

Oncology Dose-Finding Workshop Part 3

Transcript: Session II, Key Translational and Design Questions for IO Agents

Liz Jaffee: [00:01:08] Everyone could try to get to your seat so we can start the next session, I'd appreciate it. Try to keep on time today. (silence) It's been a terrific discussion so far with the first session. I do want to encourage the audience to participate a little bit more and get up there sooner so we can hear what questions you may have. We've also loved to have the panelists talk as well and ask questions but certainly, we're all here together to discuss these issues.

[00:01:30] Session two will be Key Translational and Design Questions for IO Agents. I'll be moderating this session. We have three speakers. The first speaker will be Tiffany Ricks, followed by Daniel Chen, and then Bernie Fox. I'm going to start and ask Tiffany to please come up and begin the session.

[00:02:00] Tiffany Ricks: Good morning. I'm Tiffany Ricks and I'm a pharmacology/toxicology reviewer in the Office of Hematology and Oncology Products at FDA. Today, I'm going to discuss the non-clinical safety evaluation of novel cancer immunotherapy combinations. At the end of my talk, I will present a few case studies of INDs that were submitted to the FDA for immune therapy combinations and discuss some of the issues and outcomes following review. I have no conflicts of interest to disclose.

[00:02:30] The ICH S9 guidance provides the basic non-clinical recommendations for the development of anti-cancer pharmaceuticals for patients with advanced disease. The goals of the standard non-clinical program are to provide safety data to support appropriate starting dose and dose escalation scheme for clinical trials, identify potential target organs of toxicity and inform on clinical monitoring.

[00:03:00] To initiate a clinical trial for anti-cancer therapeutics, a sponsor typically needs to conduct 28-day repeat-dose toxicity studies in two species. For biologics, as discussed in ICH X6, S6, a single species is often acceptable if there's only one pharmacologically-relevant species. These studies are the primary data used to determine the acceptability of the proposed starting dose for first-in-human trials. However, for immunotherapies, additional considerations are needed for the safety evaluation and selection of an appropriate starting dose.

[00:03:30] For example, there may not be a pharmacologically-relevant species for safety evaluations if the epitope or target is not expressed. If the epitope or target is expressed, there may be differences in binding between humans and animals that are typically used for toxicological evaluations or there could be differences in thresholds for activation and sensitivity. For example, for toxicology studies conducted with anti-PD-1, toxicological findings in monkeys generally include diarrhea and minimal to mild multi-organ diffuse immune cell infiltration that's

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observed histologically with no clear clinical or clinical pathology correlates, where clinically, anti-PD-1 antibodies are known to cause immune related adverse events.

[00:04:30] For immunotherapy products, monkeys generally under-predict human toxicity and toxicology studies alone are insufficient for selecting an appropriate starting dose. Therefore, it's recommended that a minimally-anticipated biologic effect level or MABEL be used to select an appropriate starting dose. I'll discuss the MABEL approach in more detail in the next couple of slides.

[00:05:00] Immunotherapies also have unique safety concerns. There's potential for cytokine release syndrome, aberrant T-cell activation and immune related adverse events. Then, finally, what additional considerations are needed for combinations of cancer immunotherapies when there's an expectation of additive or synergistic toxicities.

The ICH S9 guidance specifically mentions concerns about using standard methods based on toxicology studies alone to set the starting dose for immune agonists. It states that for biopharmaceuticals with immune agonistic properties, selection of the start dose using a minimally-anticipated biologic effect level or MABEL should be considered. This approach relies heavily on a variety of pharmacology studies.

[00:05:30] There's no universal approach for determining a first-in-human dose based on a MABEL and the assays used will depend on the biology of the intended pharmacological effect. Useful data endpoints include in-vitro pharmacology data from target cells from human and toxicology species and concentration effect data from in-vitro and in-vivo studies. If using animal data sponsor should

[00:06:00] provide a comparison of differences between animals and humans with regards to exposure or drug distribution expression level and distribution of targets, affinity of target binding intrinsic efficacy, there should also be an evaluation of the duration and reversibility of the biologic effect and dose exposure relationship.

[00:06:30] The ICH S9 guidance also provides the basic non-clinical requirements for combinations of anti-cancer pharmaceuticals and the draft S9 Q&A provides additional clarity for implementation of this guidance.

[00:07:00] As stated in ICH S9, pharmaceuticals planned for use in combination should be well studied individually in toxicological evaluations. In essence, there should be sufficient data to support clinical trials of each drug alone. The sponsor should also provide data to support the biological rationale of the combination and this can include in-vitro or in-vivo data conducted or in-vitro or in-vivo studies conducted by the sponsor or a literature assessment based on mechanistic understanding of the target biology. This data may provide additional support for dose selection and safety.

In general, combination toxicology studies are not warranted to support clinical trials with combination anti-cancer pharmaceuticals.

[00:07:30] ICH S9 also states that if there is sufficient clinical data to support the combinations so for example a completed phase I clinical trial or a completed monotherapy phase within a phase I clinical trial additional non-clinical data may not be warranted. If there is no or very limited experience with one or both products, for example, a first in human study or a drug with limited phase I safety data, a combination pharmacology studies are often recommended and types of studies that we've accepted include in-vitro cytokine release assays from human PBMCs, in-vitro studies examining the potential functional dose response curve of T-cells and in-vitro T-cell activation assays. These studies should include an assessment of concentration response curves for determining EC-50, EC-20, and EC-90 values. This can be used to justify a combination start dose.

[00:08:30] For combinations of cancer immunotherapies, there's an expectation of overlapping immune-related adverse events, however, other toxicities may be difficult to predict, therefore dose reduction is generally recommended relative to single-agent maximum tolerated dose or recommended phase II dose.

[00:09:00] Now, I will discuss or present three case studies of INDs submitted to the FDA and discuss some of the issues and outcomes following review of these applications. In the first example, the sponsor proposed a combination of a kinase inhibitor with an anti-PD-1 antibody. Both compounds or both agents were unapproved by the FDA. However, there was significant clinical experience. The sponsor did not provide a pharmacology or toxicology data to support the combination.

[00:09:30] The key issue with this case study was that the kinase inhibitor has a class effect of cardiac toxicity that was severe in animals and both rodent and non-rodent species, there were findings of cardiac valvulopathy, severe inflammation of blood vessels, and associated mortalities in rats, suggesting a potential risk for aneurism. Clinically, no clear cardiac findings have been noted to date.

[00:10:00] While there was a lack of clinical findings today, there was a concern that combining a kinase inhibitor that causes severe cardiac inflammation in animals to an anti-PD-1 antibody known to cause vasculitis may exacerbate this finding and make it clinically significant. The review team did not request additional non-clinical studies to address this potential risk. However, the sponsor was asked to lower the starting dose of the kinase inhibitor to a dose with the predicted exposure of approximately 20% of that, causing cardiac inflammation in non-clinical studies. The sponsor also included clinical monitoring for cardiovascular changes using echoes and ECG.

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In the second example, the sponsor proposed a first-in-human combination of a checkpoint inhibitor, which I'll call drug X and an anti-PD-1 antibody. There was a previous clinical experience with the anti-PD-1 antibody and experience with similar products targeting the second immune checkpoint. The sponsor proposed a two-cycle lead-in phase with the drug X followed by combination with the recommended phase II dose of an anti-PD-1 antibody.

[00:11:00] To support the clinical trial, the sponsor provided data from three month toxicology studies in monkeys with drug X alone and in combination with the anti-PD-1 antibody. Of note, the FDA did not request the combination toxicology study and this was not needed to support the combination clinical trial. The toxicological findings included immune cell infiltration in multiple organs including CNS and kidneys, however, these findings were not dose-limiting. The sponsor also provided pharmacology data with drug X alone and in combination with anti-PD-1 antibody.

The combination pharmacology studies included in-vitro antigen recall assay using pre-stimulated human T-cells in the presence of antigen-loaded dendritic cells. With drug X alone, they absorbed little activity. However, in the presence of anti-PD-1, they absorbed a potent interferon gamma response that was greater than anti-PD-1 alone.

[00:12:00] The sponsor also provided data from a syngeneic mouse tumor model where they observed greater anti-tumor activity with the combination compared to either agent alone.

The key issue with this particular case study was that drug X alone had little pharmacodynamic activity but there was a significant increase in activity in the presence of anti-PD-1 antibody and there was concern that adding a fully active dose of anti-PD-1 antibody to the proposed starting dose of drug X may greatly increase the toxicity of the combination.

[00:12:30] After reviewing the data, the review team determined that there was sufficient non-clinical data to support the combination of drug X and the anti-PD-1 antibody. However, due to the significant increase in activity observed with the combination and in-vitro and in-vivo pharmacology studies, the review team considered the proposed starting dose to be too high and requested that the sponsor use a more conservative MABEL-based approach. The sponsor was

[00:13:00] requested to reduce the starting dose to a dose that was 20 fold, a dose that predicted a concentration that was equal to the EC50 for T-cell activation from the in-vitro combination assay.

The review team acknowledged that drug X alone was not expected to have any significant clinical activity and this was based on pharmacology data provided by the sponsor as well as experience with similar products.

[00:13:30] The review team recommended that the sponsor modify the protocols so that all dose escalation cohorts receive the combination rather than starting with the two cycle lead-in phase.

