells, we don't get rejection. Priming is important and it highlights the special role of CD 40, which I'll come to. It also presents a different way of looking at things. Instead of PD-1 plus X, we need X then PD-1. That's actually my main point today. It may seem simple but I think that's where we are.

With that logic in mind, Liz and I and so many other people have been begun to think about combination immunotherapy for pancreas cancer, which goes far

[00:19:30] beyond single agent checkpoint therapy or even combination checkpoint therapy alone. We don't think this will work. We noticed with great fanfare, FDA approved PD-1 for MSI high effective mismatch repair tumors including pancreas cancer, that actually has set our field on fire, by the way because now we have something to look for, only one percent of cases. But, it does also highlight that we can be successful even in this disease. What I'm showing here is not a complete list but an exhaustive list of clinical trials, which are open now in which the idea is to vaccinate the patients and come in with a blockade of immunosuppressive features.

Speaker 1: Come in with a blockade of immunosuppressive features. I think that and pancreas cancer, perhaps, and other tumors will be our way forward. Let me spend the last bit of time on the role of agonistic CD40 antibodies. We think this is critical and a special pathway for helping to prime T-cells. The mechanisms are many-fold. Fifteen, 20 years ago it was predicted that the ability of CD40 to activate antigen-presenting cells and therefore prime T-cells would be critical in tumor immunology.

[00:20:30] CD40 can also reactivate and educate macrophages and what caused those macrophages to become tumoricidal. But in those experiments we do not see long-lived immunological memory, which we think is ultimately the goal. These agents, mostly but not exclusively agonistic antibodies, not blocking, agonistic antibodies have gone forward in the clinic. What has been observed so far, summarized very briefly, is that there is an acute activation of antigen-presenting cells that's possible even in tissues. There is a mild-moderate transient cytokine release syndrome and elevation of liver function test abnormalities, which is entirely clinically manageable. And multiple CD40 agonists are now in clinical, although most of them-clinical development, although most of them are first in human studies.

[00:21:00] Let me outline some myths that I have perceived over the last decade working on this pathway. It is stated and I've seen discussed that CD40 agonists will create an unmanageable and inevitable severe cytokine release syndrome. That's not true. There is a dose dependency to this drug as well as others. We have seen liver function abnormalities, but nothing clinically significant. Not every CD40 antibody is built the same. Some require cross-linking, but not all. And that's important because this is not a single class. And the fact that some folks say there's not clinical activity, we actually have a fairly decent amount of clinical activity that we've reported on.

[00:22:00] In pancreas cancer, in combination with gemcitabine, we reported a few years ago an objective response rate of 24% with a medium progression-free survival and overall survival that matches that of a gem and Abraxane, with a metabolic response rate even higher, a majority of patients responding as evidenced by FDG pet. You can see an example of a patient from this study a few years ago, treated with gemcitabine and CD40, and the reduction of the tumor. When we looked and inspected the tumor, hoping that we would see T-cells, we mostly saw macrophages and it sent us back to the laboratory to understand, how can

[00:23:00] we better induce T-cell immunity? And here we return to the KPC model and instead of just using gem, long story short is we added nab-paclitaxel 'cause the FDA had approved that for this drug. And it turned out that made all the difference. And what we were able to observe with gem, nab-paclitaxel, and a prototype for agonistic anti-CD40 shown there, is the tumor regressions in the KPC model and long-term survivors that we had never seen before.

[00:23:30] And these regressions were entirely dependent on T-cells and interferon gamma, as evidenced here, and we've published this recently. It depends on the nab-paclitaxel, interestingly enough, and it's the addition of nab-paclitaxel to gem CD40 that converted the mechanism to a T-cell dependent, macrophage independent way. So having done that, we then identified, what can Checkpoint do? So if that's the X, can Checkpoint blockade add something to this? This is data, again, from a recent paper showing that we can achieve long-term survivors when we combine gem, nab-paclitaxel, CD40, and Checkpoint blockade.

[00:24:00] This was considered kind of a crazy idea, but when you think about it, of the drugs I just said, of those five drugs, four of them are FDA-approved, two for this indication. So we decided to keep going. Looking further into mice, what we identified is if this is a genetically engineered animal at baseline with scant T-cell infiltration, following treatment with gem, nab-paclitaxel, and agonistic CD40 we're able to put T-cells, prime T-cells now, into the tumor microenvironment, and when those are activated with PD1 and CTLA-4 or both, that's where we see the effect.

[00:24:30] This is now taking hold in the clinic. I'm showing you two clinical trials where CD40 monoclonal antibodies are used in pancreas cancer. I don't have time to go through them in detail, but to highlight to you the opportunities. So again, working with Liz and others at Stand Up to Cancer and the NCI-CITN and PanCan, there's an open clinical trial at a number of sites, including Penn, Hopkins, and University of Washington, others, in which patients with resectable pancreas cancer undergo treatment with chemotherapy and the Roche anti-CD40 agonistic antibody, both in the neoadjuvant setting and in the adjuvant setting.

[00:25:00] This is a two-armed study, ten patients per arm, and the primary endpoint here is safety and feasibility.

[00:25:30] A study that is now open and just appeared on ClinicalTrials.gov is for first-line patients who have metastatic pancreas cancer. This is the clinical trial shown on the bottom where the IND sponsor is the Parker Institute for Cancer Immunotherapy. I serve as the overall PI of this study. Each site in the Institute has a site PI. And this is a clinical trial where patients will be treated in the Phase 1B-Phase 2 design and receive treatment on one of three arms. Chemotherapy plus CD40, and here we're partnering with Apexigen and their agonistic CD40; chemotherapy and nivolumab, where we're partnering with BMS; or all four. And the idea here is to look at one-year overall survival and compare it to what we understand to be the case for gem, nab-paclitaxel.

[00:26:00] There are special challenges in using CD40, and I would say any agonists, where in oncology we're pretty good at antagonists and understanding the PK and PD effects there. Agonists are much more difficult, and so determining the optimal schedule of the use of CD40 has been a challenge, and also the sequence. For example, does it come before or after chemotherapy? And there's been quite a bit of interesting preclinical data in that regard. And so here we always use chemotherapy first, wait two days, and then give the CD40. Other ways of sequencing this are much less effective and can be highly toxic.

[00:26:30] We need to still understand the optimal route of administration. We're giving all these drugs intravenously, but that may not be the optimal way. And every CD40 antibody's a little bit different, and we have still yet to understand the importance and the priority of whether or not we need to use antibodies that require cross-linking to be activated. And, of course, we're still searching for ideal partners and, as I said, the sequence.

[00:27:00] So I'll leave it there for today's presentation. I want to thank those in my laboratory at Penn, particularly those who have helped with the preclinical data. Some of these scientific and clinical collaborators not only at Penn but elsewhere, and acknowledgement to funding sources and the Parker Institute for making these studies possible. Thanks very much.

David McDermot: [00:27:30] Good morning, my name is David McDermot. I'm from Beth Israel Deaconess in Boston and Dana Farber Harvard Cancer Center. I'd like to talk to you today-I'd like to thank, first, the organizers for the invitation to speak on how we're improving kidney cancer therapy through novel clinical trial design. And what I hope to get across today is how what we're learning in kidney cancer might be applicable to other tumor types.

[00:28:00] Here are my disclosures. This isn't my talk, unfortunately. Can I give you my talk that I'd like to give? [PAUSE]

Speaker 1: [00:30:30] So I apologize for that. Alright so those are my disclosures, okay, so while the application of VEGF and Immune Checkpoint Blockade has improved outcomes for patients with metastatic kidney cancer, new strategies are clearly essential to overcome treatment resistance and improve patient selection. Our preliminary preclinical studies have suggested that anti-VEGF might enhance the anti-tumor activity of Immune Checkpoint Blockade by improving T-cell infiltration, [inaudible 00:30:35] MHC class one expression and reversing meloid immunosuppression. This work provided the rationale for combination clinical trials.

[00:31:00] We're now in an era where there at least five, by my count, very large phase three randomized trials with all very similar design for patients with untreated kidney cancer. Thousands of patients are gonna be enrolled in these trials. Comparing essentially VEGF plus Immune Checkpoint Blockade versus the current standard of [inaudible 00:31:03] Sunitinib. I think the question though for the field, for all of us in kidney cancer, is are the approaches advances in

[00:31:30] immunotherapy. I think if I had to predict, I think many of these trials are gonna be positive and you're gonna see FDA approvals for these combinations, but it's not entirely clear to me that we're improving immune therapy endpoints and I'd like to focus on what I mean by that. So here's an example, couple months ago the FDA approved the combination of PD-1 Blockade and chemotherapy for patients with lung cancer and in my opinion I think while there were clearly benefits to this approach and this approach generated interesting hypothesis, it's not clear to me that this combination improves immunotherapy outcomes for patients with lung cancer.

[00:32:00] Why do I say that? Well here's the design of the trial. This is the Keynote 021 Study, a study patients were randomized to receive either Carboplatin Pemetrexed or chemotherapy plus Pembrolizumab. The patients as I've said had non-small cell lung cancer. They hadn't been treated before. It was 123 unselected patients. The primary endpoint was overall a response. I think there were several aspects of this trial that I think are an issue. First, is the trial design. In my opinion I don't think this trial had the proper controls and I don't think it was adequately sized. I think it was good for a hypothesis generating trial but not necessarily for a confirmatory trial.

[00:33:00] Here's an example of a hypothesis generating trial that I think had some advantages in its study design: This is the Emotion 150 trial. This is the first randomized frontline trial to explore anti-tumor activity of PDL-1 Blockade with Atezolizumab both alone and in combination with the VEGF binding anti-body Bevacizumab versus the most commonly applied kidney cancer therapy at the moment: the VEGF TKI Sunitinib. 305 patients with metastatic kidney cancer were enrolled in this hypothesis generating trial, and the co-primary endpoints were progression free survival and the intent to treat population and impatience with PDL-1 Expression on greater than or equal to one percent of their tumor immune cells. The trials exploratory endpoints identified for the first time in kidney cancer potential predictors of response and mechanisms of treatment resistance through the pre-specified analysis of gene expression signatures associated with the tumor micro-environment.

[00:34:00] Today what I'd like to focus on is how the insights from this trial might educate the rational development of IO Combination Therapy in kidney cancer and beyond. In contrast, in my opinion, I think the Keynote 021 trial could've been improved if it had had a single arm, Pembrolizumab alone, and we'll talk about why that is. It also could've been proved if it was larger. So, once again this is a good hypothesis generating trial but not large enough in my opinion to be confirmatory.

[00:34:30] Back to the Emotion 150 trial, so what did we learn? Well as presented at ACR earlier this year, while the Kaplan-Meier curves for progression free survival, in the ITT population we're overlapping. In the PDL-1 positive population curve separation was seen at the first treatment visit, that first scan, that benefited the combination. This effect was also seen with Atezolizumab monotherapy for the first time in patients with PDL-1 Expression on greater than or equal to five

percent of their tumor immune cells. This observation that the clinical activity of the combination improves as PDL-1 Expression increases, suggested that BEV might be improving the anti tumor immune response.

