FDA-AACR Immuno-Oncology Drug Development Workshop
Transcript from October 13, 2016

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[00:03:00]
Marc Theoret: Good morning. Welcome everyone, we're going to go ahead and get started here. We're running a couple minutes behind but we're going to get back on schedule here. My name is Marc Theoret, I'm a medical oncologist and serve as the lead medical officer of the melanoma and carcinoma team in the office of Hematology
[00:03:30] and Oncology Products in the Center for Drug Evaluation Research FDA. I'd like to welcome everyone here and welcome to those who have joined by webcast.

I understand that there's over 1,200 now enrolled, but person and online. At the outset I would like to thank AACR for cosponsoring this workshop with FDA. My
[00:04:00] fellow co-chairs, doctors Hazarika, Topalian, Wolchok, for their time and expertise in putting together this agenda. As well as the moderators, additional moderators, of the individual sessions, doctors Helms, Kim, Canetta, and Sridhara, for really putting in their input and shaping the content of the individual sessions. All the presenters and panelists and numerous staff at AACR and FDA, without whom this
[00:04:30] workshop would still be a concept as oppose to us holding this over the next two days.

Especially doctors Anna Sadusky, Nicole Boschi, and Beverly Gallauresi. Why are we holding this drug development workshop on Oncology or I-O products? Clearly we're in this unprecedented time for drug development in Oncology in general but
[00:05:00] most importantly for this workshop with Immuno-Oncology products. Cancer immunotherapeutic products can possess unique characteristics that question utility of a traditional drug development paradigms. The purpose of this two day workshop is to provide an interdisciplinary forum to foster robust scientific discussions on the potential need for new non-clinical toxicology models, clinical dose finding considerations, traditional clinical safety monitoring and potential
[00:05:30] unique considerations in the safety monitoring for I-O products, the need for new efficacy end points are potential modifications of the traditional end points.

As well as alternative statistical methods for evaluation of treatment effects with I-O products, and really the goal is to develop a path forward to evaluate in Immuno-Oncology focused non-clinical and clinical development paradigm. The scope of
[00:06:00] Immuno-Oncology products that we'll be discussing today at this workshop and tomorrow, include not only the Monoclonal antibodies such as the Checkpoint Inhibitors but also bringing into discussion development and unique considerations of other I-O products, such as vaccines and cellular therapies.

This workshop, I'm just going to go over a brief organization of this workshop, it's
[00:06:30] organized into four major sessions. Session one is going to be focused on the considerations for non-clinical evaluation of Immuno-Oncology products with a goal of identifying and discussing key issues in early drug development to support the first in human trials with Immuno-Oncology products. Followed by session two

which is focused on the early clinical development and considerations for I-O products and is going to be separated into two sub-sessions, both related. The first which will focus on unique dose finding considerations for I-O products and the
[00:07:00] second on the identification and characterization of unique safety findings associated with different types of I-O products.

Then session three tomorrow is going to be separated also into two sub-sessions. The first with the goal of discussing unique considerations for developing I-O products with use of the conventional efficacy end points, both tumor response based end points such as objective response rate and progression free survival but
[00:07:30] also others such as overall survival and to discuss possible modifications of these traditional end points. As well as possible necessary modifications of the analysis for these traditional end points when evaluating Immuno-Oncology products. The second sub-session will be to discuss potential novel end points other than the traditional end points, which will capture unique characteristics related to cancer immunotherapeutic products.

[00:08:00] Followed by session four which will be the last session and the goals of session four are to discuss the design on Immuno-Oncology trials that consider these novel and potentially modified end points, new statistical assumptions and methods appropriate for analyzing and reporting the treatment effects in Immuno-Oncology trials. Really all these sessions are set up with similar organization, that is they're designed to have refocused presentations on specific aspects of the drug
[00:08:30] development considerations for Immuno-Oncology products and then these will be followed by 30 to sometimes 60 minutes for discussion by the panel. We really intend for these panel sessions to be very interactive with the audience, both in attendance here and we have the ability to take questions from those participating by webcast as well.