[00:14:00] The last example is for a first-in-human trial of an antibody against a novel target. This target is an immune receptor expressed on activated T-cells and in k-cell subtypes. There are subsets, it's associated with impaired T-cell mediated anti-tumor immunity. However, it's role in immunology and tumor biology is still being explored. Based on data in the literature, this receptor has multiple ligands, potentially unidentified ligands and has been shown to play a role in promotion of Th2 responses and allergic disease and a role in Treg maintenance. The sponsor proposed a first-in-human trial of drug Y alone and in combination with the recommended phase II dose of an anti-PD-L1 antibody.

[00:14:30] The sponsor also proposed to start the combination after a DLT evaluation of at least two dose levels of drug Y alone and that the combination start dose would be no higher than the monotherapy start dose.

[00:15:00] To support the clinical trial, the sponsor provided data from pharmacology studies. This included an in-vitro [inaudible 00:14:47] reaction assay where they observed a concentration dependent increase in interferon gamma response. They observed potential for cytokine release in-vitro and provided data demonstrating or provided data in a syngeneic mouse tumor model demonstrating greater anti-tumor activity with the combination compared to either agent alone.

The sponsor also conducted a four week toxicology study in monkeys with drug Y. They observed multi-organ immune cell infiltration and anaphylaxis-like reactions after several infusions of the low dose, which resulted in one mortality after the fifth dose.

[00:15:30] Due to the role of the target in promoting Th2 responses and potential hypersensitivity reactions in monkeys, there was concern that the antibody may have agonistic properties in this context. The sponsor did not provided data evaluating the monoclonal antibody on Th2 cells.

[00:16:00] The sponsor proposed a starting dose based on an integrated assessment based on the mechanism of action in pharmacology and toxicology data. However, based on the available non-clinical data including toxicology studies suggesting hypersensitivity reactions in monkeys and literature suggesting that the target may have multiple functions, in particular promoting Th2 responses, the review team recommended a more conservative MABEL-based approach for selecting a starting dose. The sponsor was requested to lower the starting dose 10 fold to a dose that was predicted to result in a concentration that was equal to the EC50 for interferon gamma release in the mixed lymphocyte reaction assay. Of note,

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this dose was still pharmacologically-active based on provided pharmacology data.

The review team agreed that the combination with anti-PD-L1 antibody may proceed after a DLT evaluation of at least two cohorts and that the combination start dose should be no higher than the monotherapy start dose.

[00:17:00] In summary, to support cancer immunotherapy combinations, non-clinical studies should include a toxicological evaluation of each drug alone. The sponsor should provide data to support the biological rationale and safety of the combination. If there is sufficient clinical experience, for example, a completed phase I clinical trial or a completed monotherapy phase within a phase I clinical trial, additional non-clinical studies of the combination may not be warranted. However, they may aid in the preliminary safety assessment and support dose selection of the combination. When there is no or very limited clinical experience, for example, first-in-human clinical trial or a drug with limited phase I safety data, combination pharmacology studies are recommended. Finally, the safety evaluation and justification for the proposed starting dose should be based on the totality of the data. This should include in-vitro and in-vivo pharmacology data, what's known in the scientific literature and experience with similar products.

[00:17:30] I would like to acknowledge my FDA colleagues for their help with this presentation. Thank you for your attention.

[00:18:00] Daniel Chen:
[00:18:30] Sorry. It was good thing I wasn't taking a coffee break at that moment. Thank you very much for having me. As noted in the previous panel discussion, this is a very, very complicated topic. Is there an approach that we can take as this field continues to emerge that is both rational and also pragmatic? I hope to discuss some of this with this presentation. I'm going to focus primarily on how we think about the next wave.

[00:19:00] With over 1,200 cancer immunotherapy combination studies already in the clinic today, it's pretty important for us to get a good grip on how we're going to approach the development of so many different potential combinations with immunotherapy.

This is my disclosure. I'm an employee of Genentech, a member of the Roche Group.

[00:19:30] As we all recognize, the emergence of cancer immunotherapy early on has primarily focused on the class of PD-L1 and PD-1 inhibitors. These molecules seem to be able to demonstrate transformative outcomes at least in a subset of patients. Unfortunately, for the majority of patients with advanced cancer, while the benefits can be very real and on very real endpoints like survival, they're not

[00:20:00] always as life altering as in some of the most impressive cases that we discuss. Thus, an important objective for all of us in the field to further develop the potential for cancer immunotherapy. Can we start to deliver really these life altering types of benefits in not just a minority of advance cancer patients but in the majority?

[00:20:30] To start on thinking about these combinations, certainly an important place for us to start in the field of cancer immunotherapy is to really focus on the underlying biology that we're trying to drive here. The cancer immunity cycle is just one such framework to help us think about the complex interaction between the human immune system and human cancers in a simplified fashion so that we can develop rational approaches to this field.

[00:21:00] As we all recognize, the primary action of PD-L1 and PD-1 inhibitors is on this last step, that is the interaction between anti-cancer T-cells and tumor cells and their ability to actually mediate killing of those cells. When this happens, you get revolution of the cycle and the beauty of the immune system is its ability to self-amplify.

[00:21:30] However, we also recognize that the field of immunology is actually far more complex than that simple depiction. This figure comes from a recent publication this year, Nature from Ira Mellman and myself referred to as cancer-immune set point. This review obviously draws upon many of the important advances that we've made in the last several years in our understanding of immune biology as it relates to human cancer. In this case, rather than try to simplify that biology, we try to bookend that framework with developing something as complicated as possible with the idea that having a framework that is complex enough that it can incorporate all of the new advances in this field would be important.

[00:22:00] This refers to the cancer immune set point. It essentially is an attempt at a unifying theory for cancer immunotherapy. You can note the equation at the top where we try to, at least in a hypothetical sense, mathematically define what a unifying theory could look like. It primarily focuses not only on both the pro-stimulatory and inhibitory immune factors that are going to be present in any given patient but also on that patient's ability to have a T-cell population that expresses T-cell receptor that is highly specific for tumor antigens and the strength of the interaction between that T-cell receptor and its cognate antigen. Finally, the actual frequency of those T-cells.

[00:23:00] As we recognize in this field, there are many emerging factors that can influence this immune set point. It includes host genetics, not all patients are wired genetically the same immunologically. Age, we know that our immune responses change over our lifetime. The microbiome, viral infection, and even something as obscure as sunlight exposure. Finally, of course, more obviously, immune modifying drug.

[00:23:30] When we take these two frameworks together, I think we're able to find what is a complex set of tumor-driven, host-driven, and environmental factors that ultimately govern the strength and timing of anti-cancer immune responses. This is important for us to understand biologically. From a clinical experiment standpoint, this is complicating because what it tells you is that there are a lot of inputs that go into our ultimate readout for both efficacy and safety as it relates to immunologic therapies.

[00:24:00] Where do we go from here? How do we take this field forward? I'll lay out four major areas that I'd like to focus on. It includes how we assemble the right regimens for testing, how do we assess benefit risk early on versus later in the development course of any different immune therapy or combination? What biomarkers can we interrogate and how would we use them? Finally, how do we actually prioritize and accelerate the successes that we see in the clinic?

[00:24:30] First, how do we start the right regimen? I'm not going to spend a lot more time on this but one approach is to focus on that underlying biology. What was it that we're actually trying to do in patients with cancer immunotherapy. I would propose that really what we're trying to do is re-assemble a set of biologic steps. Those steps can be defined as laid out in the cancer immunity cycle. What you want is all seven of those steps to happen in an individual patient that we treat and we want revolution of that biology. As we think about either new single agent cancer immunotherapies or combinations, what we're really trying to do is make all of those steps active in a given patient.

[00:25:00] Now, of course, different patients walk into the clinic presenting in different ways. This is where we get to patients subsets. One way to look at those different subsets is really to start to dissect out the immune phenotypes that we see in any given patient.

[00:25:30] This comes from a figure from the recent Nature paper as well. We refer to this as an immune phenol type nodal diagram. What you'll note is in the larger subsets, we think that we can start to break out human cancer into three major phenotypes. Immune deserts, immune excluded, and inflamed tumors but within each of those nodes is our smaller subsets of patients. Why did you present as an immune desert? It may be because your cancer may express no cancer antigens that the immune system can actually see. In that case, that patient would be invisible to that patient's immune response but a very different reason would be a failure to get activation or priming of those T-cells and those neo-antigens may be there. You can imagine that the strategies that you have to enhancing immunotherapy in just those two types of immune deserts could be vastly different.

[00:26:00] All right. Moving onto the second topic, how do we assess benefit risk in our early studies? What I'd like to do is focus on a couple of the different considerations. One is that the types of patterns of response to immunotherapy

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[00:27:30] are highly variable. Far more variable than we're used to seeing with chemotherapy or even targeted therapy. On this slide, you'll note two figures. These are patients that were treated with atezolizumab, a PD-L1 inhibitor in the phase II setting in two different trials in lung cancer in the left and bladder cancer on the right. What you just note that there are many different ways to see patterns of efficacy or response to these immunotherapies.

[00:28:00] They can include classical responses that are easily measured by any way you measure them but there were also patients that benefit in terms of non-classical patterns that can either reflect delayed responses or what we refer to as pseudo progression, trying to reflect the possibility that immunotherapies may inflame tumors, that that would be a good thing and that inflammation can lead to radiographic increases in either the appearance or size of lesions. Of course, this complicates our ability to assess efficacy in the early setting.