[00:35:00] To explore this hypothesis further, whole Transcriptome RNA sequencing data was used to classify patients' tumors into three distinct biologic sub-groups representing tumor angiogenesis, preexisting immunity, and immunosuppressive meloid inflammation gene signatures. High and low gene expression was defined in relation to the median, which allowed us to categorize tumors as T-effector high and low, angio high and low, etc. The heat map shows the relationship between the three previously published gene signatures, which were interrogated to evaluate the association with PFS, an objective response in each treatment arm.

[00:36:00] Consistent with the prior PDL-1 analysis, the T-effector high gene signature was associated with greater anti-tumor activity when the combination was compared to Sunitinib, reinforcing our hypothesis about the potential impact of BEV in tumors with preexisting immune responses. However, with longer follow-up, the PFS curves for the IO arm seem to come together, suggesting that the impact of VEGF Blockade may be transient in some patients.

[00:36:30] The novel study design allowed us to explore mechanisms that might be driving improved anti-tumor activity of the combination in the T-effector high cohort. We went back to our Transcriptome map and noted that the T-effector high cohort could be divided into tumors with high and low expression of meloid inflammatory genes. As several investigators have linked meloid inflammatory cells to VEGF mediated immunosuppression and poor outcomes of kidney cancer, we explored the impact that they might be having on response to therapy.

[00:37:00] So, in the context of tumors with a preexisting immune response, while Atezo alone and in a combination with BEV resulted in encouraging anti-tumor activity in the meloid low sub-group shown here, compared to Sunitinib, Atezo alone performed poorly in the group of tumors in the T-effector high, meloid high sub-group. The reduced clinical activity in this sub-group suggests a potential mechanism of innate resistance to Atezolizumab Monotherapy, which might be overcome by the addition of Bevacizumab, possibly through its proposed ability to target meloid inflammatory cells.

[00:37:30] So, we think about patient selection, I think, with the Emotion 150 trial has suggested that maybe RNA sequencing will take us a step further than just PDL-1 expression with IHC, not only doing better at selection but exploring potential mechanisms of resistance. So, back to the Carboplatin Pemetrexed trial, the keynote 021, I think one of the issues I also had with this trial is in unselected group of patients. I think the prior trial with Pembrolizumab and untreated patients was a true advance for the field, where Pembrolizumab versus chemo was shown to be better in patients with PDL-1 positive non-small cell lung cancer. A clear difference that allows selection in first line patients. So what's the problem with an unselected subset of patients? Well in my opinion, just going back to the kidney cancer data, if you look at [inaudible 00:38:29] activity in

[00:38:00] So, we think about patient selection, I think, with the Emotion 150 trial has suggested that maybe RNA sequencing will take us a step further than just PDL-1 expression with IHC, not only doing better at selection but exploring potential mechanisms of resistance. So, back to the Carboplatin Pemetrexed trial, the keynote 021, I think one of the issues I also had with this trial is in unselected group of patients. I think the prior trial with Pembrolizumab and untreated patients was a true advance for the field, where Pembrolizumab versus chemo was shown to be better in patients with PDL-1 positive non-small cell lung cancer. A clear difference that allows selection in first line patients. So what's the problem with an unselected subset of patients? Well in my opinion, just going back to the kidney cancer data, if you look at [inaudible 00:38:29] activity in

[00:38:30] kidney cancer, over a third of patients best response to PD-1 Blockade and kidney cancer will be disease progression. My sense is in lung cancer that number is probably at least that high if not higher, so by approving a combination in an unselected group of patients at least in a third of patients you are giving them a treatment, which is not likely to work and can only produce side effects. To me that's not a step forward.

[00:39:00] Looking at how angiogenesis gene expression impacted response, I think this is the other reason why having a three arm trial is helpful, because you can look at the impact of your other agent in this combination. So looking at how Sunitinib performed in tumors with angio low or angio high tumors, for the first time we're seeing a potential predictor of response to VEGF TKI. We hadn't had one in kidney cancer before this. So, in the patients who had angio low tumors,

[00:39:30] Sunitinib performing poorly, the IO therapy's performing better, but in the angio high subset Sunitinib outperforming the immune based regimens. Suggesting, in those tumors maybe the patient should start out on a VEGF TKI. This trial design allowed us to figure that out. Obviously, all of this work is just hypothesis generating and needs to be validated in the ongoing phase three trials, but I think in this study what we learned is that Sunitinib probably primarily targets

[00:40:00] angiogenesis, and is most effective in angiogenic tumors. Atezolizumab monotherapy has impressive activity in tumors with-

Speaker 1: [inaudible 00:40:00] monotherapy has impressive activity in tumors with preexisting immunity, or the T Effector high, amyloid low subset. Activity that in the long term is probably as good as the combination, in these patients.

[00:40:30] However, the activity of the combination was good across many of these subsets, it seemed like the patients were deriving the most benefit of the combination in this T Effector high, amyloid inflammation high subset, suggesting that maybe in the future, this is the place we could use this combination to greatest effect.

So also, word in the last few minutes about novel end points. In my mind, I think we should be focusing on end points that are immune oncology end points for our trials. Not end points that we use for molecularly targeted agents or chemotherapy.

[00:41:00] Back to the O21 study, the primary end point of this study was overall response. I understand why that's important, and the trial clearly showed improvements in not just overall response and median progression free survival--which led to it's approval--but what about overall survival? When you look at the survival curves for this trial, they're overlapping. There's no difference in the number of deaths on these arms. And I would predict this is not likely to be, so in my mind, this is potentially an advance, but not a huge advance if we're not impacting overall survival.

[00:41:30] So when we think about combinations, a lot of them look good. A lot of them look good in small trials, but I think we need to focus on immuno-oncology outcomes if we truly want to make impacts on our patients' lives. What do I

[00:42:00] mean by that? Well not every combination is gonna be immune therapy. If you think of combinations, here's what we typically see with a lot of immuno-therapies: a small number of patients benefiting; some of them benefiting after you stop the drug; with VegF Blockade, by adding it, I would predict we're gonna be moving the curve to the right. We're gonna see higher response rates, we're gonna see improvements in median progression free survival, but unless we see this, I don't know that we've helped patients that much. We need to see tail-of-the-curve benefits for the combinations. If we see them, then in my mind, these combinations have become standard of care on the frontline. If not, then I personally would favor giving these drugs in sequence. VegF then PD1 in some patients, PD1 and then VegF in other patients.

[00:42:30] And I want to get, I want to believe that as we improve our selection criteria through novel biomarkers, this will help support sequential single agents for some patients. Because just remember, while we may show in the future that PD1 and VegF is better than VegF alone, none of these trials are gonna show whether PD1 and VegF in combination is better than the sequence. And for many patients, it won't be.

[00:43:00] What about other end points for trials? People have talked about landmark end points, I think those are interesting. Unfortunately, they take awhile to develop. This is an end point we're trying to develop, and bring to the clinic, this so-called treatment free survival. We've seen these swimmer plots before, in many publications with iotherapy and it's these red intervals that I think are most important for our patients. These are our patients who benefit from treatment and then can stop treatment. They are off-therapy in these end points, in these intervals. These are treatment free intervals.

[00:43:30] Now the concept of treatment free intervals is not a new one to oncology, we see this in patients for example who have CLL, where they get treatment, get a "benefit and come off" treatment, the difference though with immuno-oncology is when you stop the drug, the side-effects don't always stop. The way we look at a potential treatment free survival would be free of both treatment for the cancer and significant treatment for the side-effects. This might be a way of comparing regimens together, if the goal is increasing the remission rate with these agents, focusing on what the patients truly want, which is treatment free intervals.

[00:44:00] Why is this also important? We talked about side-effects, obviously side-effects get better when you stop the drug, but also the cost gets better. This is my sort of "back of the napkin" calculations of the cost of combinations, one of the more prominent combinations now in the clinic is PD1-CTLA4, when you combine these, they're obviously more expensive. But if you drive in more remissions, the cost goes away. Not only that, the patients go back to their lives, which is what they want. So I think we need to be focusing on these treatment free intervals

[00:44:30] and judging combinations in the future by whether they produce more of them.

[00:45:00] I think in conclusion, I think the rational application of iotherapy in kidney cancer and beyond, is gonna require some collaborations, some discussions with the FDA and the NCI about innovative trial designs and permission to use some of these novel end points that I talked about. We also may need to get HMOs involved, I think one of the ways to speed development would be to get places like Signa and Kaiser to fund our studies, because then we can look at stopping treatment and looking at these benefits off-treatment.

[00:45:30] We need to focus on the goals. So what are our goals? We want improved patient selection, I think the IMmotion150 trial gives us a sense that next-generation sequencing may do that. We obviously have to confirm that work, we obviously have to do a much better job of customizing the appropriate duration of treatment. You're gonna hear a lot more about that during this conference. And finally, increasing the remission rate so there are more patients living off-drug. If we do that, then you can change the name of the organization to the "Food and No Drug Administration." Thank you for your attention, I apologize for the screw-up in the beginning.

[00:46:00] Leisha Emens: Good morning. I'd like to thank the organizers for the invitation to come and speak to y'all today about breast cancer immunotherapy. And the title of the talk is "Provoking Breast Cancer Immunity with Strategic Immunotherapy Combinations."

These are my disclosures.

[00:46:30] So one of the challenges with developing immunotherapy for breast cancer is that historically, it's really been considered a non-immunogenic tumor. And this slide just shows you a stain of an untreated breast tumor for CD3 Positive T-Cells. And you can see that some breast cancers on the left are cold and they really have no T-Cells in them. But there's a few that actually have a fairly robust T-Cell infiltration. The cold tumors tend to be more likely to occur in breast cancers that are ER Positive. The breast cancers that are triple negative that don't express the estrogen receptor, the progesterone receptor, or HER2, tend to be more likely to be inflamed, and the HER2 positive breast cancers also are more likely to be inflamed than the ER Positive breast cancers, but somewhat less likely perhaps than the triple negative breast cancers.

[00:47:00] It's clear now from a lot of data sets, that tumors with poor prognostic factors, those that are ER Negative, PR Negative, of high grade or lymph node positive, tend to have higher T-Cell infiltrates at diagnosis, higher numbers of CD8 Positive tills and higher T-Cell to FOXP3 Treg ratio, predicts better clinical outcomes in terms of complete pathologic response to [inaudible 00:47:31] chemotherapy, disease free survival, and overall survival, except for in ER Positive breast cancers.

Importantly, both triple negative and HER2 positive breast cancers are really high value targets for cancer immunotherapy: triple negative breast cancer because it

[00:48:00] tends to be inflamed and there are no approved targeted therapies for that disease, leaving us only with chemotherapy; and HER2 positive breast cancer because we have a lot of drugs for that disease and some of them are potentially synergistic with immunotherapy. ER Positive breast cancers present the challenge of transforming tumors from cold to hot for breast cancer patients.