Throughout the two-day workshop there will also be standalone presentations,
[00:09:00] really for specific scientific and regulatory topics to provide the framework for these individual sessions where needed. With that brief introduction I look very much forward to the workshop and the discussions, we'll begin with our first presentation on cancer immunobiology by Doctor Suzanne Topalian to set the stage for the entire workshop. As you can see from the bios, Doctor Topalian is a
[00:09:30] member of the AACR regulatory and science policy subcommittee, professor of Surgery Oncology at Johns Hopkins University School of Medicine where she is the Director of the Melanoma program at the Kimmel Cancer Center, and Associate Director of the Bloomberg-Kimmel Institute for Cancer Immunotherapy. She's widely recognized for her contributions to the field with multiple awards, to name
[00:10:00] a few the Karnofsky Award from ASCO in 2015 and more recently the 2016 Taubman Prize for her discoveries in immunotherapy.

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Marc Theoret: Time and prize for her discoveries in immunotherapy.

Suzanne Topalian: Thank you, Marc. Good morning everybody and welcome to this workshop on IO drug development. What I would like to do this morning is just lay the background
[00:10:30] by talking about the principles of cancer immunology underlying the practice of IO drug development. The basic idea here is that, unless we understand the underlying science, we're not going to be able to rationally develop this class of drugs. I do have some disclosures for the talk today.

[00:11:00] When I think about the immunology behind cancer immunity, I think about dualities and here are some of them, which I will cover in the talk today. There can be endogenous anti-tumor immunity, meaning, something that is already present in the host before any therapeutic is applied. Or, immunity induced by our therapeutics. Immunity can be innate, meaning that it engages certain cells of the
[00:11:30] immune system, such as NK cells and macrophages. Or, it can be adaptive, involving TNB cells, and we'll discuss that. There is also tolerance, and that can be either central or peripheral. All of the above can be regulated by stimulatory or inhibitory pathways.

When we think about therapeutics, they can be active, meaning that the host's
[00:12:00] immune system needs to be engaged or they can be passive, meaning that the host's immune system is not necessary. We supply everything in the drug or the treatment that is needed for an immune response.

When we think about endogenous anti-tumor immunity, which is a very important concept especially for checkpoint blockade. Let's look at the case of melanoma. This was probably the earliest evidence that there could be an endogenous anti-
[00:12:30] tumor immune response in humans. Clinically we know that primary melanoma lesions on the skin can regress spontaneously and if they're biopsied, they do have lymphocyte infiltrates. We also know that melanoma incidents is higher in immuno-suppressed patients. Under the microscope, we can see that these tumors are infiltrated by T-cells. Here I'm showing you an example. We know that if we take tumor-infiltrating lymphocytes, or peripheral blood cells, into the laboratory and
[00:13:00] tweak them a bit with cytokines and other stimulation that those cells can show anti-melanoma activity.

The big question has always been why do melanoma cells and other kinds of cancer cells coexist with the sheets of infiltrating, CDA-positive, killer T-cells? Why have these T-cells have not destroyed these tumor cells? These are the same T-cells that,
[00:13:30] in the laboratory, have a lot of activity against those very tumor cells. So, the first approach that we took in the 1980's to helping the endogenous anti-tumor immune response was to treat patients with high doses of cytokines that these T-cells need for activation. So Interleukin-2 was eventually approved for treating patients with advanced melanoma and kidney cancer based on these kinds of
[00:14:00] responses that we saw in the 1980's. This is a patient with melanoma, with lung metastasis and very nice partial-regression after just a few weeks on high doze IL-2 therapy.

But the problem with giving high doses of cytokine systemically is that they're not

really meant to work that way. So we encountered a lot of toxicity with Interleukin-2 and other cytokines, which are very important to the immune system but they act
[00:14:30] on a local level in the tissues and they're not really meant to be at high levels systemically.

Cytokines had the capacity to simulate both the adaptive and innate immune responses and it's really the interaction between these two systems that we are now realizing is very important to have a diverse and a powerful anti-tumor
[00:15:00] immunity. So the characteristics are somewhere dichotomous. The innate immune response, which includes neutrophils, macrophages, and natural killer cells, occurs very rapidly. It was meant to reject bacteria, so foreign invaders. It's relatively non-specific. There's no memory component involved in this kind of immune response. In contrast, the adapting immune response, which is mediated by T-cells and B-cells
[00:15:30] producing anti-bodies, is much slower to develop. A new adaptive response might take 10 days or more to develop. It is very specific. It's the kind of response that the immune system uses to reject viruses. And very importantly, the adaptive immune response has memory so the implication here is that if we can properly tune the adapting immune system to recognize cancer, that immune memory should last for
[00:16:00] years or potentially for a lifetime.