[00:28:30] In terms of what I won't go over here are some of the ways to try to get around measuring efficacy based upon those different types of response patterns. They include things like immune-related resist or IRRC but they also can utilize other endpoints that we as a field are working on and whether that means an immune version of progression-free survival or, as you'll hear later, tumor growth kinetics can be alternative ways to try to measure the benefit in the early disease setting.

[00:29:00] But here, I'd like to focus on something different, which is this idea that as we think about optimizing immunotherapy, we have to think about this in terms of both acute and chronic effects on immunity. This is, again, a figure from the recent Nature paper. It's based upon advances by many people in the field including John Wherry, that was alluded to in one of the earlier talks. That's this idea that when we think about the T-cells that we're trying to help recognize and kill cancer cells, that these T-cells have many different states. This is not a static feature of the immune response. When you think very broadly about this, you have naïve T-cells. You have early short term memory T-cells. You have t-effector cells. You have cytotoxic T-cells. You have memory T-cells. And of course, you have exhausted T-cells, which we can further break down into exhausted and a different term we coin here, which is hyperexhausted T-cells.

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[00:30:30] That's a lot of different states to try to understand and reflect in our early development programs. What is one way to start to at least incorporate this type of biology into our thinking around these trials? One way to think about this is really the two major parts of this figure. That is some patients have strong pre-existing immunity. This can be measured by many different ways. PD-L1 IHC has been one way that's been utilized. Gene expression is a different way to start to reflect pre-existing immunity. Looking for signatures of the interferon gamma pathway upregulation in a patient's tumor but really what we're trying to reflect here is the right-hand side of this figure. T effectors and cytotoxic T-cells and in some cases we're also measuring exhausted and hyperexhausted T-cells.

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When these patients are given a checkpoint inhibitor, particularly a PD-L1 and PD-1 checkpoint inhibitor but potentially others, you can see very acute activity because those T-cells are there. They recognize the cancer cells. If you take away the inhibitory signal, they are ready to go but there's a different group of patients, which can be reflected by patients that may not have strong pre-existing immunity. Can these patients benefit from something like a checkpoint inhibitor?

[00:31:30] Some of the emerging data, particularly looking at the phase III data start to give us some hints into the translation of biology and the ability for checkpoint inhibitors to actually help stimulate activation of new T-cell responses against cancer with endpoints like survival.

[00:32:00] Here, we're looking at results from the OAK study. This was a phase III study of atezolizumab versus chemotherapy in second line non-small cell lung cancer patients. You can see the unselected patients' survival curves here with blue being the atezolizumab arm and red being docetaxel. However, very interestingly, if you start to separate out the patients that likely have strong pre-existing immunity versus patients that have very weak or no measurable pre-existing immunity, you actually do see survival benefit to atezolizumab in both groups of patients. This doesn't matter how you measure it. You can measure it by PD-L1 IHC that incorporates tumor cells and immune cells. You can measure it by PD-L1 IHC using a different assay looking just at tumor cells. You can look at it through gene expression with interferon gamma.

[00:33:00] The answer that it's giving from this data set is essentially the same, which is that both sets of patients can derive survival benefit from PD-L1 inhibition. However, the kinetics and the magnitude of that benefit may be different. You'll note here that even the timing of separation of the survival curves are different in these two patient populations. They're offset by about two months. Interestingly, that's about the same amount of time that we expect it would take to prime and activate a new anti-cancer immune response in a patient that may not have had strong activated or primed immune responses. We see that in the clinical setting with drugs like CTLA-4 inhibitors. You can look at the entire experience on how long it takes to actually see the immune effects of an immune modulator like CTLA-4 that may have a primary effect on activation or priming of immunity.

[00:34:00] As we think about this, incorporating that study of acute endpoints versus really more chronic endpoints is very important, important in terms of what combinations we take forward but also important in terms of how we look at dose and schedule. We have to recognize that optimization of dose and schedule based on early readouts like response rate may or may not ultimately correlate well with readouts for chronic endpoints like survival, like survival hazard ratio or like survival tails of the curve. That's because these therapies could have differential effects on acute immunity versus chronic immunity.

[00:35:00] All right. Second topic here relates to how we might utilize biomarkers to help assist in our ability to address early optimization of these therapeutics in the clinic. One thing to recognize is that biomarkers are an important feature of these trials but biomarkers are also very complicated themselves. There are a number of different complexities to them. One is the following, that there are three major compartments for immune biomarkers that we can sample. They likely reflect circulating biomarkers that you can measure from blood draws, tumor biomarkers that are measured in the tumor microenvironment and biology that occurs in lymph nodes, either local draining lymph nodes or lymph nodes distant in the body.

[00:35:30] As we measure these different compartments, the answers we get may or may not be the same. Part of that is because those tumor microenvironments are different in these three compartments and our ability to even sample these varies. We recognize that tumor biomarker compartment is probably the most relevant compartment for immunotherapy assessment but clinically it also represents generally the most difficult compartment for us to sample in the clinical setting.

[00:36:00] What can we do here? There are a lot of different approaches to biomarkers in this space. If we want to sample the tumor microenvironment, we can get biopsies in some of our patients. Many of our patients have baseline tumors that can be assessed for biomarkers and the biomarkers we can utilize to address the tumor microenvironment include PD-L1 IHC, include tumor gene expression, particularly focused around immune gene expression, mutational burden but then how do we look at the other compartments? There are some ways to do that. There are interesting approaches around antigen-specific monitoring in the blood, plasma cytokines. Then, in terms of measuring beyond that into the lymph node compartment, other approaches including imaging can be helpful.

[00:36:30] What are some of the ways that this can be utilized? One way to utilize this is to try to identify predictive biomarkers as Dr. McDermott mentioned earlier in his talk, an ability to address which patients will likely derive the most benefit from any given approach but there are multiple applications for the biomarkers to our early development programs. One is actually just to understand the underlying biology. What biology are we actually affecting? This is a slide that I think Dr. McDermott also showed. This is from a combination study randomized phase II, three-armed study of atezolizumab versus atezolizumab plus bevacizumab. It really starts to get to the heart of what kind of biology is VEGF inhibition actually affecting when it comes to immunology.

[00:37:00] One of the interesting findings from this large randomized study was it appears that, at least on progression free survival, one endpoint may not be the perfect endpoint but one endpoint at least to reflect biology, the addition of VEGF inhibition appears to primarily affect a subset of patients that not only have evidence of pre-existing immunity, which is common in renal cell carcinoma but

[00:38:30] also pre-existing immunity in the setting of myeloid-derived suppression. This is an important point because it helps us think about how to utilize different approaches. Obviously there are many ways to try to further enhance anti-cancer immunity in the setting of renal cell carcinoma. VEGF inhibition is only one such approach. By understanding this, it helps us start to position how VEGF inhibition may be both acting and may both be helping in the most, in this very specific disease setting.

[00:39:00] That's not the only approach for biomarkers for this early phase setting. A different approach is to better understand what kind of pharmacodynamic effect you might be having, what effect you might be having in different tumor lesions. I'll just briefly mention that this was data presented by Elisabeth de Vries' group bench et al. at AACR earlier this year, looking at radio-labeled atezolizumab to track PD-L1 in a patient through non-invasive method. As you'll note interestingly, this approach does lead to very nice marking of the tumor lesions. You start to get a sense of how you can use non-invasive measures that are emerging to measure immunity. It doesn't just have to be PD-L1. You can start to do this with other radio-labeled tracers to measure immunity in these different compartments.

[00:40:00] Ultimately, we'll still have to separate out what is immunity that is directed against cancer versus not but at least this is one way to start to get to a better sense of how the immune system is functioning in a patient without having to do invasive biopsies on every patient we treat.

[00:40:30] Next, moving on, how do we help to accelerate and prioritize drug development in a space where there's very high unmet medical need, where patients are still dying of advanced cancer and still answer the appropriate questions that are going to be necessary? One of the things that we've been seeing is that even our patient populations, whether it's for phase I studies and then even in some cases in phase III studies is rapidly changing. It's rapidly being changed by the utilization of different therapeutics in the clinical setting. The one that's likely having the greatest effect are the approvals and access to PD-L1/PD-1 inhibitors that is changing the kinds of patients that we're likely seeing in our phase I studies in the later line setting but it's probably not just that alone.

[00:41:00] It may be also affected by the number of biomarker-driven studies that are available that affect the kind of patients that enter into these trials and numerous other factors. It could even be due to influences of non-immunotherapy that have immunologic effects that can have downstream impact on the kind of patients we're enrolling.

[00:41:30] One approach that we've taken to try and cut through a lot of the complexity that we're discussing in the phase I setting so that we can get appropriate answers on the types of endpoints that are going to be important to cancer immunotherapy in the future is approach here as noted by the MORPHEUS trial

[00:42:00] design. MORPHEUS is a platform that we've been using or have started to use. This has been developed in partnership with the FDA so that there has been input into how this is done but essentially what this is combining is the idea of testing multiple combinations, which of course we're seeing across the board in clinical development right now with early randomization so that response rate isn't the only endpoint that you see and that you get a better sense of the patients you're actually enrolling because, again, as I noted, the patients we're enrolling on these trials is rapidly changing. It's becoming more and more difficult to compare the result from a combination study with the historical response rate for a single agent checkpoint inhibitor.

[00:43:00] One of the things this allows you to do is rapidly look at different combinations, utilize a control arm, be efficient in the sense that you can utilize a single control arm for multiple combinations and quickly adapt these studies based upon the findings that you're seeing in the early experience.