[00:48:30] From a clinical point of view, we classify breast cancers for standard treatment by whether they express the estrogen receptor or progesterone receptor, and will respond to endocrine therapy. HER2 will respond to HER2 directed therapy, or none of those, which leaves us with chemotherapy. That's a pretty simple classification scheme. If you look genomically, you can classify breast cancers into an array of different types, these are the major ones shown here on the left. The HER2 positive, the Basil Light--which is Triple Negative--Luminol B and Luminol A are ER Positive. But you can see that these aren't clean distinctions. If you look on the right hand side, on the top are triple negative breast cancers, and you can see that within these that are classified as triple negative genomically. Some of them will express the ER and some of them will express HER2. And the same is true for HER2 enriched, that's a heterogeneous group, as well as with the ER positive. The lines in these classification schemes really are blurred.

[00:49:00] The same holds true for the immune features of these cancers. If you look at Luminol A and Luminol B, they are much less likely to be lymphocyte predominant, only about 3%. They have fewer stromal and intratumoral tills than either HER2 Positive or Triple Negative breast cancers. And again, tills at diagnosis are not predicted for those tumors, so very different immune phenotypes and immuno-biologies in those tumors. HER2 enriched are more likely than ER Positives to be lymphocyte predominant, about 11%, similar rate for that in triple negatives. Both HER2 Positive and triple negative breast cancers are more likely to contain tills at 15 and 20% in the stroma, as well as intratumoral at 3 and 5%. And again, tills present at diagnosis are predictive a response and clinical benefit.

[00:50:00] There are several data sets that are then reported for-

Speaker 1: So there are several data sets that have been reported for targeting the PD1 pathway in breast cancer. This is the first large data set reported and this is for the anti-PDL1 agent avelumab. This is a trial that looked at 168 patients that were unselected for either subtype or PDL1 expression. You see the spider plot on the left, the objective response rate was only about 4.8% in this unselected patient population. However, there were some patients that did benefit and we need to develop ways to really pick these patients out. There was one complete response and seven partial responses.

[00:50:30] This is data for the anti-PD1 agent pembrolizumab and this was in PDL1 selected patients. You can see the activity of this agent on the left in triple negative breast cancer with a response rate of 18.5%. Again, a complete response as well as four partial responses and many patients with prolonged benefit from treatment. On

[00:51:00]

the right, you can see the activity of this agent in ER-positive breast cancer. Again, this was PDL1 selected. Of note, they had to screen a lot of tumors in order to identify this small group of patients for testing this agent, and the response rate was somewhat lower than for triple negative breast cancer at about 12%. Here, there were no complete responses and there were three partial responses. And in breast cancer, you do see evidence of pseudo-progression with these agents.

[00:51:30] This is the data for the anti-PDL1 agent atezolizumab in PDL1 selected triple negative breast cancer. Peter [Schmid 00:51:36] presented this this past year at ACR. You can see the spider plot on the left, with many patients progressing and if you take those away, you see that there is a subset of patients who derive significant response. The median duration of response is 21 months by both RECIST and immune related RECIST. And you can see that again, that you see this evidence of pseudo-progression and that there's clinical benefit in some patients who actually are classified as a progressive disease by standard RECIST.

[00:52:00] These are the response rates, so overall, in 112 patients, the response rate was 10%. If you look at patients who express PDL1, the response rate rose to about 13%, and importantly, if you look at patients who were treated first line, the response rate appears to be higher at about 26%. Again, small numbers of patients here, only 19, but this is hypothesis generating and suggests that treating these patients earlier with immunotherapy is likely to be more beneficial.

[00:52:30] This looks at overall survival by response status. For the patient group overall, the median overall survival was 9.3 months in all patients, with landmarks at one year of 41% and three years at 22%. Importantly, the people that had a complete or partial response had 100% survival out to two years. This data continues to mature and even the people that had stable disease had significant survival benefit as you can see here.

[00:53:00] This data is by standard RECIST, you can see this tail of the curve here for people with progressive disease. this really reflects the pseudo-progression, which when you look by immune RECIST, this tail goes away. So important to really thoughtfully assess the response of these patients to these agents so you don't take someone off therapy who's likely to benefit.

[00:53:30] This begins to drill down into patient selection and biomarkers that can predict response. So if you look at overall survival by PDL1 status, you can see that the survival at one year for PDL1 positive versus PDL1 negative patients was 45% versus 37%, so this was somewhat predictive. Again, you have this tail of the curve out to three years for PDL1 positive patients with an overall survival of about 28%.

[00:54:00] If you look at the association of response and survival with [TILs 00:54:01], there was a significant association of both. You can see that the response rate is higher in patients with high levels of TILs as shown here. And importantly, the overall

[00:54:30] survival was much better in patients with greater than the median level of TILs of greater than 10% relative to those with less, with a P value of .0028, and this is by multivariate analysis. Here you can see that in TIL low tumors, the median survival was 6.6 months and TIL high was 12.6 months.

[00:55:00] So this data actually is very similar to the data more recently reported at ASCO by Sylvia Adams for pembrolizumab in metastatic triple negative breast cancer. This is a cohort of 170 patients who were enrolled and treated. 105, or 62% approximately, were PDL1 positive and about 64% were PDL1 negative. You can see the response rates are fairly low across all of the patient cohorts, about 4.7%. This reflects the avelumab data somewhat. In a different cohort of patients who were treated first line and were PDL1 selected, the response rate was 23%, very much like the first line data for atezolizumab, again suggesting that selecting for PDL1 and treating earlier selects for a patient population more likely to respond.

[00:55:30] So PDL1 appears to be an imperfect biomarker. It can enrich for responses, TILs appear also to be predictive of benefit and the context really is important in terms of how these patients do. So there's two primary challenges for the field now, one is deepening responses to single agent immunotherapy. The second is converting non-responders to responders, because the fact of the matter is the vast majority of patients with breast cancer don't respond to PD1 and PDL1 [inaudible 00:55:58].

[00:56:00] This is a slide that just summarizes some selected promising combination immunotherapies for breast cancer and it gets back to Bob Vonderheid's comment at the beginning that we're really kind of in an era where we're thinking about PD1 and PDL1 plus X. So this illustrates PD1 and PDL1 as a backbone here, and then building on that by adding a variety of different agents with significant rationale, actually, for the combination, which puts us in the position of really having to try to prioritize which ones are the most important to take forward.

[00:56:30] Thinking about these combinations, the important variables are the drug, which chemotherapy agents are the best to combine, the dose of the drug, the sequence, we just heard from Dr. McDermott about sequencing issues. What this cartoon doesn't show is the issue of individualization to the phenotype of the tumor and the genotype of the tumor. So considering mutated versus shared antigen load and different mechanisms of immunoregulation present in the tumor, which will really drive which other immune checkpoint inhibitors or immune checkpoint agonists to combine with targeted therapies.

[00:57:00] So I'll just talk a little bit about the four that I've highlighted with an arrow. This is data that shows the combination of PD1 and PDL1 blockade with standard chemotherapy. In triple negative breast cancer, these were patients with metastatic disease that are not PDL1 selected. This data looks at the combination of atezolizumab with [inaudible 00:57:29]. Overall in this group, the response rate was 41.7%, but consistent with the idea that first line may be better and the

[00:57:30]

[00:58:00] nine patients treated first line, the response rate was actually 67% relative to patients treated second line or greater, where it was 25 to 28%. So taxanes actually have immune modulatory activity, they promote antigen release, they can signal through the [inaudible 00:57:54] receptor for and augment dendritic cell activity and antigen presentation. So good rationale for that combination. [inaudible 00:58:01] also doesn't require steroid pretreatment.

[00:58:30] Another study has combined pembrolizumab with eribulin, the response rate here was 33.3%. And again, eribulin has immune modulatory activity in addition to antigen release that decreases immune suppressive cells within the tumor microenvironment. So this, I just included to stimulate some thinking about novel trial designs. This is a trial that I did in collaboration with Liz Jaffee based on some preclinical modeling that she'd done in her lab. And it looked at a fixed dose of vaccine in combination with a variety of low doses of chemotherapy. Cyclophosphamide given one day prior to the vaccine to mitigate regulatory T cells and doxorubicin given one week later to promote T cell expansion.

[00:59:00] We tested different doses of cyclophosphamide in a 3x3 factorial design and then ultimately mapped it out by mapping the induced [inaudible 00:59:00] specific antibody response on this 3x3 factorial matrix and determined that the optimal doses of cy and dox to include with the vaccine were 200mgs/meter squared of cy and 35mgs/meter squared of dox. So the advantage of this type of design is that you can test the optimal combination of multiple interacting

[00:59:30] variables using as few resources, ie patients, as possible. And you can really adapt this, this is brainstorming a little bit, to think about different variables. So possible inputs might be a dose by dose question. Another option might be a dose on the Y axis by schedule question. And different possible outputs here for this analysis would be components of the immune response, now that we have more sophisticated ways of looking at that. Clinical response if you're lucky enough to have a clinically active intervention, as well as potentially toxicity and look at toxicity in the-

[01:00:00] Speaker 1: As well as potentially toxicity and look at toxicity in the context of dose. There's a lot of promise in terms of combining immunotherapy with HER2 directed therapy, both immune checkpoint blockade where you can see in her two positive tumors that are untreated. They grow out fairly quickly. If you treat them with either HER2 directed therapy or PD1 alone, you get some benefit, but the two together result in the best. This looks at the combination of anti PD1, CLA4 and Kadcyła, and you can see that you get the best tumor free survival with the combination of all three agents.

[01:01:00] Herceptin-based therapies actually have a lot of immune modulating activity, both promoting antibody dependent [inaudible 01:00:47] toxicity, and actually priming the immune response. Kadcyła, which is Herceptin with a chemotherapeutic agent attached to it, the chemotherapeutic component of it actually can activate dendritic cells and promote immune priming as well. This looks at the combination of HER2 directed therapy in combination with vaccination in a tolerant HER2 model where the vaccine alone doesn't work with

[01:01:30] Cyclophosphamide to get rid of Tregs. You get some benefit. With the HER2 directed antibody you get more benefit and you get the best benefit with all three together. Triple therapy resulted in the greatest T-cell response and this translated in the clinic pretty well where a vaccine alone gave them very modest T-cell response. With chemotherapy it was slightly higher and it was the best with the addition of Herceptin. This is a cross trial comparison here.

[01:02:00] Finally, what about those cold tumors? There's another type of vaccine strategy with intratumoral vaccination. This looks at activating the sting pathway. T-cell inflamed tumors in humans typically have an interferon beta transcriptional signature, and sting is the critical receptor to activate immune cells, including dendritic cells. Tumor drive DNA can induce interferon beta by tumor resident DCs through the sting signaling so you can have cyclic dinucleotides that therapeutically activate this pathway, induce interferon beta and activate intratumoral tumors specific CDA positive T-cell priming.

[01:02:30] This looks at the evaluation of this approach in a paired mouse model system of non-tolerant mice, the FEB in mice, and the tolerant HER2 transgenic mice. The non-tolerant mice have inflamed tumors with lots of T-cells, both CD4 and C8, whereas the non-tolerant mice really have a paucity of T-cells, both CD4 and CD8.