Now what do these innate effector cells, NK cells, recognize? They recognize invariant ligands that are expressed on tumor cells as a result of stress transformation and DNA damage and these are some of the ligands: MIC, ULBP
[00:16:30] and, in mice, RAE. NK cells have an activated receptor, NKG2D. When they recognize these invariant ligands, they will then secrete effector cytokines and actually release chemicals, perforin, which can directly kill cancer cells.

Getting back to dichotomies, the function of NK cells is controlled by both stimulatory and inhibitory receptors and this is important because these are
[00:17:00] druggable receptors and actually some drugs modulating NK activity are already in the clinic in IO trials. I mentioned NKG2D which is a stimulatory receptor. There's also FC receptors which bind antibodies. If these antibodies are specific for tumor cells, this ligation can lead to the killing of tumor cells. This interaction is very
[00:17:30] important as we now know antibodies that are directed at tumor cells, such as herceptin and rituxan, work differently in patients who have different allele types of FC gamma receptors. On the inhibitory side, we have killer inhibitory receptors which recognize self-MHC, class 1. This interaction turns NK cells off but antibodies
[00:18:00] in the clinic that block [inaudible 00:18:00] can turn that interaction on. This is just a bit about the dual nature of the NK cell activity.

For the adaptive immune system, this is a very diverse immune system with highly specific receptors. T-cell receptors or B-cell receptors, which are immunoglobulins.
[00:18:30] As a result of somatic DNA rearrangement, different variable segments combined with diversity regions, joining regions, and constant regions in the genome, to produce these unique clonal receptors.

If you think about innate and adaptive immunity together, when the innate

[00:19:00] immune system recognizes tumor cells, it immediately springs into action. Again, this is a fairly non-specific interaction but just a bit later, these tumor antigens, proteins released from tumor cells, presented by antigen-presenting cells, such as dendritic cells, are going to be recognized by cells of the adaptive immune system and so here we see T-cell recognition but then helper T-cells are going to educate
[00:19:30] B-cells to produce immunoglobulins and all of this will be directed back against the tumor cells at the same time these T-cells, which are secreting cytokines or expressing certain ligands, can help to activate components of the innate immune system. There are a lot of interactions going on here. As we go through this conference, we should think about ways to activate all components of this anti-tumor immune response.

[00:20:00] We used to think that the natural balance between the immune system and cancer was one of rejection

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Suzanne Topalian: ... Balance between the immune system and cancer was one of rejection because cancer cells are so different from normal cells. It was only later that we learned that actually the natural balance is what we call tolerance, where the immune system tolerates cancer because cancer is viewed as self. There are two mechanisms that underlie immune tolerance: One is called central tolerance. This
[00:20:30] occurs during T-cell development in the thymus where T-cell clones that strongly recognize self-antigens are deleted, so those responses just do not exist anymore in the adult. What we're going to be mainly focusing on in this conference is the phenomenon of peripheral tolerance where specific immune cells in the periphery, mature T-cells are inactivated by various tolerance mechanisms in the tissue.

[00:21:00] What are some of these tolerance mechanisms that underlie this peripheral inactivation of anti-tumor immunity? The major categories, we have regulatory immune cells such as T-Regs, which are a subset of CD4 cells. Myeloid-derived suppressor cells, which are similar to neutrophils and monocytes. We also have
[00:21:30] inhibitory cytokines, which are secreted by components of the immune system or by cells in the tumor stroma or by the tumor cells themselves. These include substances like IL6, IL10, TGF-β, VEGF. Then we have this group of T-cell inhibitory receptors such as CTLA-4, PD-1 and LAG-3 that we'll discuss this morning. These receptors are expressed on activated immune cells and all of these components
[00:22:00] have a normal function, which is to turn off adaptive immune responses at the right time so that the immune system does not damage normal tissues as it's trying to fight off invaders like bacteria and viruses.

What we know now is that cancer can co-opt all of these mechanisms to essentially turn off anti-tumor immunity and fly below the radar of the immune system. Therapeutically, we need to think of solutions so by knowing the mechanisms we
[00:22:30] can think about solutions. On this side, how do we overcome immunosuppressive cytokines in the presence of regulatory T-cells? One way to do that is to remove tumor reactive T-cells from the body, engineer them or activate them in the

laboratory and then transfer them back into the patient. This is the essence of adoptive cell transfer therapies, which we'll talk about in this conference.