[00:43:30] Part of doing this well is really having a good understanding of that control arm, obviously using a single control arm in the setting of multiple treatment arms does have one very important potential consideration, which is that variation in that control arm can have an effect on how you interpret multiple arms. One of the things that I think is an important component of this is understanding the biomarkers associated not only with the patients on the treatment arm but biomarkers associated with the patients enrolled onto that control arm and bolstering that confidence in the control arm through real world data.

[00:44:00] One of the things that does is give you a sense of who exactly it is you're enrolling on your studies and how well do they really reflect the broader patient population that we're trying to treat with immunotherapy.

[00:44:30] Really, to wrap all of this up, we need to ensure that as we rapidly move forward in the field of cancer immunotherapy and cancer immunotherapy combinations that we're really being thoughtful to the types of combinations, the rationale for the combinations that we're moving into the clinic, that we have to be clear that immunotherapy is different than chemotherapy or targeted therapy. It tends to drive a difference in terms of both acute effects of efficacy and on safety as well as chronic effects of efficacy and safety and being very clear as to which question you're answering in those early trials is very important. Biomarkers can help you understand which patients you're talking about, whether you're talking about an effect in an inflamed tumor versus a non-inflamed tumor can be very different and so can help you understand who these patients are in your earlier trials as well as start to interrogate predictive biomarkers on the right subset of patients to be treating.

[00:45:00] Finally, we need to be thoughtful about how to prioritize and accelerate this next wave of therapies. There are a lot of trials in the clinic. The good side of that is it was likely to help accelerate the optimization of immunotherapy in this field. The

[00:45:30] downside is it could generate a lot of data that could be difficult to interpret. By having a framework to think about these combination trials will hopefully help us all as a field generate a data set that is not only interpretable within itself but is interpretable within the landscape of 1,200 combination immunotherapy trials. Thank you.

[00:46:00]
Bernard Fox: Good morning. I'd like to thank the FDA and the AACR for inviting me. I'd like to share with you some thoughts we have on addressing some of the topics that were supposed to be targeted for this meeting. My disclosures?

[00:46:30] Objectives of the workshop included to identify best practices regarding dose selection and optimization for IO combinations. I'd like to share with you some information we have from pre-clinical models that I think is important and relevant and may help in the discussion and thinking about that.

[00:47:00] A fourth point was to discuss how the expectation of the demonstration of the contribution of each agent has to a combination and strategies to isolate the effect of each individual agent. I'd like to present a proposed model where we might use this to address those question. The topics I was going to cover were these three important considerations for developing effective immuno-oncology combinations. Those were immunity, what I consider co-stimulation to augment the response and then checkpoint blockade.

[00:47:30] Under immunity, there were three questions. Do patients have T-cells that can recognize their cancer, do these T-cells exhibit cancer destructive properties and can those T-cells traffic to the cancer? That means, to the stroma, to invasive margin, and to the tumor.

[00:48:00] First, what do T-cells recognize? Neo-antigens are an important source of these nontolerized epitopes. They're very much in vogue and they're very important targets. Also, viral antigens from many of the viral-induced cancers. Then, there's this whole normal proteins, which are over-expressed or selectively expressed in cancer. I think many people have seem to have been forgotten those a little bit but the NCI a number of years ago went back and reviewed in really a community effort with centers and from investigators around the country to identify about 70 or so. The vast majority are non-mutated epitopes.

[00:48:30] We need a functional assay if we're going to go ahead and look at these. For neoantigens of viral antigens, you have the mutated or viral sequence. You can sequence the antigen and test that. This has been well-described and basically you're sequencing the tumor. You're getting the gene sequences. You're then going ahead and getting a mini-gene, which you're going to put in dendritic cells. You're developing peptide-based strategies. Then, you use those dendritic cells that have the antigens present in them to stimulate T-cells and see whether or

not those T-cells are upregulating some marker that you can identify so in that way you can identify the antigen's specific T-cells.

[00:49:00] For normal proteins, it's much more difficult and I think this is why the field has greatly ignored this in the recent past but I don't think it's impossible. It turns out that in general, B-cells and T-cells have a coordinated response to antigen. I've modified this nice cartoon from Chuck Drake published a number of years ago but essentially, you've got, when a dendritic cell is presenting antigen to T-cells, it's also presenting antigen to B-cells. It turns out there's a coordinated response for the B-cell to undergo a class switch to become an IGG-producing cell. It needs CD4 T-cell help. In the vast majority cases, that T-cell help is specific for the same antigen, not the same epitope but the same antigen that the B-cell's making antibody against. This is the idea of a coordinated response.

[00:50:00] The way to assess this might then be using seromics or protein-array technology. There are two basic technologies, which are really high-throughput screens. One is from InvivoGen and one is from the CDI [inaudible 00:49:55]. They range between 9,000 and 19,000 proteins can be detected with about a microliter of sera. You can do a lot with a very little amount. You've got proteins essentially spotted in duplicate on these sorts of arrays. You get to then look at your pre-treatment serum or your post-treatment serum, put it on the array, come back with an anti-secondary antibody and you can detect responses and characterize B-cell responses or antibody responses against a whole spectrum of antigens, maybe as much as 70% of the [inaudible 00:50:25].

[00:50:30] Is this useful? Now, five years ago, actually Larry Fong was really ... I credit him as being the first to, in a blinded fashion, he had patients that had been treated with a combination immunotherapy, GM-CSF and ipilimumab, anti-CTLA-4. He had patients who had responded to that. He did protein arrays on those patients and he found that they made strong antibodies responses. He characterized the responders. He found that there were several proteins that a couple of the responders had made antibody responses against ...

[00:51:00] Oop. Pardon me. One of those was against a target called PAX6. PAX6, he then went back and looked at a patients biopsy. He saw that they were expressing, he could see message for PAX6. He did immunohistochemistry and showed that the PAX6 was actually expressed in the patient's tumor. Then, he went back and took pre- and post-treatment PBMCs, stimulated them with control or with PAX6. He found that about 6% or 4% of the circulating T-cells could actually recognize the PAX6

[00:51:30] epitope. That was actually the first demonstration of that in a blinded fashion. Many people had shown that with other antigens where they knew they had made responses.

Then, there was this recent paper last year from Tripathi and colleges where they essentially had a whole panel of non-small cells and cancer cell lines. They alluded the peptides off the class one molecules and characterized them by mass spec. They've got a large panel of common, normal, overexpressed proteins in

[00:52:00] lung cancer. They then ran protein arrays on a cohort of patients that had just been recently diagnosed with non-small cell lung cancer. They found that there were a large number of strong antibodies responses against about 120 targets. About 75% of those were against proteins for which the peptides for those proteins had been alluded off the non small cell lung cancer cell lines.

[00:52:30] That was very interesting. Then, they went on to show in five of those cases, if they took a non-mutated peptide, a common overexpressed target and just stimulated with a brief in-vitro simulation in-vitro, a patient's PBMCs, they could find that that they had cytolytic activity against tumor targets that were [inaudible 00:52:40] matched for that patient but were not that patient's cancer. This is looking here at this one patient and a 20-to-1 effect for the target ratio. They've got 50% killing, which is very good for those targets.

[00:53:00] For me, this is very provocative because it's telling us that patients with lung cancer, a number of them, large number of them, some number of them, have broad pre-existing anti-cancer immunity against non-mutated epitopes and once stimulated with antigen, can exhibit cytotoxicity.

That's very different. There's lots of reasons we heard from many of the speakers today why that might be inhibited but it's a fascinating, to me, it's very interesting thing. That's in the human.

[00:53:30] One of the PhD students in my lab, Tyler Hulett and this was some data he's presented at CTSI last year or at AACR last year. He looked at a vaccine strategy in mice. He found an interesting paradigm where he found, when he looked at antibodies responses, was looking at them not with protein arrays but with peptide arrays. He found that this cancer vaccine induces antibody responses to the proteins or actually the large peptides that correlated with peptides that had high affinity domains for MHC class I. It's very interesting. He found that he could actually identify cytolytic function against both the mutated and normal peptides. That has been submitted. Actually Tyler is graduating, so he's looking for a job if anybody's looking for a post-doc.

[00:54:00] Three important considerations for metaimmunity. Kendall's T-cell traffic to tumor. It's a difficult question with non-marked cells but could we use TCR analysis to follow a peptide-specific T-cell? There's a question. How do you know if they're tumor specific?

[00:54:30] It's an interesting paper recently published in March in Cancer Discovery where essentially do the same thing. You identify the peptides. You figure out what the antigens are. You get those and you take PBMCs. You can take single peptides now, stimulate the PBMCs, expand them up, get that T-cell receptor. Now you know what the T-cells receptor is for the peptide of interest. Now, you can go back and look at that T-cell receptor in the blood, in the tumor. I think this is really going to be a fascinating strategy and give us lots of insights in terms of

[00:55:00] what happens, what changes, at the levels of detection that we have because there's limits to all this but in a biopsy, what T-cells are actually getting there? Are they ones that were expanded to cancer immunotherapy or not? I'll fall back up on that in another minute.

[00:55:30] Now, I'd like to switch gears to co-stimulation. When we focus on one molecule, which our institute has had because of Andy Weinberg's efforts in anti-OX40 and Brendan Curti, a long-standing interest in anti-OX40. It's active in immunogenic mouse models, less so in what we would call poorly immunogenic tumor models but there's OX40 is essentially upregulated within 24 hours of T-cell stimulation constitutively expressed on Tregs but can be expressed on activated CD4 estimates. At least a proliferation, activation, and survival signaling and stimulated by OX40 ligand on APCs and the numerous phase I clinical trials, actually phase II now.