[01:03:00] If you look at the intratumoral injection of this agent into tumors in the FEBN mice, which are not tolerant, you can see that you get a good tumor rejection, and actually protection from a second challenge, just with the intratumoral injection of this agent alone. In contrast, in the tolerant mice you get a little bit of delay, but by no means the best type of an effect.

[01:03:30] If you isolate the T-cells that are present in the new transgenic mice and look at the immune checkpoints expressed on them, you can see that for a CD8 positive T-cells you have lots of PD1 in the tumor micro environment relative to the spleen as well as lots of OX40 in the tumor micro environment relative to the spleen. Testing that combination pre-clinically, you can see that the triple therapy results in the best tumor free survival relative to intratumoral injection alone or checkpoint blockade alone. You actually get the greatest infiltrative T-cells as well as the greatest activation of antigen-specific T-cells here as well.

[01:04:00] I just threw this slide in. We're talking a lot about the tumor microenvironment and drugs to effect this part of the tumor, the tumor biology and the immunobiology of the tumor. There are many things that are super imposed on this, including treatment history, the obesity that maybe present in the patient, the BMI, the microbiome and other hormonal factors that can come into play as well. It's important to keep those factors that can influence a response to immunotherapy in mind as well.

What I've tried to show you is that breast cancer can be immunogenic contrary to historical beliefs, but most breast cancers inherently are not, so we have to figure a way to transform them. Multiple layers of regulation within the tumor

[01:04:30] microenvironment shut down the immune response. Vaccines and sting agonists can prime the tumor microenvironment for response to immune checkpoint modulation, whether it be blockade or agonists. Standard cancer therapies can augment the activity of immunotherapies. The future's really in the combinations, which should have synergistic clinical activity ideally, but may come at a toxicity cost that we have to keep in mind. We need to do smart trials that'll elucidate mechanisms and response and resistance in patients.

[01:05:00] These are my acknowledgements. I really want to thank the patients who participate in all these trials because without them we couldn't advance to better treatments so that they can live longer, happier lives. Thank you.

[01:05:30]  
Joaquim  
Bellmunt: Hi. Good morning everybody. My task will be to discuss about strategic immunotherapy combinations and sequencing in [inaudible 01:05:35] cancer. Also I will go a bit through the doses. This has been mentioned initially with [inaudible 01:05:41]. We haven't seen any of those limiting in several trials, so it's quite difficult to select those. We know that the exposure response to toxicity has quite a flat dose, as has been mentioned in the beginning of the presentation. With combination probably this is going to change and we may need to tune a bit our trial design. Those are my disclosures.

[01:06:00] We are in exciting times for [inaudible 01:06:06]. After 20 years now we have agents that provide some prolonged responses and survival benefit, but we know that only 15-20 percent of patients with bladder cancer are benefiting from immunotherapies single agent. The future is obviously going to be combination or sequentially use of this new agents.

[01:06:30] My lecture will be divided in three parts. First I will review what's going on in terms of new combinations of IOIO or IO targeted agents. The second, I will discuss a bit about the trial design on the settings that we can take advantage to optimize our trial design. In the end I'm going to talk about the new findings that have been recently presented that probably are going to help us to select patients in order to derive a higher benefit when giving combination immunotherapies.

[01:07:00] Potential synergy [inaudible 01:06:59] of the first part we have standard CDLA4, PD1, PDI1 combinations, IOs with the other immuno approaches. The first question that comes to our mind is there is combination better than sequential? You have seen these [inaudible 01:07:14] 67, although this was not the trial designed to analyze combination retro sequential because patients, the sequential therapy was not defined. We can see that there is no that much difference. These are the codes of a high toxicity, so 58% verse 20%. We can see that the volume outburst was [inaudible 01:07:32] is not that much different.

[01:07:30] In bladder, although we don't have randomized trials comparing combination versus single agent. We have the results of this checkmate 32 that combine [inaudible 01:07:45] in patients previously treated. You can see here the survival

[01:08:00] is 10.2 months. When we compared that to the, although as mentioned, these are not fair because I'm comparing phase two with the phase three, when you see the survival obtained with the keynote 45, the same survival is being observed.

[01:08:30] Obviously we need randomized trials to address this question. If combination is superior to single agent? In terms of combinations, we have now several trials ongoing on first line therapy in bladder exploring combination of [inaudible 01:08:18]. This the [Daniv 01:08:19] trial. This trial has closed to patient [inaudible 01:08:22] so we are going to answer the question if combining the [inaudible 01:08:25]. Those are PDL1 plus CDLA4, is superior to immunotherapy or superior to standard of care chemotherapy. This is without patient selection. This is the [inaudible 01:08:37] patients being feet or unfeet. There is another one that is accruing comparing the volume of in combination with [inaudible 01:08:43] compared to standard of care. These trials of first line will provide some answers if a combination is superior.

[01:09:00] What about the new IOs? We know that there is an oral [inaudible 01:08:57] inhibitor and presenting these data here because some [inaudible 01:09:01] results have been presented at Osco this year. [inaudible 01:09:04] induce intercellular enzyme that catalyze the first and rate limiting step of [inaudible 01:09:10] and that these lead up to the immunosuppression. If we combine this idol inhibitor with a [inaudible 01:09:21] like this trial, this is a trial that was presented, the keynote 37. You can see here in terms of the way that the dose was found to move to this cohort, expanding cohorting bladder. Initially the recommended dose of [inaudible 01:09:36] was two millimeters for kilogram, because these coming from the very beginning with different doses of [inaudible 01:09:41] that this is oral [ido 01:09:43] agent.

[01:09:30] You see here that we jump to this [inaudible 01:09:46] to 100 milligrams because these are the approval dose. I want to remind you this [inaudible 01:09:51] paper published recently by Goldstein showing that probably you can save money if we use this dose at this more personalized dose.

[01:10:00] Anyhow, obviously we need to wait for the paper. We don't know about finally the ...

Speaker 1: Immune-Derived PD-PD-L1 Gene Expression Defines a Subgroup of Stage II/III Colorectal Cancer Patients with Favorable Prognosis

, 4-1BB and induced by lymphocyte activation (ILA)

[01:10:30] And obviously, we need to wait for the paper. We don't know about ... Finally the dose that was selected was these of at avacado the start of 100mg with 200. The results of this combination is quite nice, although it's a Phase 2 study you can see that 40 patients with Ki carcinoma the overall response right 35% this is more than this 20 % that we usually see with a [inaudible 01:10:25]. You see see here in patients having PD-L1 over expression the recidivism rate goes up to 64%.

Presumably, as mentioned in the Phase 2 patient this might be potentially an attractive way to treat bladder cancer patients. Specially in those having the PD-L1 expression.

[01:11:00] Another agent that is being tested in bladder cancer is an antibody that is an agonist. This is 4-1BB this against CD137. It seems that it's able to alleviate dell exhaustion, post IOS, induced CD8 T-cell activation for T-cells and also Natural Killer cells. There is a Phase 1 trial combining this agent name [inaudible 01:11:08]. Where you can see here note? those limiting toxicity is seen in those range used with this agent. It's very difficult to select those for further development. This combination is ... well here you can see the responses in the different tumor types. Renal cell [inaudible 01:11:25] from cell. This is an active combination, Phase 1 . heavily [inaudible 01:11:30] patients, but at least the combination was thoroughable.

Now this is moving to a different tumor types. You can see here the design of this trial. Obviously [inaudible 01:19:57], a single dose , is the one that is a proof of a [inaudible 01:11:43] as singulation for [inaudible 01:11:47], the dose of immunization will follow with a standard cohort and then if there is no dose limiting toxicity, this will move to expanding in different cohorts including bladder cancers.

[01:12:00] Obviously this is a nice way to design a trial and as mentioned is going to move forward, pretty soon.

[01:12:30] Another io is the ox40 the difference from the CD40. CD134 not to get confused with the high end that presented before. This is again an anticarismal with antibody that in presence of the T-cell receptor simulation and produced and enhanced T-cell response. It can also diminish the immunatory factor growth rate of T-cells.

There are trials including bladder cohorts but, as mentioned, that is no patient selection. This is for all comers. Just trying to synergize combining two of these new ios. The trial ox 40 alone, or in combination with the other agonist 4-1BB.

[01:13:00] Synergize the other trials on going. With other IOS agents. CSF1 and some interesting responses have been seen in bladder. We have combinations with the TGD. A new way of combining the IOS is with a light antibody that conjugates. An interesting approach being done at the with different patient cohort. You can see bladder rcc melanomas where we are combining the volume up with a personalized vaccine using new antigens using personalized peptides. This has already been presented at the breast lecture. To target, in a more precise way, the tumor antigens & optimizing with a standard [inaudible 01:13:43] inhibitors.

[01:14:00] Other potential combinations that is the IOS will target a therapies. This might be more personalized for patients. One of those is the combination of an io with Cabozantinib this is a work done by Andrea paolo? Where he analyzed the

monitor. The [inaudible 01:14:05]sacs of that is approved for second line renal carcinoma.

[01:14:30] It was an observation here at the decreasing T rates among CD4 T-cells and increasing PB1 expression in the CDLA4 expression. Trex. Presumably, producing an immuno-modulotarae property that could be used to combine with a PV1 inhibitor. Here the trial is designed so that this trial was presented primarily at ... As more data has been presented with a combination of [inaudible 01:14:39] volume up. And if you do up, there is no patient selection. This is a dose finding looking for safety [inaudible 01:14:47].

(whispers to self) I'm a go back

[01:15:00] Those are the responses seen in different tumor types including g tumors, bladder, nontraditional histologies like Squamous Cell carcinoma of the bladder, penile ... Interesting responses overall response rate with a combination of Cabozantinib and the volume up of 43 per cent in a heavily predicted patient population. This has shown to be quite horrible.

[01:15:30] Focusing more on trying to target different [inaudible 01:15:28] prevalence of bladder cancer. We know that like breast cancer, basing RNA sequencing. We have the luminal type and the basal type. What we have seen with a dissolution map that it is the cluster to the luminal tool that is able to respond more frequently to a dissolution map. We know for example that the Plaster 1 is the one that is in rates for amular 3 mutations and those are phases that the likelihood of responding is pretty low. Why not combine avia 3 inhibitors with immunotherapy?

[01:16:00] This is the type of trial design that we started at the Farber so combining the pambrolusion map with this 701. It might be we are targeting this two different ironies two times that can be found in bladder cancer. Unfortunately this trial was activated in 2016 and, because of some concerns of potential toxicity, is now on hold. At least this is an attractive way to expand the way that immunotherapy treats the bladder cancer.

[01:16:30] Let's move to the second topic: Taking Advantage of Strategic Designs and Specific Settings. One important strategic area in bladder is the duodenum setting because with that we can gather biopsies. We can treat the patient, have the cystectomy, and correlate on what's happening with the treatment.

[01:17:00] There are several trials combining mainly chemotherapy because chemotherapy is the standard of care that is in [inaudible 01:16:57] setting and there are trials in patients who are unable to receive blood platinum meaning that you can use combination to target through IOS in this setting.