[00:23:00] This is a form of passive immunotherapy where we make the immune reagent in the laboratory and then we provide that to the host. On the other hand, we might be able to devise potent vaccines to enhance endogenous anti-tumor responses and so this is a form of active immunotherapy and so we'll be talking about cancer vaccines in this context. How do we get around these immune checkpoints? Here
[00:23:30] we're going to use antibodies or other kinds of drugs to block these checkpoints, essentially releasing the brakes on the anti-tumor immune response.

Let's first consider adoptive cell therapy. This was first developed in melanoma and this has been a decades-long process of discovery and development. There are many different types of adoptive T-cell therapy. In the 1980s we started with bulk
[00:24:00] cultures of tumor-infiltrating lymphocytes, those same cells that were present in the tumor but not effective in situ in controlling the tumor but when they're removed from the body and grown in the right way they have potent tumor-killing capacity. After the development of tumor-infiltrating lymphocytes, our approach became more specific in which we engineered T lymphocytes from patients to
[00:24:30] express T-cell receptors that very specifically recognized one MHC molecule and one tumor-associated peptide complex to that MHC molecule.

As we became more specific, some of the response rates dropped and what we found when we biopsied recurrent tumors from these patients is that in many cases they had lost expression of the MHC molecule or the target peptide. The
[00:25:00] more specific that this technology became, the more likely it became that the tumor could find a workaround by deleting these non-essential molecules. When we got to the point of growing individual T-cell clones that recognized shared melanoma antigens such as MART GP-100 ESO, we found that the response rates dropped to a very, very low level. This, I think, illustrates that we want a specific
[00:25:30] anti-tumor immune response but we don't want it to be too specific. When it becomes too specific the tumor can easily find a workaround.

This is an example of a trial of adoptive cell transfer therapy with T-cell clones from Cassian Yee when he was working in Seattle showing the loss of a non-essential target antigen under the selection pressure of immunotherapy. In this trial, from patients with MART-1 expressing metastatic melanoma the investigators grew CDA-
[00:26:00] positive T-cell clones that recognized MART-complex HLA-A2. They demonstrated in the lab that those clones had killing ability for MART-positive melanoma cells. They expanded the cells, they gave them back to the patient. What these investigators saw initially was that some tumors regressed but then tumors recurred and when they biopsied them, as you see in this case, the MART-1 antigen
[00:26:30] was lost, even though other melanoma antigens such as GP100 and tyrosinase were still present in the resistant tumor. This is a very specific loss of the antigen that is being targeted by the adoptive cell therapy. On the one hand, good news, the T-cells are doing what they're supposed to do but on the other hand bad news, the tumor recurred.

[00:27:00] One very potent approach now, which I think is as close as we've come to an off-the-shelf reagent for ACT is chimeric antigen receptors. This combines the specificity of antibodies with the activation mechanism of T-cell receptors. These are molecularly-engineered receptors which are hybrids of variable regions of immunoglobulins with T-cell signaling domains and they can be further engineered
[00:27:30] to include additional signaling domains which make them more potent and make it more likely that the transferred cells will persist for a long time. As you know, CARs directed against CD-19, which is found on certain lymphomas and leukemias, can cause the durable regression of very advanced cancers, including pediatric
[00:28:00] leukemias. However, even in this case, CD-19 negative tumor escape variance have been reported. Once again, we need to think about combination IO approaches, even with this very powerful technology.

In terms of vaccines, there are many varieties also of cancer vaccines. Many have
[00:28:30] been tested in the clinic over the past decades. They have certain advantages and disadvantages and we can think about peptide vaccines, they are based on peptides found in tumor cells. Recombinant protein vaccines, recombinant DNA plasmid vaccines, vaccines based on viral vectors and even bacterial vectors. The hope for vaccines is that they would be generic, in which case they have to be
[00:29:00] based on shared antigens, although more recently intratumoral vaccine injections have been used to take advantage of the host's endogenous immune response and these may be able to incorporate mutant antigens that are unique to different cancers.

With vaccines we always consider production issues, are they easy to produce, of
[00:29:30] course, are they safe? On the other side, are they immunogenic? Some vaccines that are very easy to produce, such as peptides, are poorly immunogenic and because they are HLA-allele specific cancer, resistance to this kind of vaccine is a huge issue. One thing that we learned from patients who were vaccinated against shared antigens is that T-cells that are primed with these vaccines express immune
[00:30:00] checkpoints and so this brings me around to discussing checkpoint ...