[00:56:00] It's immunogenic. It augments T- and B-cell responses and an important component, it reduces contraction of T-cells. This is the concept and some work that was published a long time ago but essentially, if you look at the effect of anti-OX40, it can really augment, and this is a model so it's not actually to scale, but anti-OX40 can actually augment the response but also prevent the contraction so you maintain longer.

For an insight, combination vaccine with anti-OX40 to increase therapeutic efficacy, it may be because it augments responses and reduces contraction. Wrong way, sorry.

[00:56:30] Coming back to those considerations for the goals, discuss how to expect how the expectation of the demonstration of the contribution of each agent has to a combination and strategies to isolate the effect of individual agents could we actually add OX40 there. I'll give you an example. This is not an evaluation of a patient on a clinical trial, which is a vaccine in patients, an adjuvant setting of non-small cell lung cancer. I'm just showing you this is the patient's responses, this is with time. This is an antibody response assessed by a seromic approach.

[00:57:00] Here's one of the antigens green. You can see the antibody response starts up at about six. It's up at about week 10. It's coming back down. Here's one going up in blue here and coming down. Here's one in red coming up later. Different times that they're going up. Here's the CD4 responses. CD4 response is going up. This is matched to week 11, week 15, coming up and coming back down.

[00:57:30] This idea of inducing immune responses and then the immune responses tracking down, CD8 may be less so. How could we use this information? If, in fact, with OX40, we think part of what OX40 does is augment the response and then can you actually look at a change in contraction in these patients? Could you actually follow the effect of your immunotherapy or the impact combining things like antibody arrays and T-cell receptor analysis?

[00:58:00] We do know that OX40 can have a profound effect in combination immunotherapy with vaccines. This is some work from my colleagues that was published last fall but here's an effect of OX40 alone and this is in an established 4T1 model that if you combine it with a vaccine, it's either allogeneic or syngeneic. It can augment that therapeutic efficacy and so based on these data, we're preparing to launch a combination mid-therapy trial in women with triple negative breast cancer.

[00:58:30] I'll move onto checkpoint blockade. The main focus here is on combinations. I'd like to talk about Doctor Vonderheide talked about X+PD-1 or PD-1+X. We were thinking that way so PD-1 blockade added to OX40 because we've been studying OX40 for a long time. We know that it has an impact in several models. Would it impact tumor growth? Would it improve the effect?

[00:59:00] Here's a model, which is the PYMT model. It's a transplantable tumor into the FEB mouse. David Messenheimer, another PhD student who's graduating, looking for a job, is ... We treated mice with OX40, add some PD-1. The combination or no treatment. He followed growth. This is a PD-1 resistant model so anti-PD-1 has no effect. If you just give OX40, OX40 has a significant effect in this model, extends survival substantially but no animals are cured.

[00:59:30] If you combine OX40 with anti-PD-1, it's significantly reduces the effect. The combination of those two agents in this model. I know of two other models where this effect is happening. It significantly reduces effect. That's interesting. Why is that? David noticed that what he saw was in the combination. Red is the combination. Blue is PD-1 alone. Black is OX40 alone. OX40 has no impact on serum cytokines interferon gamma TNF46 but the combination, you see a striking increase. What we also saw correlate along with that was when he did that treatment, he looked at the [inaudible 00:59:40] cells and the tumor cells. He saw that there was an upregulation in inhibitory receptors. It was most profound in the combination of the OX40 and PD-1 consistent with the idea that you're upregulating cytokine secretion but it was interesting because it's also upregulating co-stimulatory receptors. It's providing us with other opportunities both on the positive and the negative side to impact this treatment.

[01:00:00] One of the questions he asked is he said, "Okay. What if we delayed the addition of the anti-PD-1?" Essentially, the OX40 was given on day 7, 9, and 11. The PD-1 was given on day 13, 15, and 17. Interestingly, he saw, and this is now a different scale, a highly statistically significant increase in survival with just that small change. The interesting part for us is this is a very difficult tumor model. Lisa Coussens, who uses it, told me they've never been able to cure mice but essentially, with that combination, we could now cure animals at about a 30% rate. We're very excited about this concept of schedule of combination agents.

[01:00:30] I know it's not of great interest to many people in the pharmaceutical sector, at least they've told me that. I know that's not true for all. Dan was talking about

[01:01:00] some of that just a little bit ago but I think this is one of the things that's going to be really important. It's going to be developing the trials and asking the right kind of questions so we can actually get insights, not wait for the ultimate effect of whether the patients has had a response or not but to look at the immune parameters and really gain insights into what's going on.

In concept, anti-OX40 provides anti-tumor therapeutic effect. It looks like it's better than untreated. It is in a number of animal models. The combination reduce the effect. Is it actually leading to increased contraction? The idea that OX40 puts PD-1 delays it, you get a higher response. We think this is our hypothesis for how this is all working.

[01:01:30] If you take this, how can we apply this to the clinical trials? Maybe, if we were to use seromics and T-cells receptor analysis and B-cell receptor analysis, we could overlay that and look at whether or not our drugs, if in fact, contraction, which plays a role in every immune response, if that's important cancer, which I'm sure it is, how can we assess that, in the near term, in the short term as we're doing these trials, to see if we can really use intelligent design to do this?

[01:02:00] My conclusions, IGG antibody responses may be useful to identify the scope of immunotherapy-induced augmented immune responses. The characterization of cancer peptidomes and correlation with IG antibody responses may provide opportunities to better characterize the scope of the anti-cancer T-cell response following immunotherapy. T-cell receptor characterization of tumor peptide, expanded T-cells may provide a way to track trafficking of tumor specific T-cells and ala this paper. Vaccines may introduce B- and T-cell immune responses that subsequently contract addition of [inaudible 01:02:23] or checkpoint inhibitors may increase expansion and reduce contraction, providing a way to monitor the

[01:02:30] contribution of individual agents and in the transplantable PMT model is what I showed you is that anti-OX40 plus concurrent PD-1 significantly reduce therapeutic efficacy, provided by anti-OX40, concurrent combination increase serum cytokines and upregulation of inhibitory and co-stimulatory receptors. Anti-OX40 and delayed PD-1 provide significantly better therapeutic efficacy with long-term survivors.

[01:03:00] In 35% of treated mice and these findings in one tumor model that I showed you but in a couple other models that I'm aware of and again, this doesn't happen in all models, they raise the possibility that combination [inaudible 01:03:06] may have unpredicted activity and underscores the need for monitoring strategies at evaluated parameters that are predicted to show positive impact of combo.

[01:03:30] I'd like to just recognize the people that, who did the work and especially call to people in Oslo, [inaudible 01:03:21] Johansson, who have helped us with the seromic strategies as well as Walter Urba, my colleagues, Hong Ming. People in my lab who did the work. Thank you very much.

Liz Jaffee: I'd like to ask the speakers to come up as panelists as well as the other panels we've identified, which include Marc Theoret, Todd Bunch, Leisha Emens, and David McDermott.

[01:04:00] I thought I'd start and just mention what I thought were some of the themes from the three talks, which were wonderful. Certainly, this session's about what do we need to consider to design the best combinations in patients. I think, of course, the first consideration is toxicity but as we've learned, I hate to use that word again. It's complicated. It's complicated because, as I think many of the speakers in this session pointed out, patients have tumor that are phenotypically different. We need to consider these differences when we think about combinations. Not all patients are going to respond to the same checkpoints because of genetics, because of differences in the checkpoints that have occurred from other therapies they've received from their type of cancer. We need to take all of this into consideration when we start to try to develop these combinations.

[01:05:00]

I think, also, you know, we're hearing from everybody that the only way we're going to do a very good job scientifically of doing combinations is to have biomarkers that can help us drive these combinations. We need these biomarker to define, which patients will respond to which combinations. That's the best way we're going to be able to develop these clinical trials.

[01:05:30]

In fact, I liked what Dan said. He basically said that we need to consider multiple parameters as we start to think about the tumor microenvironment in designing these different combinations. It almost sounds like we can't just say, "Well, this patient has this checkpoint based on IHC or this particular pattern based on RNA seek," but we need to start to integrate multiple parameters to really identify patients who going to most respond to which combinations. Certainly, I'd be interested to hear comments from the panel on such a concept.

[01:06:00]

But also, we need new platforms for testing our combinations. The current platforms are probably not very good. We don't want to be doing large patients studies trying to get at the best combination. We need to have good pre-clinical science. We need to have good toxicity data that will integrate into how we design these next set of studies.

[01:06:30]

Most importantly, what I've heard from all of the speakers was that we need to better understand the T-cells and their biology as well as other cells within the tumor microenvironment such as B-cells and dendritic cells and macrophages and how they play into the anti-tumor immune response. T-cells are very complicated, as are B-cells but T-cells in particular are what we are mostly focusing on at this time point. We really need to understand not only the signals that are expressed at one given time point but T-cells are going to change depending on what's going on with the different therapies. It may be that if we

[01:07:00]

can understand this T-cells over time, we'll know better how to incorporate with scheduling the different agents.

I'm going to stop there. I think those summarize the themes that were raised and begin with questions. Any questions from the audience? Anyone want to start? Okay. Sure. Please.