I'm bringing this design, from the breast world, to bladder cancer is what is called actively randomized [inaudible 01:17:19] bladder trial. This is coming from breast cancer trial despite there is a biomarker reached clinical trial with multiple

- [01:17:30] platforms & sealed tumor specimens. A lot of studies are being made to identify the most likely to benefit based on the studies designed meaning that this is a way that we can screen combinations pretty quickly and being able to decide what's the best combination for a specific group of patients.
- [01:18:00] Another way of ban settings is obviously the next type of trial design. We have examples of that trial now accruing patients and based on the profile through [inaudible 01:17:57] that this PD-L1 inhibitor is being combined with different AstrZeneca compounds. The one targeting the ezr one, two, or three. This tiresome can is this inhibitor different from these other compound that I explained before that was an [inaudible 01:18:09] antibody.
- [01:18:30] Patients having [inaudible 01:18:12] repair or DNA operations and we're going to see that this impressing area usually this color for bladder. Combination of the [inaudible 01:18:20]. Might be a good option for this patient. Monotherapy is here as a single arm and we want inhibitor is also included in one of these arms. Genomically driven trials assigning combinations based on the specific genomic alteration.
- [01:19:00] Finally, [inaudible 01:18:40]versus [inaudible 01:18:41] and here I want to focus on chemotherapy. We have been using chemotherapy forever in our patients. When combining with chemotherapy we need to put the chemotherapy in the right context. It's not like to put together and see what's going on. Initially where companies were very reluctant to combine chemotherapy with immunotherapy presumably because you are killing the lymphocytes giving chemotherapy. Secondly we have seen that this is not happening and the responses are seen in a synergistic way.
- [01:19:30] In bladder cancer the first example was this trial combining [inaudible 01:19:15] platinum plus. In patients with a metastastic [inaudible 01:19:19] carcinoma. This was a completely negative trial. Know all of this was a single-arm Phase 2 trial. No increased responses were seen combining EP plus amphetamine and [inaudible 01:19:31]
- [01:19:30] There are first line files trying to answer this question. There are four first line trials. Two combining [inaudible 01:19:43] and these others combining chemotherapy and immunotherapy is the keynote putting together [inaudible 01:19:51] versus chemotherapy or this other one that is combining [inaudible 01:19:57]
- [01:20:00] There are trials in Europe that are designed just to look for logistic reasons including proving in europe and
- Speaker 1: Just for logistic reasons, Benflunin is approved in Europe and why not still try to have Benflunin in place, and there is this trial design, there is an ISD trial where Benflunin and Pembrolizumab is going to be compared to Benflunin, with no rationale, just because of the regulatory approval of Benflunin in Europe. So what about the best way to combine chemotherapy and immunotherapy? And

[01:20:30] this is an interesting paper on mainly these referents where the different actions or ways to combine chemo-immunotherapy are addressed. It's an issue of the type of drug, the dose, and the schedule that might matter when combining chemotherapy and immunotherapy. And one of the things that have not been addressed is giving, in an adequate way, chemotherapy with immunotherapy.

[01:21:00] Based on this paper, we have designed this trial that these patients who are unfit for [inaudible 01:20:53]. In this case you can see that these randomizations to standard chemotherapy for unfit patients [inaudible 01:21:00] versus Avelumab plus [inaudible 01:21:02] but given in this way, patients are receiving immunotherapy as a boost, trying to boost the immune system, and then subsequently the patients receive chemotherapy, and thinking that this is going to increase the release of new antigens, immunotherapy is given subsequently. And we are going to re-cycle. Obviously this is linked to a lot of transnational work with self-DNA and also immune parameters in order to know if in fact there is some type of increase in the effect of Avelumab when using chemotherapy given in this sequential way.

[01:22:00] So the third part is focusing the new genomic findings, the way to optimize bladder cancer patients, mainly that chemo-mutational burden meets mismatched repair alterations, on DNA repair gene alterations. This is the data that is coming retrospectively from an Atezolizumab trial showing that the mutational burden is associated with overall survival, but this is retrospective analysis and the question is, is this predictive or is this prognostic? So initially it was thought to be predictive, so we can see that there is an increase in survival in patients with high mutational burden, but we know that urothelial cancer has a lot of genomic abnormalities. We have the APOBEC signature that is driving the type of mutations seen and this is linked to an increase in the PDL-1 in patients that have these APOBEC type of signature.

[01:22:30] And in a retrospective analysis that we published in Annals of Oncology we saw that mutational burden in patients receiving chemotherapy was associated to a better survival. This has been confirmed in the recent TCGA analysis so the updated TCGA analysis is going to be published in cell [inaudible 01:22:47] for 112 patients, and you can see here the survival, and those are patients that are muscle invasive pilot cancer patients. They didn't receive immunotherapy, and you can see here that mutational burden per se, or the APOBEC signature or the MutSig clusters or the new antigen load, is per se, prognostic.

[01:23:00] So this is not a predictive issue. Maybe with immunotherapy we are increasing this benefit, but this is important to know. We know that in one cancer, for sure we have data that mutational load is predictive for bladder or, you can see here, this patient's receiving surgery and some of them are receiving chemotherapy, the survival is much better if you have more mutations meaning that your immune system is in better shape, if you have more mutations.

So what was new from our description that the germ-line DNA alterations are seen frequently and this is important to remember in order to design subsequent trials. This is another report by Faltas at ACR showing a higher incidence of germ-

[01:24:00] line DNA snips [inaudible 01:23:56]. Also mismatched repair is not frequently seen but occasionally seen in 3% and this is occasionally linked to upper tract tumors and Lynch Syndrome. And if we put all this together and also this other presentation by Thea, from the memorial group, the deleterious DNA repair mutations, were seen in 26% of patients with bladder cancer. And we need to take this into the advantage of putting these patients with immunotherapy. And [01:24:30] in fact, [inaudible 01:24:29], he showed that there was a correlation between response with immuno therapeutic agents and mismatched repair alterations or DNA repair alterations. So this predicts response to immuno therapeutic agents. We know that [inaudible 01:21:58] indicated for mismatched repairs so we need to remember that in bladder cancer there's going to be this 3% of patients having these MSI instability. And why not combine with [inaudible 01:21:58] inhibitors so this is one of the arms of this trial that we have seen before.

[01:25:00] And then the most recent data published by the TCJ was highly criticized, it is a classification in different molecular subtypes and I think that we can take the advantage from this TCJ analysis. This was written by Seth Lerner asking if this is a future treatment paradigm? Based on RNA subtypes we are able to further classify on the standard liminal or basal. You can see here liminal [inaudible 01:25:25], liminal infiltrative, liminal basal [inaudible 01:25:28], and a new type [01:25:30] that has been described not linked to the morphological aspects of bladder cancer, that is a new [inaudible 01:25:34]. And we can see here based on that, and this is a proposal to be explored in future trials based on this profile, you can use targeted therapy here. For example, in this case of liminal infiltrated, this is where IOS can work much better but for example, in the liminal papulary as mentioned before, the likelihood of responding is pretty low and probably using agents like [inaudible 01:26:01] inhibitors will be the best way to treat these patients. And this could be applied in the new [inaudible 01:26:06] setting in patients with muscle invasive.

[01:26:00] So the way to move forward in the daily basis, what we need to do is to sequence and look for all genomic abnormalities in the tumor, in the germ line, and this is a paper that hopefully is going to be published, where we have been meta-analyzing to 149 IO treated patients with some of them having biopsies before treatment or after treatment at the time of relapse. And you can see here [01:26:30] that there are a lot of genomic abnormalities that are linked to a better outcome. We know the mutational burden but even specific mutation of genes, like JAK2 mutation and so on, can predict response to immunotherapy and this needs to be implemented in all the patients that we are treating.

[01:27:00] To conclude this, my last slide, Understanding Immunology and Genetics, has identified groups that responded well to PD-1 therapy. We have seen that the highly mutated tumors in bladder cancer's mutational burden, MSI, all the facts in DNA repair, we have seen these. And this is obviously [inaudible 01:27:07], these genetically fine groups in describing TCJ that will be published pretty soon. And obviously we need to come into an integrated analysis of response and resistance, with mutations, mutational signature, clinical annotation, annotational [inaudible 01:27:20] in all our patients.

With that I conclude my presentation and thank you very much for your attention.

[01:27:30]

Speaker 2:

So, with that I'd like to invite back to the stage for our panel discussion all of our speakers and in addition to all of our speakers, I'd like to invite also Daniel Chen, from Genentech, and Nolan Wages from the University of Virginia.

[01:28:30]

So while everyone's sitting, I think what I'll do is I'll summarize a little bit. I heard a lot of common themes in these talks. Some of these common themes were, first of all, patient selection is going to be key for combinations. We already have a response rate that, with duration of response, that the duration is impressive but with single agent immunotherapy agents perhaps the response rate isn't as high as we want, and so we want to make sure we're selecting the appropriate patients for combination therapy or sequential therapy, with an eye in mind of who's going to respond best to monotherapy and who might need combination therapy and how do we identify those patients from the start.

[01:29:00]

Other common themes I heard were dose optimization, is not necessarily just what dose are you giving but are you giving it sequentially, what kind of schedule are you giving it in, do you need to stop therapy at some point because really what a patient would view as clinical benefit is when they're off therapy and that's something that, at the agency, we're exploring. What is clinical benefit to a patient, and what could be other novel ways to demonstrate that from a regulatory standpoint?

[01:29:30]

The other common theme I heard was, there are hot tumors that we know will probably respond to immunotherapy agents, but what do we do with these cold tumors and how do we prime t-cells, and what are the different methods we've been using to do that. And then finally, novel trial designs. How do we optimize when we have multiple inputs into a trial, how do we optimize these trial designs so that while we're looking at dosing optimization, how do we take all these factors into account when you have multiple agents such as, you know, 2 chemotherapies or 1 molecular target agent, 1 chemotherapy and an immunology agent? So these are the themes that I heard.

[01:30:00]

Speaker 1:

The target age at one chemotherapy and an immuno oncology agent. These are the themes that I've heard throughout all of these talks. One of the questions I wanted to ask has to do with, one of the first questions and this can go to anyone but in particular to the people who spoke about priming T cells, with this CD 40 method to try to overcome [limitational 01:30:24] burden diseases, is this priming approach being used in other disease areas?

[01:30:30]

Speaker 2:

The CD 40?

Speaker 1:

Yes.

Speaker 2: Absolutely. I had the opportunity to tell you about trials that involve pancreas cancer patients but there's a growing portfolio of clinical trials looking in other tumor types, particularly studies in combination, CD 40 antibodies in combination with PD 1 or PD-L1 antibodies.

Speaker 1: Has this been used in breast at all since you touch on some of the same topics?

[01:31:00]

Speaker 3: There are trials of CD 40 in combination with PD 1 and PD-L1 in particularly PD-L1 in a variety of tumor types including breast.

Speaker 1: By the way, just so everyone knows, if you have a question, please come to, there's a microphone up there and my panelists, if you have questions for each other, please indicate if you have a question. The next question I wanted to ask had to do with dose optimization in terms of stopping therapy. Dr. [McDermott 01:31:31], have you stopped therapy on patients to see what happens?