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Suzanne Topalian: ... immune checkpoint. So this brings me around to discussing checkpoints, which is a very important category in mechanisms of peripheral tolerance.

So, for instance, in our lab we studied peripheral blood T-cells from patients who had received a GP100 melanoma pep-tide vaccine. And what we saw staining these
[00:30:30] cells with tetramers that could identify a GP100 specific T-cells is that percent of those T-cells could rise to very high levels in circulating blood. But at the same time that those specific T-cells were increasing in numbers as the vaccination continued over a year, those T-cells also expressed increasing levels of programmed death 1. PD-1, which is an immune checkpoint. And lowering levels of CD 28, which is a co-
[00:31:00] stimulatory receptor.

And so maybe this is one reason why vaccines given over a long time period are not very effective but this kind of information led us to hypothesize that blocking immune checkpoints might augment the efficacy of cancer vaccines. And this is one kind of IO combination that we will be discussing today.

[00:31:30] Now, what about these checkpoints? Well, this is a very complicated situation. And so, this graph shows you what we call the immune synapse. It's where T-cells encounter antigen presenting cells like dendritic cells or tumor cells. Again, the T-cell recognition event occurs through this very specific T-cell receptor recognizing
[00:32:00] MHC and a tumor derived pep-tide. That's fine but then the T-cells need a second signal to tell them what to do. Either to become activated or inhibited. These are all the second signals. The ones in red are inhibitory signals but there are also stimulatory signals in green. For purposes of this conference, it's important to know that every one of these interactions can be targeted.

So, the receptors on the T-cell side can be targeted and the ligands on the tumor
[00:32:30] cell or antigen presenting side can also be targeted. And they can be targeted in various combinations.

Now, the first two pathways to be targeted in the clinic were the CTLA-4 and the PD1 pathways. A drug blocking CTLA-4, Ipilimumab, was approved by the FDA in 2011 for treating patients with advanced melanoma. And this approval was based
[00:33:00] on results from two randomized phase 3 trials. I'm showing one of the trials here where it was obvious that the patients receiving Ipilimumab fared better than those who were receiving the control and interestingly in this trial, the control was a GP-100 pep-tide vaccine. What was very interesting about the outcome here is that we saw development of this tail on the curve, this plateau level of overall
[00:33:30] survival, which persisted for years. And longer follow-up recently has shown us that this tail goes out even to 10 years. So, this tail on the curve with overall survival, we think, indicates something about the memory of the adaptive immune response, which has been tuned by anti-CTL4.

However, what we also saw in this and other trials is that the rate of severe drug
[00:34:00] related toxicities, mainly immune related side effects, was about the same as the clinical benefit rates so both were about 20 percent. So, we couldn't stop here. What we wanted to do is find other drugs in class which might have a higher rate of effect and a lower toxicity rate.

Let me talk a bit about the PD1, PDL1 pathway. This was next to move into clinical
[00:34:30] development. This pathway is very important in the periphery for mediating peripheral tolerance at the site of tumor. And again, the way it works is that the T-cell recognizes tumor components presented by antigen presenting cells through a very specific TCR.

The next thing that happens is those T-cells become activated through stimulatory co-receptors such as CD28. So when they become activated they will proliferate,
[00:35:00] produce cytokines, they develop killing activity against the tumor, and then they

migrate throughout the body, looking for sites of tumor. But at the same time, and actually fairly quickly within hours to a couple of days, those same activated T-cells begin to express checkpoints such as programmed death 1, PD1.

So when those T-cells reach the tumor, if the tumor is expressing PDL1, the major
[00:35:30] ligand, the interactions of those two molecules is going to turn the T-cells off. Here it's important to realize that the problem is not T-cell recognition. It's not T-cell trafficking. The problem is occurring at the tumor site, when the T-cells just poised to kill those cancer cells. It is then paralyzed by the interaction of PD1 with the ligand PDL1.

The drugs that have been developed recently blocking mono-clonal antibodies
[00:36:00] either bind the PD1 receptors on T-cells and block that or they bind the ligand on tumor cells. And it turns out that no matter which side of this equation you block, you can see a clinical impact with regression of advanced tumors.