Aron Thall: [01:08:00] My name's Aron Thall. I'm from Pfizer. I think this applies to a couple of the different talks, one from Dan and the last talk we just heard about. It basically relates to sequencing. We're designing these studies, we're giving these therapies concurrently. Is that really the best way we should be approaching combination therapies, perhaps not from our last talk. I'm wondering how or what your thoughts are in approaching this in new clinical study of designs.

Bernard Fox: You first? All right. You're the expert.

[01:08:30]

Male: It's a great question. We think it's complicated to identify dose and schedule for one drug or even a combination. The moment that you start thinking about scheduling, suddenly, you open an entire other dimension because it becomes which drug first, for how long but at the same time, biologically, especially when we talk about the immune system, few things make more sense. We know that there are modifiers to the immune system that are dynamic and could be important based upon the timing. You might want to sequentially drive particular biology versus trying to drive it all at once.

[01:09:00]

[01:09:30]

Yeah, it is complicated but it gets to the importance of understanding of what it is you're trying to do. If what we're trying to do is take an immunologic term like prime boost, sequencing is probably really important. For us in the clinical setting to do these experiments, I think that you need multiple inputs. You need good hypotheses to go into the clinical with. You need a testing platform that allows you to ask the question that you think is important. You need a readout that you're cognizant of, acute readouts, chronic readouts. Then, with those three things, you can start to design the trial that's right for the question you're asking.

[01:10:00]

That's the best I can do with a complicated scenario and a pragmatic approach.

Bernard Fox: From my side, it's much simpler because I don't have the big pharmaceutical side [inaudible 01:10:12] having, I'll take OX40 because we spend about 17 years developing it, did a first clinical trial with a mouse antibody. We could only give it for three days because then you made a rat anti-mouse antibody response. You have to study it really intensely in that first couple weeks. Andy Weinberg and his colleagues in his lab made some interesting insights.

[01:10:30]

As you think about the biology in human biology. If I think about OX40, for instance, I got to focus on that for a second because I see it as working in the more immunogenic tumor models. I see it as not having an impact on the more

[01:11:00] poorly or less immunogenic models like I presented that on 4T1. I think many human cancers are like that and they may not be but I think they probably are. I'm thinking we're going to have to vaccinate and give a co-stimulant to get a stronger response. That's what I'm focused on. I think in humans, I think those precursors may be very low. We're going to use hypotheses to lay out our clinical trials. We think, "Okay, you're not going to get the big boost in expanding the T-cells in one vaccine," so we're going to give two vaccines a couple weeks apart with OX40 or, "Looking for OX40. Has anybody got OX40 in their ..."

[01:11:30] Working work OX40 with a vaccine and then to combine that later plus or minus with anti-PD-1 because that and, "If anyone's got PD-1 or PD-L1? I'm easy." Those are things. Then, study the things I showed you. Look at the T-cell receptors. Really look at the functional assays. We do N of 1 kind of clinical trials to really get insight into see if our hypotheses are correct or not. That's how I think the important way to develop it in our area.

Liz Jaffee: Great. Another question?

[01:12:00]

Ling Liu: Hi. My name is Ling Liu. I'm from Eli Lilly. I have a question for Dr. Ricks. First, your very nice presentation. You basically out of what the package would be look like from [inaudible 01:12:08] to do, to run novel combination trial.

[01:12:30] My question, in your presentation, you gave three examples. I noticed two examples. Actually the starting dose from regular point of view activity was 10 fold, 20 fold, et cetera. I'm just assuming that's probably due to the definition of the MABEL. There is disconnection. I just wonder whether you can't elaborate and little bit more how from the regular point of view how do you define the MABEL in the context of monotherapy, combination therapy as we can here, you know, or talk about the sequential combination as well. Can you give us a little bit further elaboration from regular point of view, how you base that on the pre-clinical package. You've mentioned about in-vitro assay, pre-clinical in-vivo animal model. You also have difference regarding to the expression level in animal, in human. If you can elaborate a little bit more on that, be very helpful. Thank you.

[01:13:00]

Tiffany Ricks: Okay. As I discussed in my talk, there really isn't a universal approach. It's really going to require looking at all of the information that's given. All of the pharmacology studies, what's known in the scientific literature, what's known about similar products. The examples that I gave where we reduced the starting dose. It was based on the data that was provided by the sponsor and trying to pick a dose that was predicted to give a concentration that was equal to an EC50 for an activity assay. Basing the MABEL on that approach in order to select a safe starting dose. That was the idea for those particular examples.

[01:13:30]

Male: If I could add ...

- Ling Liu: [01:14:00] Sorry. [inaudible 01:13:52]. Let's see. I notice two examples, when you mentioned reduce dose is based on in-vitro assay so what if you have some pre-clinical animal model, you also had direct some EC50 value. If there is consistency, I think it's good. If there is a disconnection how the pre-clinical animal model EC50 derived from, going to play a role in definition of MABEL.
- Tiffany Ricks: [01:14:30] You really have to look at it as a case-by-case basis. Taking into account what the animal data as well as the in-vitro data is hard to say in general what we would do. It really depends on what the data is and what the products are.
- Ling Liu: Okay. Thank you.
- Male: [01:15:00] Yeah. If I could just add to that from an industry perspective, I think MABELs described in ICH S9 as a way to select a starting dose, I think historically at that time at least, people in companies were looking at about a 20% effective or receptor occupancy or activity level but I really have to applaud some of the work that the FDA has done recently. They published on this, I think last year and that's what Dr. Ricks referred to where higher levels of ... They observe that I think it was taking sponsors a long time to get to an effective dose. They did publish that higher levels of receptor occupancy. She mentioned that EC50 level. [01:15:30] Have also resulted in safe starting doses. I 100% agree. It's a case by case but there is some additional guidance out there that should help.
- Liz Jaffee: Next question.
- Female: [01:16:00] Hi, everyone. This is [inaudible 01:15:45]. I was [inaudible 01:15:46] from Roche Genentech. Based on their previous presentation within that, they a lot of parameters and knowing in the area and also, we also have quite a lot of trials going to target on this high places. I just wondering maybe sort of [inaudible 01:16:08] can be answered by multiple trials. Just want to ask the panel have you considered that over industry and academia, to pool the data together, maybe to help answer for example when's the best timing of those certain molecule and also when maybe the best order something that have. I know they're probably will be challenge as well but just want to hear from the panel what's your consideration and what could be the potential challenges. [01:16:30]
- Male: [01:17:00] I think one of the things that has been really encouraging in this field is we have started to see much more collaboration, not only across academia and industry and government in this field but also between different industries and different companies involved in this space. I think that that work has primarily focused on endpoints so starting to look at the larger data sets available, looking at what the right endpoints are in this field and some work around biomarkers. I don't think we've gotten to the point of trying to identify dose and schedule in this field through cross-company collaboration. I don't know if anyone else can speak to that. [01:17:30]

Male: It's a slightly different answer but we just reviewed our files from ... My institute is in the second largest not-for-profit health care corp in the county. There's about 40,000 new cancer patients a year. We would pack the medical record off protocol. There are about 1,000 patients who received the anti-PD-1. The goal is now to go back and look at those 1,000 patients and try and put all that together and try to glean some other interest. I think that's going to be an area of interest. If we can find other health systems that might be interested in doing that, maybe another approach to get access to data that won't be perfect but may give us some insights.

[01:18:00]

Liz Jaffee: Please.

Dinesh De Alwis: Dinesh De Alwis with Merck. Some very interesting presentations. My question is actually on the concept of immune set point. I think we are now in a paradigm when we are testing in the phase I setting in that the patient population that we actually testing this combinations are, if not already, all probably exposed to a PD-1 inhibitor or PD-1/PD-L1 inhibitor. We're effectively the immune set point is different.

[01:18:30]

If you're going to understand the simultaneous and sequence of administration and what's optimal, should we figure out first and foremost the actual patient population. I'll be effectively walking away from potential combinations that couldn't work simply because we've gone into a different immune set point.

[01:19:00]

Set: I'm really glad you brought up that question because it highlights an important nuance for us to all be thinking about. The concept of an immune set point I think is very real. We've talked about all the different factors that can go in, host genetics, environmental factors, drugs but one way to look at this I will invite all of you to consider is if you used a metaphor and you took a student in high school and they took the SATs cold or they took an SAT test after they've gone through a year of preparation. What's more important in terms of the readout? Their score on a test before they took the training or after?

[01:19:30]

I raise that because we all recognize that there are certain parts of the set point that are likely intrinsic to a given patient and there are other parts of the set point that can be modified through environmental or therapeutics. One of the really interesting things for us to think about is, okay, if we believe that an immune set point is an important concept. What part of that are you trying to read? If you read for example and try to read the immune response in a patient's tumor before they've ever received any therapy, you might be better measuring the kind of things that are related to number of actual antigens that that tumor expresses, intrinsic immunity or immunogenicity, host genetics, like are they wired in such a way that their immune response is on a hair trigger as opposed to one that's more slow moving and difficult to initiate, whereas if you start to take tumor specimens from patients that are further down the line that have

[01:20:00]

[01:20:30]

[01:21:00]

been exposed to multiple therapies that may have seen a prior either checkpoint inhibitor or other immune modulatory therapy, you may start to shift some of that immunity.

[01:21:30] How much are you then measuring the immune set point as opposed to further modification that's not intrinsic to either that patient's genetics or that patient's intrinsic tumor genetics? This is a concept that's really important for us to think about as a field. I say this because I think that we're all already doing a great job at treating the patients that have really high pre-existing immunity.