Dr. McDermott: I think that's an interesting concept. Looking back to one of the first phase 1 trials where the PD 1 antibody that was done largely at Hopkins, I think there are Hopkins people that can correct me if I'm wrong. I think on that trial they can get one dose of what was MDX 1106 at the time and if you got some benefit you can get more therapy. Early in that trial you saw benefit with just one dose and several people went on to get subsequent treatment. There was a concern about over treating people at the time.

[01:32:00]

We went from that experience, which was interesting to the larger NEVO phase one trial, which gave up to two years. Two years in my mind was somewhat arbitrary end of treatment meaning there was no exploration or not enough of a detailed exploration of whether 6 months versus 12 months versus 24 months made a difference. I think we need to work backwards there because some patients were clearly over treating. That said on that NEVO 003 trial, when patients stopped at two years, some of them progressed. There are probably some patients who are in response at whatever time you want to stop who need chronic therapy which is sort of an interesting concept.

[01:32:30]

In some of those patients, and this is data that Steve [Hodee 01:32:59] presented I think last year, maybe two years ago at AACR. When you reintroduced NEVO in this case, some of them regained a response, many of them did. It wasn't a large number of patients but that sort of opens the door in my mind to looking at different lengths of treatment, considering novel designs like randomized discontinuation designs. Those kind of designs are very hard to execute in humans because they don't like to be taken off treatment when it's working, particularly if it's not adding side effects, which is one of the interesting things about PD-1, most of the talks happen in the first six months. Patients are not as eager to come off, in my experience, PD-1 as they might be Taxol for example where they're accumulating side effects.

[01:33:00]

[01:33:30]

[01:34:00] We need to look at different durations, we need to look at novel designs because there are probably some patients who need chronic blockade and others that can come off, particularly those with deep responses. Many of those patients, and you learn this from the [CTLA4 01:33:55] PD-1 experience where there are more deep responses. Some of those patients come off tox in their first three months and never need to go back on treatment. I think from our point of view, while we need to reduce the tox, that's where we need to be going. We need to be going shorter courses of treatment, stopping the drug, see what happens, reintroduce the drug if patients progress. That's what I'd like to see.

Speaker 5:  
[01:34:30] Maybe I could just add to that. David and I, I think have tried to address this questions over many years as have many people in this field. In fact, the original [tesolism 01:34:31] after phase one, large phase one expansion study actually limited therapy to just a year to ask this question. I would suggest as David has said that this is an unanswered question for our field, what optimal duration of therapy is for immune based therapy. It probably lies with the idea that in our patients being treated, there are some very specific subsets that we don't understand.

[01:35:00] Perhaps for some of these patients, there really is early eradication of their tumor based on a very intense immune response and for some of these patients you see that you can stop treatment early and have very prolonged durability of that efficacy. That may be because of eradication of tumor. Whereas other patients perhaps what's happening is you actually have a chronic ongoing battle between tumor growth and tumor efficacy, anti cancer immune efficacy. That's just a chronic biologic reaction. You can imagine that for those patients stopping therapy, could be detrimental.

[01:36:00] And I think in the larger experience that David is summarizing, some patients when you stop therapy have very durable responses, other patients have some durability but ultimately progress. Other patients might immediately progress upon stopping the immune based therapy. I think what has been difficult is that there haven't been any clear identifiers for which patients belong to which subset and even the deep depth of response hasn't itself been the perfect measure. One might assume that a CR might mean eradication, unfortunately it might not. It may just mean that the tumor is at a microscopic level that we can't measure. I think that the clinical experience has suggested all possible outcomes are still in play.

Speaker 1:  
[01:37:00] We had a really interesting patient on that phase 1A with triple negative breast cancer who enrolled on the study when it was written for one year of therapy and then stopped. She had pseudo progression. She had a nice clinical benefit if you take the pseudo progression out of the picture, she had a PR but was classified as a PD because of the progression. She was benefiting clinically from the drug.

At about the time she reached her one year point, the protocol was modified to allow for continued therapy. We sort of had the option to decide what to do. We

[01:37:30] talked about it and we decided we might be able to learn more by taking her off therapy and watching her closely. She came off therapy, we watched her very closely for a year and about a year off therapy she developed an enlarged lymph node, which we biopsied, saw tumor cells and restarted therapy. She's gone on to have a complete response. That's one anecdote of a patient that was discontinued from therapy, did pretty well for a pretty good period of time and then went on to have a better than the initial response when we restarted her immunotherapy after that evidence of progression.

Speaker 6:  
[01:38:00] I wanted to make one comment. I find the notion that potentially we're overdosing PD-1 antibodies and I think of a paper John Wary and [Tara Gongitar 01:38:05] published in nature just a few weeks ago looking at systemic biomarkers of response in patients with melanoma who were treated with PD-1. They clearly identified changes in proliferative CD 8 cells in the periphery as a biomarker when combined with tumor burden predicted response.

[01:38:30] If you look carefully at their data, you'll see that that pharmacodynamic effect happens after a single dose but when the same patients were followed receiving the same drug over the course of several more months, the PD change was lost. The big bang happens with the first dose in the first six weeks and then it goes flat. We're not yet sure what that's teaching us yet but prolonged use of these drugs, you lose at least that biomarker I think is provocative.

Speaker 7:  
[01:39:00] Just adding on what Bob said, I think some of this is disease specific. I think in melanoma, I also feed melanoma, there I think there's more evidence that you can stop treatment particularly in responders and get a benefit and more of us, Mike [Atkins 01:39:10] is an advocate for this, is after about 18 months of treatment in a responding patient do a PET scan and if the PET scan is negative, consider stopping drug. I think that's the type of thing we need to explore and randomize trials and not just stopping early but are there other predictors of who will be off.

[01:39:30] For example, immuno [pat 01:39:30] isn't something people are exploring. The NCI and other places, that's something that should be considered but there are a couple of concepts that have leaked into our practice that I think need to be proven correct before we adopt them. One of them is this concept of unlimited treatment. I mentioned the first Hopkins study, which was one or three doses, whatever it was, we went to the larger study that was 2 years of treatment. Dan mentioned one year. Now we're in a concept where many of our trials are unlimited PD-1. We haven't proven you need that. I think before we adopt that as a rule,

[01:40:00] Speaker 1: ... that, and I think before we adopt that as a rule, is we need to prove that that's real. The other concept that I worry about is this treatment beyond progression issue, which has been explored in retrospective analyses of giving PD-1 after a patient progresses and showing that the patients who continue on drug do better than those that stop.

[01:40:30] I think those analyses are very biased. I think they are set up for people in community over-treating patients, and I think that's a particular problem because most progression, in my experience, outside of melanoma, is real progression, and if you don't move that patient onto something else, they are going to be in deep trouble. I think this is a problem, not just for the patients, but for our field, meaning to make advances going forward.

[01:41:00] These drugs are so convenient to use, they are getting used so widely in the community, we need to get those patients when they progress for our trials if we're going to make progress, not when they're treated beyond progression. It's harder to get those patients because I think they fall apart, and they can't come to large centers to go on trials. In a way, by advocating for treatment beyond progression, we're slowing down progress in this field, potentially harming patients. We need to prove in a randomized way that treatment beyond progression is useful before we adopt it as standard care.

Speaker 2: Dr. Jaffee?

Dr. Jaffee: Yes, I'd like to raise a slightly different way of looking at this problem. Is this a problem of over-treating, or is it a problem of not adding the right combination of drug? Because the emerging data suggests that PD-1 blockade isn't able to keep cells stay activated, and maybe by repetitive treatment, we're trying to reactivate or bring in new activated cells, and in fact, I think the data's emerging from John Wherry, from Rafi Ahmed, and also preclinical data that PD-1 blockade can push these T cells into exhaustion.

[01:42:00] So, maybe what we really need to do is limit that therapy once it reaches a certain response rate where we can't move it anymore. But, think about how do you make sure those T cells don't become exhausted? Obviously, OX40 agonists, there are another agents as well, but I think we need to really think a little bit differently about this problem and say, "Yes, we don't want to continually treat patients if we don't see benefit."

[01:42:30] Biomarkers, of course, would be the best way of knowing if this is happening, and we need better biomarkers, and I think there are many people looking at this as well, but I think we have to pay a little bit more attention to what is happening and not make decisions based just on clinical outcomes.

Speaker 2: Speaking about biomarkers, I mean, that's a theme that I think we're going to be hearing a lot about today, so we need better biomarkers to identify which patients to treat, either with mono-therapy or perhaps with our current standards of VEGF, TKIs, lets say, or which patients do we need to select for combination immunotherapy, but also, clearly, which biomarkers can we use to select length of treatment, when to add something, and those things.

[01:43:00] My question regarding this is do we continue to embark on trials using PD-L1 as the marker, or what other markers have you been using to try to identify those patients from the start who should be not just ... I mean, we know mutational

[01:43:30] load, and we'll probably hear a little bit more from Dr. Chen about the things that they're using in his company to identify the proper patients, but what are the biomarkers are you exploring in the lab right now to identify the appropriate patients for combination therapy?

Speaker 4: PD-L1 is the first biomarker, so folks are still looking at that. Whether or not there is T cells present there is an important consideration, and what the phenotype of those cells is in terms of what checkpoint molecules they express is also pretty important, like what I showed with pre-clinical data combining STING intradermally with PD-L1 and OX40. I think you can map the micro environment of the tumor and define things based on that, ideally.

[01:44:00]

Speaker 2: Can you envision a trial, the multi factorial trial that you discussed, in which you would use these different biomarkers with different doses to select an appropriate dose for different populations, or do you think it has more to do with the biomarker in the patient and whether or not the therapy is appropriate for them at all?

[01:44:30]

Speaker 4: I think that unusual trial design, which you could try to optimize a combination pre-clinically using that approach and then maybe in a simplified approach in the clinic. I think I would use biomarkers for patient selection, and then explore a directed combination based on the biomarkers that we targeted for selection in the combination.

[01:45:00]

Speaker 2: My next question had to do with, you brought up a little bit about other extrinsic factors, or intrinsic to the patient, such as obesity and gut microbiome, has this played out at all in breast cancer to date?

[01:45:30]  
Speaker 4: In breast cancer, that's definitely an emerging data. Breast cancer is lagging a little bit behind in terms of clinical responses with these agents, so there are a lot of people that are interested in looking at that and incorporating that into the trials, but there's not a lot of data for that so far.

Speaker 2: For those of you in other disease areas, has that come into play at all?

Speaker 5: We perspectivevely analyze patients that did receive antibiotics before starting [inaudible 01:45:57] because this might impact in the microbiome, and I think there is in other diseases that there is an impact, if you give antibiotics, you might change the intestinal flora, and this might lead to a different outcome, so there is an emerging issue.

[01:46:00]

[01:46:30] Now, we have a trial that we are perspectivevely taking the rectal flora in these patients and trying to see the B cell population there that is impacting on the outcome. Absolutely, it is an emerging area that we need to explore more, or even low dose steroids. What's the impact of low dose steroids, antibiotics, let's say, even three weeks before starting therapy or during therapy, so there is a need explore further.