Now, CTLA1 and PD1 are cousins. They're in the same molecular family. They're very similar to each other. And yet, they're very different from each other. So,
[00:36:30] many reviews have been written about this. This is a figure from one review that we published a few years ago, just highlighting that CTLA4 is very important for the activation of naïve or resting T-cells. So these are T-cells that are located at sites of antigen priming, such as lymph nodes. When those T-cells are activated, they will
[00:37:00] express CTLA4. And when the T-cells later encounter antigen presenting cells that express the major ligands B71 and B72, those T-cells will then be turned off.

In contrast, PD1 is very important as a turn-off mechanism for experienced T-cells, not naïve but experienced T-cells that have already reached the tissue where the antigen is located. Their ligands are very different. So, whereas B71 and B72 are
[00:37:30] expressed everywhere throughout the body on antigen presenting cells, the major ligands for PD1, PDL1 and PDL2, are mostly expressed in tissues at sites of inflammation or cancer. And so just by virtue of where the ligands are expressed in the body, this pathway should be more specific than the CTLA4 pathway. The
[00:38:00] expectation based on genetic animal knockouts was that the toxicity encountered with blocking PD1 or PDL1 might be less than what we had seen with CTLA4. That did turn out to be the case.

To summarize a lot of work that's gone on in the past several years, we now know the following about drugs that block the PD1 pathway and I'll just describe some of the highlights that I think are going to be important for the discussions that will
[00:38:30] occur here over the next two days.

First we know that drugs blocking this pathway are active against multiple cancer types. Some of them are listed here. And in fact, the first six have now had FDA approvals of either drugs blocking PD1 of PDL1. In various studies, we've seen substantial percentages of patients with very advanced cancer responding. Most of
[00:39:00] these patients had been previously treated with other systemic cancer therapies and had not responded to those therapies before coming on these clinical trials.

There's emerging evidence now from additional cancer types which may have significant activity.

On the other hand, there are tumors that are not on this list, like prostate cancer and pancreatic cancer, which have proved to be very resistant to these mono-therapies. But again, here's where we think about combination therapies to
[00:39:30] overcome the resistance of particular tumor types or resistance encountered in patients within these cancer types who are not responding.

Another important thing we've learned from these trials is that the response to PD1 pathway blockade can be very durable. This is some information presented recently at the ASCO meeting from a trial of Pembrolizumab anti-PD1 compared to
[00:40:00] Ipilimumab, where I showed you that there's a very durable tail on that Ipilimumab response curve ...

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Suzanne Topalian: ... That there is a very durable tail on that ipilimumab response curve. Now we're seeing over a fairly long observation period that the responses to anti-PD-1 drugs are also very durable, very durable over this period of observation and, of course, we will continue to observe these patients in follow up. Another interesting thing that we learned was that there can be unique response patterns seen with IO drugs
[00:40:30] that are not seen with other kinds of cancer therapies, such as chemotherapy or TKIs. This is an example of what we call an immune-related response pattern and we'll discuss this a lot more in this conference.

This is a patient with metastatic lung cancer treated with anti-PD-1 who after the first cycle of therapy appeared to have progression, and you can see that all of
[00:41:00] these tumors are enlarging. After the second cycle of therapy, and this was a trial that allowed us to continue giving therapy even after one cycle of progression, after the second cycle now you see a very nice partial tumor regression compared to the baseline scans. There are two possibilities here: Perhaps this tumor really did grow at week eight and maybe it just took a while for the immune response to kick
[00:41:30] in while the patient was maintained on anti-PD-1 therapy, but the other possibility is that this apparent enlargement really reflects inflammation at that site of tumor with edema and swelling. Looking at these scans it's impossible to know which hypothesis is correct. The only way that we can know is with biopsies. This speaks to the importance of on-treatment biopsies as well as pre-treatment biopsies to
[00:42:00] better understand how these therapies are working.

Here's something else that we have observed with anti-PD-1 is that progression-free survival often underestimates the true impact of this class of drugs. Here's an example in which 100 patients with advanced melanoma were treated with anti-PD-1 with nivolumab and then were followed for survival. Here you can see in this
[00:42:30] graph of progression-free survival, this median of 3.7 months is not remarkable at all, it looks just like chemotherapy and many other treatments that we might give to a patient with melanoma. It's the overall survival that is actually impressive in

these patients, some of whom had received five prior systemic therapies before they came on to this trial. Yes, progression-free survival is an earlier readout of
[00:43:00] activity but it may not serve us well with certain drugs that we are evaluating in the IO space.