Female: Set, I just wanted to add ...

Set: The rest of the problem may become more difficult.

[01:22:00] Female: I just wanted to add, that's where I'm trying to go when I said one of the themes that seems to be coming out of this session is this concept of multiple parameters that lead to a metrics. It's equating it to someone who you're trying to determine if they have a higher risk of getting a specific cancer. You look at their genetics. You look at their family history, et cetera and you put it into a database and come up with a metrics to figure out what their risk level is.

[01:22:30] This may be a similar situation where maybe we need to rethink how we determine who goes on what therapies based on multiple parameters that may include their checkpoint at the time of biopsy, RNA seq, T-cell biology, et cetera but again, it is complicated because what's going to be the case pre-treatment may be different during treatment. We may need to determine this over a period of time as they start to get treated and alter how we treat them based on how these metrics are changing.

[01:23:00] I'd be interested to hear if anyone thinks this is worth considering. Any comments?

[01:23:30] Female: I think you're moving towards personalized immunotherapy for a given individual patients so you biopsy their tumor or you have some idea where they are at baseline. That's a great way of thinking about it is that a pretreatment immunobiology reflects the intrinsic nature of the patient. Then, there's a lot of things that can influence that. If you start someone on immunotherapy and they don't respond, then you can adjust if they do respond and then progress. You can biopsy that and see how that's changed. I think we can potentially move in a way where we're really continually adjusting things to meet the immunotherapy of any given individual.

Female: Right. As someone who deals in cancer, pancreatic cancer where you don't naturally have a T-cell so whether you want to call it a cold tumor or not, the environment is going to change when you finally do get a T-cell in and we can get

[01:24:00] a T-cells in. That doesn't mean the patients necessarily respond but vaccines do get T-cells in. That's when they upregulate checkpoints.

[01:24:30] Within a few weeks, you've now changed that tumor microenvironment. Their risk or their chances of responding before may have been lower but they may a different chance now that they have a T-cell coming in and changing the tumor microenvironment. The same thing could be said with some of these agents where they do work as single agent. You may not necessarily see T-cells sitting in the tumor at the time of treatment. You have higher mutations potentially or something else. It makes them more susceptible but now, all of a sudden, you've recruited those T-cells into the tumor with your agent. Now, that tumor microenvironment may change. They may go on to respond but maybe those are the patients who still need something more to keep them responding rather than those curves that we saw where you have the time to response and the T-cells fall off. That may be when patients are recurring.

[01:25:00] Anyway, I think again, we need to not think about patients in one time point but we need to be able to understand what that T-cell biology is over time.

Willy Holmes: Hi. Willy Holmes, FDA. I had a question maybe, probably more for industry colleagues but you're talking a lot about sequencing. By the time the data comes to FDA, we're seeing whatever studies you're giving us. We're not necessarily seeing whether you're doing these sequencing studies. I was wondering if they're being done and are they influencing the kinds of trials that you're designing and sending in. We probably get hundreds of INDs a year at this point just looking at different IO combinations. It's easy to come up with a plausible rationale for doing almost anything if you really work at it but it's not clear to us how you're making the decisions to go forward with a specific combination sometimes.

[01:26:00] Male:

[01:26:30] Look, it does come back to that it's complicated. Because it's so complicated, we can't do everything for every program. One of the ways that we've looked at this problem is, again, you go back to your fundamental understanding of the biology you're trying to induce. That's the important of pre-clinical models. It's the importance of understanding the overarching biology. It's the importance of incorporating biopsies in all of these programs so that we can learn as we go so that we're not just getting, if you get a negative answer, you haven't learned anything from your study. Really, for us, it's that entire integration of that data set to ask yourself what is it you're trying to do? Biologically, if you're trying to do something that requires a step-wise biology, that's where sequencing becomes important but trying to integrate sequencing into everything will likely lead to very large phase I trials of agents in some cases that just aren't active. We've tried to prioritize based on biology and a certain sense of pragmatism.

[01:27:00] Female: That gets into another point that was raised in the discussions in this session and that is platforms. Do we need different platforms for testing these combination?

[01:27:30] Are the current trial designs not adequate to really move this field forward at the rate it needs to move and also to minimize waste, to minimize the effort that the FDA has to put into this in order to do this in a better way. I'd be interested ... We heard about one platform from Dan. Are there other platforms that people think could be of help in facilitating combinations? Again, something to think about.

[01:28:00]

Christina Mayer: Hi. Christina Mayer from Janssen R&D. I'm particularly interested in dose selection in mouse models, the mouse efficacy models. I'm curious if you guys can comment on how the doses are selected for these models. Often times, the data is presented without the doses listed. Dose ranging in these studies, the dose ratios, how much are they being explored and how are they being utilized via PKPD modeling, et cetera to impact these combination dosing to supplement the in-vitro concentration effect characterization that we have?

[01:28:30]

Liz Jaffee: Give it a try, Tiffany. Go ahead. [inaudible 01:28:43].

Male: I was just going to say that, you know what, in our case, we went back and initial studies were done with a single agent at multiple different doses, the maximal therapeutic effect was observed. It's interesting, the doses, we haven't gone back and tried to reduce the effects or to evaluate the effects again now with multiple doses when we get to the combinations. We haven't done that because we can do something like I think the very elegant model that Dr. Emens put out with her stage-wise development of going through a dose of chemotherapy. I guess we could have done something like that but we have not done that.

[01:29:00]

Male: [01:29:30] But maybe pre-clinical models are a place to get us the broad strokes. They're unlikely to define exactly what dose but they can give you the kind of large scale, big picture characterization such as do you have a v-shaped response curve, right?

Male: Yeah.

Male: That would be really important for you to know going into the clinic.

Male: Good point. Excellent point, actually. Yes.

Male: I would suspect in your non-clinical model, you may see that one combination is more effective than another. I think the caution there is that you're likely using surrogates. Someone pointed out how does that dose in that mouse translate to an effective dose in the clinic but hopefully, it is a good starting point to prioritize different combinations.

[01:30:00]

Female: Then, I just wanted to add, usually, when we get these studies, when we're reviewing this data is usually using it as a biological rationale but sometimes they will get examples where sponsors have proposed that this is a concentration

[01:30:30] where they're expecting to see efficacy and it would be interesting to know if that also translated clinically. That's not information that we would necessarily get.

Female: In the example that I presented, the sequencing was worked out in the pre-clinical model and we didn't repeat that in the clinic. We depended on the pre-clinical model because we had a pretty good feel for the mechanism. The dose, when we translated to the clinic, I took the best dose in the mouse and calculated the human equivalent dose and then bracketed that around that and actually made the lower dose the effective mouse dose and went up from that.

[01:31:00]

It turns out for the cyclophosphamide in that particular model, the dose from the mouse and the dose in the human were equivalent. The dose of docs actually in the mouse and the human didn't translate. Sometimes, I think it'll translate and sometimes, it won't. You have to bracket around it, I think.

Christina Mayer: Thank you.

Male: I'm [inaudible 01:31:26] from [inaudible 01:31:27]. I wanted to go back to the title of the work, that those finding. I was wondering for us, we developing these drugs, what you think from an academia end, regulatory perspective is more important, the dose or the dose scheduling? In the present time what should really look at more and in the future times, what can we do after an accelerated approval or after approval to optimize the dose scheduling?

[01:31:30]

Female: I'll take that.

Male: It's complicated. I know.

[01:32:00]

Female: I think they're both really important and it depends on, I think, the mechanism that I think you're going after so building things around the mechanism and what you think you're trying to do in terms of both dose and schedule. They're both very important. If you take cyclophosphamide, it has dose dependent immunomodulatory effects at very low doses and at very high doses and it's different. It depends on what you're striving to do.

[01:32:30]

Female: I think Bernie should agree example with OX40 and scheduling, you might miss an activity if you have the wrong schedule. The caveat there and I don't know how everyone else feels but it's very hard in mouse models to effectively look at scheduling because the tumors have a 24 to 48 doubling time as opposed to human tumors, which it's three months or more but I think that example is very powerful. I think, again, it gets to T-cell biology and what's happening with the T-cell at that particular time and it's changing. It's going to need different requirements to continue to be active versus become exhausted.

[01:33:00]

David
McDermott: [01:33:30] One of the things that I think will speed development along this subject is if we learn something in disease X, can we apply it to disease Y, both from a regulatory point a view and from a payer point of view? I'll give an example CTLA-4 PD-1. We have a sense from multiple tumor types if you them less lppy, you get less tox, either if you lower the dose or change the schedule of the lppy.

Obviously, assuming that translates to at least equivalent efficacy, what I would like to see is the ability to say, "Take the lung regimen and use it in melanoma," for example without necessarily having to go back to square one and do a large trial that approves that dose and schedule in melanoma.

[01:34:00] I think you could say the same thing for selection as well. For example, I think the MSI high approval of atezolizumab is a big step forward for our field so there you're taking a tumor-specific marker that's relevant across multiple tumor types. You're saying, "Pembro is active here. Then, it should be active in these other tumor types." You could imagine the same types of approval going forward for looking at the microenvironment that are similar across tumor types.

[01:34:30] Whether it's PD-L1 negative patients or T-effector low patients. I showed the data between the T-effector high, myeloid high subset to the extent that those approvals could be not individualized based on the tumor but made more pan tumor or cross tumor approvals. I think that will speed development because my guess is and I can't prove this will there'll be intratumoral differences, most of the things that we're learning are going to be relevant across multiple tumor types because we're treating the patient's immune system for the most part, not their tumors.