Speaker 2: Dr. Shue?

Dr. Shue: My name's James Shue. I'm one [inaudible 01:46:48] a review for FDA. I have a question and comments for David. You mentioned about we need to select the patients between VEGF inhibitors and PD-L1 immunotherapies. This is very remarkable and insightful. I will still review of [inaudible 01:47:11] in renal cell carcinoma in the secondhand setting.

[01:47:00]

[01:47:30]

Back in November of 2015, when FDA first approved this drug, we actually made the exploratory analysis. So our hypothesis was that, based on patients' prognostic risk categories, you can actually select between VEGF inhibitors versus PD-L1s. We made this hypothesis based on the PFS analysis. What we noticed is that, for a patient who has poor risk categories, the [inaudible 01:47:41] was doing much better in the peer [inaudible 01:47:45] versus the [inaudible 01:47:48] so what is your comments on if you think it would be worthwhile to study sequential therapy comparisons using second PFS as an end point.

[01:48:00]

We actually published this hypothesis in the oncology journal this year, so I just want to get your comments on that.

Speaker 1:

I think sequential trials are important, not just in kidney cancer, but in a variety of tumor types. I think they are hard to execute though. We've certainly proven that several times in the kidney cancer realm, where you take approved drugs, and you ask patients to consider a sequence. We've done TKI versus mTOR with a switch, for example, at progression.

[01:48:30]

[01:49:00]

What happens in most of those trials, particularly when you're dealing with approved drugs, is patients don't comply with the switch. They often drop off and that confounds the results of the trial. Those numbers improve when you're dealing with unapproved drugs and patients are motivated to switch, so in the case of the IMmotion150 trial that I mentioned, there is actually a crossover in that study that's producing some interesting insights about resistance, not just to VEGF, but to PD-L1. Patients were motivated to switch, and 70% of them did, because they could get the novel combination that they couldn't get otherwise.

[01:49:30]

I think, if we're dealing with a trial, for example, let's say Sutent, then Nivo versus Nivo, then Sutent, that's an important trial to do. I just think in reality it's going to be hard to execute if those drugs are available outside of the trial because patients will drop out. They'll choose to do what they think is right, so it's a hard question to answer. But it gets back to the larger point, which is, in kidney cancer, we're likely going to end up in a world a few years from now where the FDA is going to approve four or five different combos of VEGF plus PD-1 in the first line.

In my mind, if one of them gets approved, they're all going to get approved. Assuming they're all approved, there are going to be patients who are not

[01:50:00] benefiting from either approach of those combos, but they're going to be getting them anyway. So there will be patients that are resistant to the VEGF strategies, but they're going to be getting one because everyone is going to be switching to combos. There are going to be patients who are-

David: Should be getting one, because everyone is going to be switching to combos. There are going to patients who are PD-1 resistant, which over a third of kidney cancer patients are, that are going to be getting PD-1 on the front line. And in the end I don't think we have done them a service if we're doing that. Not just in kidney cancer, but in the larger field, because the sequence might be just as good in many of those patients.

Speaker 2: So what about, if you allow for a crossover in using the second PFS as end point.

[01:50:30] David: Well I think in theory that's a good trial to do, if you could execute it. So that ultimately, you would want to do a trial that compared, say Sunitinib Pembro versus Sunitinib and then Pembro. Or Pembro and then Sunitinib. That would be a very useful trial to do. I just think it's hard to get patients to sign up for a trial like that.

Dan: Alright, thanks. This overall question really highlights, I think, a very interesting piece for this entire field, which is that our patient populations are changing. And so this question around prognostic variables, essentially, as I understand it, a second line renal cell setting, where they got a VEGF/TKI in the front line setting. Could be something that predicts for cancer immunotherapy, but it also could predict for what your outcome was from your front line TKI. And so David, do you have a comment on whether, if by looking at prognostic variables in the second line setting, could that actually just be reading out. Whether Sutent was an effective drug in the front line setting, versus less effective.

[01:51:00]

[01:51:30]

David: It's possible. I mean I think, as James mentioned, one of the interesting parts about the Neuvax Phase III in kidney cancer was that the greatest activity of the drug was seen in our worse patients, or our clinical criteria patients who you would expect to do poorly. And that's a very exciting aspect of this whole PD-1 story, is that patients whose tumors would behave poorly with standard therapies are some of our best responders. That's truly exciting.

[01:52:00]

[01:52:30] In some tumors, that may connect to this whole mutation burden story. That's probably not the case in kidney cancer, where kidney cancer is not a very mutated tumor. It may be a more specific mutation story in kidney cancer, that may play a role. And there are people looking at that. As far as prior treatment, I think if I understand your question Dan, I'm not sure if I did, but there certainly BMS has looked of prior treatment on the response to PD-1 blockade, and seen some interesting findings, where patients for example, who got Sunitinib before PD-1 seem to do better. When they got Neuvax than those who got Sunitinib, and then PD-1, whether that's real or not, I don't know, but it generates an interesting hypothesis about whether pre-treatment makes a difference in

[01:53:00] response to PD-1, which gets to what Lichen and Bob were talking about as far as, you know, priming a tumor to respond. Is there something about prior treatment that might set you up to be a better responder.

And I think that's an area we need to push on, because most of our tumors are cold. Most of our tumors are non-responders. Even those that are responding will eventually progress. So, we need to look at those clinical criteria, including prior treatment, to see if it matters, because it may lead us to better combinations and better sequences in the future.

[01:53:30]  
Speaker 4:

I had a question for all of you. And this came up several of your talks and its come up inside the agency certainly. A great deal is, our greatest resource is our patients and with the large number of possible combinations that can be studied in each of your disease areas. How are you prioritizing which trials either at your institute or are you personally putting patients on. How are you prioritizing which trials you would like to go forward with for these combinations?

[01:54:00]  
Speaker 5:

So, I could speak for myself. I'm trying to trial selection, based on the scientific rationale. So, that evolves with the data to some degree. So, if I am looking at a combination trial, rather than just combining something, because you can. I look for a good scientific rationale for why there could be potential immunologic synergy between, behind the combination. So, that's generally how I'm choosing.

[01:54:30]

In breast cancer we have the advantage of classifying these patients, although it is not a perfect classification. And that helps guide which direction to move the patients into. So for her to direct the therapies we use her two based combinations. Triple negative breast cancers are kind of wide open, so there's

[01:55:00]

not quite so much there that's purely immunologic mechanism based. And then ER positive breast cancers are getting more complicated, because now we have not only hormonal therapy, but we've got CDK-46 simulators. So, I look for trials that fit into the treatment paradigm, that also have a good immunologic rationale for potential synergy.

Dan:  
[01:55:30]

I was going to add one thought. So those are the types of considerations, if the denominator stays the same. So, you know the question is, do we have more trials and combinations then patients can go on clinical trials. But in this country, the percentage of patients that go on clinical trials is 4% for cancer. Four. So we're not testing new ideas in 96% of our patients. That high centers of excellence, some of the ones represented here. That number is a lot higher, but if we could change the denominator and understand why that number is 4%,

[01:56:00]

there would be many more patients interested if we could solve some of the problems, which go beyond the intricacies of trial design and get into issues of access and availability and geographic challenges and inclusion/exclusion criteria, which may be limited us in ways that now in field that we could begin to open up. So, I would put that out there as another way to think of a solution.

David:  
[01:56:30] So I mean I completely agree with what Bob said and I think this gets to what I was saying before about this concept of, you know, how easy these drugs are to give in the community and patients being treated beyond progression. Not being referred when they should be. I think we have been sort of a victim of our own success, in the sense that when these trials were Phase I, we had more patients than we had slots. Now we sort of have the opposite problem and I think we can't as a field contribute to that problem by encouraging things that are unproven. But to get to your question about how do I decide about whether I want to explore a specific combination, I think most of these combinations that are out there in development have very similar characteristics, so it's not easy. They all have interesting pre-clinical data in multiple tumor models showing that, you know, they can make the tumor go away, which is great.

[01:57:00] Many of them have single agent toxicity profiles that are manageable. Most of them don't have single agent activity so if you ask, alright, which one's will want to study. I mean, to me the one's that I'm most interested in are combos that have activity in PD-1 failures. I think those are important. That's an early signal of activity of the combination. I think looking at combinations that have activity in biomarker negative patients, I know our biomarkers are not great, but they do enrich for responders.

[01:57:30] So, if you could have responses in PD-L1 negative patients, I think that's meaningful early on, because I think, and going forward, ideally the sponsor of trial would have a sense of who is going to benefit. So, they would have a sense of a marker ahead of time of who they want to treat, not just treating everyone, because I think, trials we've had great success in this field with lots of pivotal trials in unselected patients. In the salvage setting, many positive trials almost every single trials, have been positive in that setting. But as we move to front line, as we move to Adjuvant. If we move without ability to select, we're going to see the same percentage of trials be negative, in my opinion. We are now seeing positive trials, because these combos are not active enough to win in all, I don't think.

[01:58:00] Let me ask something else. In addition to all these trials that are, genomically driven with some potential markers, I mention these spy trials in breast that could be applicable in bladder. There is another thing that the concept of sequencing. One of the questions that has caught a lot of attention is that at least in bladder, and also in lung cancer, we can see that the trials we are comparing immunotherapy with chemotherapy. In the very beginning, the survival curve is worse for the immunotherapy. So there might be a need to prime the tumors with chemotherapy, before moving to immunotherapy. In the first two months, that is the time that you are required to push the immune system. Usually, in lung cancer, in bladder cancer, the survival is worse in patients receiving immunotherapy. So something is going on there. This type of concepts, I mentioned this other trial design, like trying to use the chemotherapy to prime immune responsive sequentially. Is something we need to think about.

[01:58:30] Speaker 2:  
[01:59:00] Let me ask something else. In addition to all these trials that are, genomically driven with some potential markers, I mention these spy trials in breast that could be applicable in bladder. There is another thing that the concept of sequencing. One of the questions that has caught a lot of attention is that at least in bladder, and also in lung cancer, we can see that the trials we are comparing immunotherapy with chemotherapy. In the very beginning, the survival curve is worse for the immunotherapy. So there might be a need to prime the tumors with chemotherapy, before moving to immunotherapy. In the first two months, that is the time that you are required to push the immune system. Usually, in lung cancer, in bladder cancer, the survival is worse in patients receiving immunotherapy. So something is going on there. This type of concepts, I mentioned this other trial design, like trying to use the chemotherapy to prime immune responsive sequentially. Is something we need to think about.

Not just combine the drugs. Keep both at the same time. Sequences, I think those are very relevant in clinical trials.