[01:35:00] Ideally, the FDA would continue to look at approvals that have impact across tumor types like they did with the MSI high store. I think that was a big step forward for us.

Male: Thank you. David, while that I think it's true that we're treating a patient's immune system, I guess what it doesn't take into account are are there important immune contextures that are different between different tumors?

David
McDermott: [01:35:30] I'm sure there are but I guess I'm saying is that my sense is that there probably be more similarities than differences, personally but if you have to reapply the knowledge you get from lung cancer to do a completely new phase III development program in the next tumor, that's going to slow things down. We just don't have the patients to do that. We need to be learning from each other across disciplines in my opinion.

Female: [01:36:00] Yeah. I want to second that. I think the genetics may be more important than the site development of the tumor in many ways because the genetics and the immune are inflammatory signals or highly linked. We're just starting to really understand that but the more we look at that, the more we realize that. For

instance, pancreatic cancer that are MSI high are going to respond more like a colon cancer that's MSI high than a standard adenocarcinoma of the pancreas. I agree, we do have to pay more attention to that.

[01:36:30]

Male:

I would just second that it's very complicated. I'll go one step further but I think as you mentioned, you, it's potentially the very big step forward. A lot of the considerations that were used for the approval in the MS high, high setting is very important to look at regarding moving that forward into other types of biomarkers. What is the prior information that was known about the product, for example, in terms of the anti-tumor activity more broadly as a consideration, of course.

[01:37:00]

The biomarker itself, how well ensconced within clinical practice and how reliable that information is in identifying specific types of patients. One of the considerations, thinking forward is when you're identifying potentially new tumor types based on a specific biomarker, not based on tissue but based on the biomarker itself, it's going to be very important thinking about how those biomarkers will be identified reliably across different platforms, for example, of the test. That's going to be a large consideration that the field really has to address.

[01:37:30]

Female:

Okay.

Male:

Thank you.

Female:

Okay.

[01:38:00]

Female:

Hi. To change the perspective a little bit here, I am a former cancer patient, I guess. I was one of the MSI patients who highly benefited from anti-PD-1. I was treated with FOLFOX, then FOLFIRI was at the end of the road. Within three days of anti-PD-1 started feeling really ... In my back pain within three months, 65% shrinkage of my tumor. Within a year and a little bit, there's no evidence of disease in my body.

[01:38:30]

I'm here from the perspective of the patient obviously but also just to a concern that I have the route was this idea of am I being over-treated. Did I get too much of the anti-PD-1 because I was on therapy for pretty much a year after I had already had a complete response so I guess my question ...

[01:39:00]

The other thing that I've often struggled with is the idea if we are trying to figure out the correct dosing and obviously there's all this science that needs to happen and a lot of data investigating but isn't it interesting and important to be following patients in a really detailed and specific way? What is happening to, let's say, the pro-inflammatory cytokines a year after a patient goes off an anti-

[01:39:30] PD-1 or an immune modulator? I just, from the patient perspective, believe it's important to ... Like, how do we talk to patients about the fact that we don't know what the correct dosing is, what does it mean to over-treat a patient? Does it mean that I will have more chronic side effects or is it the severity of them or do they last longer? I struggle with things that there aren't answers to such as fatigue issues and different things.

[01:40:00] I guess I would encourage both sides, both academically and industry and FDA how can we be following patients long term? Thankfully, we're getting to a point where people are surviving longer. My immune system hopefully has a memory and hopefully, this is ... The PD-1 kind of took care of that situation but it's still a long term, because people are living longer from these drugs, the ones who benefit. Fortunately, I do, how can we be better following the survivorship and how can that inform the dosage, et cetera? That's just ...

[01:40:30]

Liz Jaffee: Anyone want to try to address that?

Daniel Chen: I guess I will share a personal story with me that and I would love to hear your reaction to it. Back in 2011, I was leading the atezolizumab development. I was really championing the idea of more limited duration of therapy with the idea that you could retreat. In that experience, I know we lost some patients that because we stopped treatment. I got to say that few things have more deeply affected me personally than knowing that while I was pushing what I thought was an important scientific point, that these things have very real ramifications to peoples' lives. That affected the way I look at duration of therapy and the idea of over-treating.

[01:41:00]

[01:41:30] There are many different perspectives to look at this from. One of those ways is the way we look at how do you treat the potential for an infection of your appendix? We tend to over-treat because it's really important because patients life is at stake and we're willing to tolerate a little bit of over-treatment because we know it's that chance to save someone's life. We don't have perfect answers in this field. What I think you've seen is that, at least for the early portion of this field, we've moved to treating more because of that concern over what happens if you under-treat.

[01:42:00]

Female: Of course. Yeah. I trust that someone would rather be over-treated than undertreated. I just don't know what you think in terms of the follow up survivorship and if you think that would be helpful and beneficial in informing that decision long term.

[01:42:30]
Liz Jaffee: I think we'd all agree, it's hopefully beneficial. The question is how much have we done so far with that because I think as Dan's saying, it's a new field. Can anyone address what is currently being done to really address this question, which is the

next critical question we really need to understand? Any comments on that from the FDA or industry or ...

Male: It's certainly something that's been looked at from the early phase I trials. We're getting three, four, five year follow up. We're trying to report those long-term side effects. I presented some of the kidney cancer data last year at ASCO and most of the tox that happens, at least emergent toxicity happens within the first six months and don't seem to get much new toxicity after six months but that's different than talking about ongoing side effects and how those impact patients. To be honest, those are in some ways harder to get at because our focus is on the short term as far as data collection. There isn't as much support. Their patients go on. They go back to their lives. They're not coming in as often. There are some practical issues around long-term survivors but the good news is there's more of them. The FDA is certainly interested in that concept so we just need to collect the data because it's probably relevant across tumor types.

[01:43:00]

[01:43:30]

Liz Jaffee: Right. Just to say that was a priority of the blue ribbon panel that I co-chaired to collect that information as patients are being treated as well as post treatments so that we can better understand how long to treat, what are the consequences of that. I am hoping that the NCI will be following up with some funding to support studies looking at that.

[01:44:00]

Female: Great. Thank you so much.

Israel Lowy: I just wanted to also address ... Israel Lowy at Regeneron. We actually have a program where we are actually capping treatment at a year with opportunities to retreat. I'll be talking more about it later this afternoon. I'd be very interested in hearing about those episodes, Dan, that you've described because I can imagine, "Oh, my god. I had something in hand and lost it," but also the question is, was that person about to progress anyway? It's a question of how much was due to the break versus how much was due to the evolution.

[01:44:30]

I do think it's important. I also think what David said is also there are late-occurring toxicities, certainly the vast majority of them are soon but it's not like it's more is always better. I'm actually surprised at how vigorous a discussion there is about this because I'll be talking about it later and thought no one was going to be interested but ...

[01:45:00]

Male: I know we're running out of time here but just wanted to make one comment. I think one of the points that you had also brought up and I really appreciate you sharing your story with us is you were interested in the biomarker kind of evaluation, longer term. In terms of the clinical safety evaluations from agency perspective, there certainly the safety information that we get on from the clinical trials when we're reviewing a new drug application, for example or supplemental application, BLA or NDA, for example.

[01:45:30]

- [01:46:00] That is the extensive safety information that we receive but the expectation is that body of data will not really provide all of the information on safety, not just based on mainly the number of patients often reviewing applications with very limited number of patients based on compared to the whole population that could receive the drug once marketing. There is a pharmacovigilance system in placement watch system but certainly there are many limitations to what we can do within and certainly the biomarker question is probably best addressed on long-term protocols and that sort of thing but we're absolutely interested in other ways of obtaining information on safety in the post-market setting so we can identify these rare types of events that may occur with patient's chronic administer or even in acute setting, which, just based on the numbers of the patients we were able to review were not identified.
- [01:46:30]
- [01:47:00] Female: Sorry. [inaudible 01:47:14] question.
- Male: One really quick related question of the FDA. You have a phenomenal system with the adverse event reporting systems up to about nine million patients. For chemotherapy, conventional chemotherapy and now immune therapies, that actually has a wealth of data in it. We presented at ASCO high density data mining of the ARS and actually identified previously described in novel toxicities because it was able to go across several dozens and dozens of clinical trials.
- [01:47:30]
- [01:48:00] What initiatives would you have related to this to expand the depth of the data that's collected with the ARS in a consistent way so we could figure out who got treated for how long. Then also, are there any thoughts of actually incorporating some sort of genetic follow-up to the ARS so that actually for exceptional responses or exceptional toxicities, both the tumor or the patient's genomics are mined?
- Male: Fantastic question and comments. The issue regarding other alternative systems being looked at, certainly with the, in the media about real world data, for example, I think that's potentially a wealth of data that can be evaluated for this. That might be the same repository for where genomic information can also being looked at but that is absolutely one of the limitations with the existing systems that we have in place regarding trying to identify host factors that Dan had mentioned in terms of being pre-disposed not just to responses but also pre-disposed to these rare or even not so rare but serious toxicities. It's absolutely an excellent question. There's many other stakeholders that are potentially looking at ways to address that as well but not an easy answer, as you know.
- [01:49:00]
- Liz Jaffee: Great. Thank you everyone. I want to thank the panelists and the speakers for wonderful session. We're running a little over but if everyone could be back at 1:15. Lunch is on your own. Thank you.
- [01:49:30]