Speaker 4: So we have heard from Dr. Hemaderma, that getting sequencing trials and/or randomized discontinuation trials are difficult to do. Who's sponsoring these sequencing trials? Is it cooperative groups, is it industry? Is it investigator sponsored?  
[02:00:00]

Speaker 2: This one that we are doing, is

Speaker 1: Is it investigator sponsored-

Speaker 2: So this one that we are doing is an ISD we approach a company it's like okay, we don't want to combine immunotherapy with chemotherapy and that's it. Let's try to ... In addition to the combining, look if there is some ... This trial we are going to give immunotherapy before starting chemotherapy and then, on day 15, we are going to give again immunotherapy looking for like a, increasing antigen release via by the chemotherapy before giving the immunotherapy. So this type, and obviously you need to have strong monitoring of how the immune system is changing with all these sequences and so on. This is an ISD trial so it's ... I dunno. Companies maybe are not very very interested.  
[02:00:30]

Speaker 1: I just wanted to return to one point that you made Doctor [Vanderheide 02:00:48] about the recent study where looking at PD-1, after just the first dose you may have gotten most of your impact. So do you think there will ever be, you know we've discussed length of treatment, do you think that treating as much as one dose or three doses or six months will be within a randomized discontinuation trial.  
[02:01:00]

Speaker 4: Well, yes. I hope so. I think we have to refine those biomarkers. That was a blood test. Those investigators now looking at tissue based, see if maybe something deeper was going on in the tissue but ... yes. What we're understanding and ... CD40 is a good example you know everybody immunologically responds to anti-CD40. I think it's 80% of patients have that response to pembrolizumab, but not nearly as many people respond. As we refine those biomarkers, particularly early looks soon after treatment, I think there is a way to go forward using ever more sophisticated biomarkers to design trials around discontinuation. And, as [Alys 02:01:54] said, move on to the next step. You know we got what we got out of PD-1. What's behind it now? Is it CTLA-4, is it VISTA, is it ... you know what's next, and begin to drive trial decisions based on those biomarkers. I think it's a very real possibility.  
[02:01:30]  
[02:02:00]

Speaker 5: Just to go back to the, denominator issue that Bob raised, if you see the, at least in my experience, if you look at the referrals coming in, and talking with my colleagues in the community, there are a lot of patients out there who don't get the best access and in fact they either get the drug off label. In which case we're not really learning anything from that, or, they get referred very late when they're really not very likely to respond their performance status isn't very good.  
[02:02:30]

[02:03:00] So I think, the more that we can create relationships with the community oncologists and really work together to pull patients into the clinical trial system. That'll help advance the field, and kind of, at least, start to equalize the abundance of resources with the drugs that we have to test with. The patients that we have to test them in.

Speaker 1: And to your point also about eligibility criteria we've been working on a project of, sort of modernizing eligibility criteria, such that to encourage both companies and investigators to, think more carefully and scientifically about which eligibility criteria as you move through development are most important to encourage this, to opening clinical trials to more patients including you know, brain

[02:03:30] metastasis and HIV and prior malignancies and organ dysfunction and what's most appropriate for that agent and to think more carefully so that ... And age, as well for appropriate diseases ... To think more carefully about which patients really should be included in trials and so that potentially we would also have more representative data pre-market before a product gets approved and goes to the entire market where patients who may not have been represented on the trials will be treated. Especially with immune agents you know we have, you

[02:04:00] know there are very few patients who had autoimmune diseases who were treated in clinical trials and we know that it's being used out in the real world with patients who have autoimmune diseases so these kind of issues are things that we're trying to address at the agency as well.

Speaker 6: Okay if there are no other questions or comments are there any other questions or comments?

Speaker 7: Can I ask a question of the front row? As we begin to think about checkpoint  
[02:04:30] blockade combinations with chemotherapy, one thing that I wonder ... Medical oncologists will often use steroids for antiemetics. And not trivial doses, some of these drugs are weekly. And so ... I'm looking at Lisha and [inaudible 02:04:43]. What do you think, are we ignoring that? And is that an impact? I worry that it's an elephant in the room we're not, we haven't really got our head around yet.

[02:05:00] Speaker 5: So the data on that are a little bit mixed. There's pre-clinical data that, you can give immunotherapy and a significant dose of steroids and it doesn't impact the induction of immunity. A lot of, the early data has tried to use agents that don't require steroids like the combination with [napaclitaxel 02:05:16], that has the immune modulatory benefits of the taxane but you don't give steroid pre-treatment. But paclitaxel a lot of time we can wean the steroids off, although we have to give them in the beginning. There are clinical trials that are looking specifically at the issue of steroids and what they're impact is on, the response to the agent. A PD-1 or PDL-1 a combination with the abraxane, [napaclitaxel 02:05:45] with steroids. So that should give us some information. I think it's being systematically looked at least one trial that I've seen.

Speaker 8: We try to avoid giving taxanes in bladder so unfortunately we don't use it that  
[02:06:00] frequently because giving out bottles of 20 milligrams of dexamethasone or 10

[02:06:30] milligrams, it's, for me it doesn't make sense. There is data in melanoma saying that you can give up to 10 milligrams of prednisone and this not impacting on the outcome. And this the only data that we have. Other is speculative and, I try to avoid as much as possible doing steroids but I understand in breast cancer that you give weekly taxol, that leads you to give eight milligrams or whatever. So this my impact on ... But we don't have data on that.

Speaker 9: [inaudible 02:06:32]. This is a question with regards to clinical trial design. As you've heard that it's so important to select the right patients for your clinical trials and also, the importance of combining or sequencing these different agents. I'd like to know from the panelists what are your thoughts, especially with regards to privatizing these kinds of questions when you design your phase one trial, in the process of optimizing the dose.

[02:07:00]

[02:07:30]  
Speaker 10: I'm of course coming at this from a biostatistics point of view. I think it's a good question as we've seen the ... trials are getting more complex and, there's a need for novel designs. I think I might even pose a followup question to the group about, the role of exploring more combinations in this setting because I saw, we

[02:08:00] saw in, a couple of the talks, very small numbers of combinations being explored, with a little bit of safety data being accumulated at the beginning. In the first talk there was a two arm safety study with 10 patients in each study. I saw two or three dose levels in combinations in later talks that three plus three designs. And

[02:08:30] then I was struck by the contrast between those and Doctor [Emmond's 02:08:32] talk that explored the combination grid, of three dose levels of two agents and, and she made a great point about how one of those dimensions

[02:09:00] could be schedule, or something else. But when we're asking these more complex questions I'm wondering what the role of exploring more combinations is, and of course the trial design needs to catch up with those more complex questions I think it's lagging behind a little bit.

[02:09:30] So I'm wondering if the right questions aren't being asked, or are we sort of boxing the question into the trial design that we know how to do. And so I think that's an unanswered question from my standpoint and one that is very important.

Speaker 5: So one of the advantages of that factorial design that I showed and ... if it can be applied in the clinic in an effective way, that allows you to get information quickly, and I think we're better positioned now to do that than we were when I did it, is you can bracket what you think is likely to be the bioactive dose. And

[02:10:00] then when you generate the response surface with ... actually is across that entire dose range. So it could end up being that the best

Speaker 1: Entire dose range, so it could end up being that the best dose combination is actually not one that was tested, so you can identify that and then you can take it forward in a small cohort of patients and get more information about it. You could almost use that as really exploratory way to look at the interactions between dose ranges, identify what looks like the best, test it in a small cohort,

[02:10:30] and if it looks good then you can take it further. It's one way to potentially more quickly look at different doses, rather than a traditional stepwise three plus three or the other different types of dose escalation, de-escalation that you see.

Speaker 2: Yeah, go ahead.

Speaker 3: I was just gonna follow up, how many patients were on that factorial design study?

Speaker 1: There were 28 patients, 22 were actually in the grid. Six people got the vaccine by itself, so they weren't included in this surface, so it was 22 patients. We included two or three patients at each of the points, except for one, which only had one point. But every single point informs the response surface, so it actually has a lot of power to find good data.  
[02:11:00]

Speaker 3: Right.

Speaker 2: So I just wanted to add that I think that overall, this meeting is tackling probably the most difficult problem for cancer immunotherapy. And it's based on a number of things. First, we gotta talk about single agent activity, we're talking about combinations, you're talking about a class of drugs that have acute effects, both on efficacy and safety and chronic effects on efficacy and safety. And when we think about the chronic effects on efficacy and safety, some of those are going to be dependent on continued dosing and some aren't. So you can quickly see just how many variables there are going to be. So just some perspective on how we as a field can start to approach this. When you look at the possible different combinations when you add dose and schedule the numbers, astronomical. So going into these experiments, these clinical experiments, it becomes even more important A, number one, to start with the hypothesis. Number two, based on that hypothesis, have some near-term biomarkers so you can measure that effect in humans in a small number of patients where you can actually vary some of those parameters in an under-powered fashion.  
[02:11:30]  
[02:12:00]

[02:12:30] And then three, look for big effects. In small numbers of patients, you really can't tease apart more nuanced effects, but you can tease apart big effects. So dose and schedule where one dose and schedule works and the other dose and schedule doesn't work. Those are the kind of things that we should be able to tease apart. But be very cognizant that those acute endpoints, and we've talked a lot about inferences made upon acute endpoints, and we've already said

[02:13:00] response rate is probably not the most sensitive or specific biomarker for efficacy in cancer immunotherapy, but then we go on to talk about all these inferences around biology related to response rate. And so be very cognizant that of course the real biologic endpoint for us in these clinical trials is OS. And even with OS, that can be split into OS tail of the curve, OS hazard ratio, and

[02:13:30] those are two very different things in terms of the long-term impact to the patients that we're trying to help. So this is a very complicated topic and we can hopefully get to a point where at least we have a framework to think about it,

but it's unlikely that today in 2017, we'll have the best answers on how to address all these problems.

Speaker 1: Thank you. Okay. We are over time. If you have a super fast question or is this a long and complicated question?

[02:14:00]

Amy Van Andel: I'll make it very brief. Amy Van Andel, Boehringer Ingelheim Regulatory Affairs. I just wanted to provide a quick comment from the industry perspective about the access to clinical trials. I know you talked about inclusion/exclusion criteria and it goes along with all the hypothesis have been generated and the great desire to have public/private partnerships, et cetera, to do these studies and the community involvement. I just want to us also look at the operational aspects of doing these things and find innovative, efficient, non-bureaucratic ways to be

[02:14:30]

able to access these patients and modernize the way we conduct trials and use technology, virtual aspects, et cetera, so that we can lower the burden to being able to have to have these patients in other settings being able to engage in our trials, either in the US or globally. I think that's an area where we really have great gains to be able to make and it will require all of us industry and community regulatory and sponsors to work today to think of ways that we can conduct these trials just as clearly, with just as high quality, but lower the barrier to participation in them. Thank you.

[02:15:00]

Speaker 1: Okay, so I think I'll sum up, it's complicated. Thank you. Thank you for making that point. This is complicated. Combination therapy in immuno-oncology is complicated and clearly we are all trying to deal with this. I think the take home that I have from this session is, basic science is really going to drive how to use these combinations and we need to continue our efforts with many of the people who are here today to figure out which combination works for which patient population in which disease. And so, I'll leave with that. Thank you very much to all of our panelists. I appreciate your time. Thank you. Oh, so, wait. So, we are supposed to be reconvening at 10:30 and since we're only a few minutes overtime, I think we'll still reconvene at 10:30 for panel two. Thank you.

[02:15:30]

[02:16:00]

That was great. Thank you.