As we follow these patients longer, and this is the same group of 100 melanoma patients from the trial I just showed you, now we are seeing the tail on the overall survival curve with anti-PD-1 drugs, which is very similar to what we saw with
[00:43:30] ipilimumab. Here's this ipilimumab curve and now we have ten-year survival on thousands of patients pooled from various Phase II and Phase III trials globally. This tail did stabilize at around 20 percent but here this tail on the anti-PD-1 curve is stabilizing at about 33 percent. Interestingly, although these patients were heavily pre-treated, there are other trials in which patients with melanoma are receiving
[00:44:00] anti-PD-1 as the first drug for metastatic disease and here the tail seems to be leveling off at a higher point. Obviously, not as much follow up on this trial but this could be an interesting story developing showing the difference of using anti-PD-1 drugs as first-line versus later-line therapy.

[00:44:30] We also recognized immune-related toxicities with anti-PD-1 drugs, which were very similar to the toxicities we had seen with anti-CTLA-4. That experience with anti-CTLA-4 served us well and helped to accelerate the development of the anti-PD-1 and anti-PDL-1 drugs. Many of these toxicities have immune-related mechanisms and this is what you would expect by releasing the brakes on the
[00:45:00] immune system. We would really like it if this could be specific for the anti-tumor immune response but, of course, there's going to be spillover to other kinds of immune responses. We have seen auto-immune reactivity in some patients. This is an example where we can actually learn something more about the mechanism of action of these drugs by studying the side effects.

In this patient with melanoma who was treated with anti-PD-1, we saw a very nice
[00:45:30] response of extensive metastatic disease but eventually this patient developed an autoimmune nephritis. When we looked at the biopsy of the kidney, this was a diagnostic biopsy, what we saw was the following: We saw infiltration of CD-3 positive T-cells, here stained with immunohistochemistry, but we also saw the presence of many plasma cells from B-cell precursors. These cells are producing
[00:46:00] antibodies as part of this autoimmune nephritis side effect. This points out another distinction between CTLA-4 and PD-1. PD-1 can be expressed not only on T-cells but also on activated B-cells and on NK cells. By blocking the PD-1, PDL-1 pathway there is the possibility of activating multiple arms of the adaptive and innate immune
[00:46:30] response. This may be what we're seeing here with this mixed T- and B-cell immune related side effect.

We've learned to recognize these side effects early and to manage them aggressively and so we now believe that these drugs for most patients, for the vast majority, are very safe. IO drug development in the press has been heralded as a breakthrough but it really isn't, of course, because I've just described to you how
[00:47:00] this pathway of learning about how the immune system interacts with cancer and

then modulating the immune system with drugs and other approaches, how this has been a decades-long pathway. We're very lucky to have on our speaker list for this conference some of the people who have been in this field for a very long time who can give you their perspective on these issues.

[00:47:30] For both anti-CTLA-4 and anti-PD-1 drugs, the development pathway exceeded twenty years. We now hope with modern clinical trial design and other regulatory issues that we're going to be discussing that this pathway can be shortened for a new drug. The major events after cloning of these genes, we are finding out what
[00:48:00] the ligands are, demonstrating the phenotypes of the knock-out mice, treating animals with tumors with these drugs in the laboratory, moving it into patients, seeing activity in patients, demonstrating survival benefit and clinical trials and then finally FDA approval.

When Drew Pardoll wrote this review in 2012 he predicted FDA approval for an anti-PD-1 drug at the end of 2014 and that turned out to be right on target. We
[00:48:30] know the two anti-PD-1 drugs were approved at the end of 2014 for treating patients with melanoma. I've mentioned that this pathway involves PD-1 and PDL-1 and there are drugs that block either/or. This is not the same. People are now questioning why we need so many of these drugs. At least I think we need anti-PD-1 and anti-PDL-1 drugs because they don't do the same thing. A drug-blocking PD-1
[00:49:00] is going to block its interaction with its two ligands PDL-1 and PDL-2 but it won't block this other suppressive interaction between PDL-1 on tumor cells and CD-80 or B-7.1 that's expressed on activated T-cells and can deliver a negative signal.

Over here, by blocking PDL-1, we would block the interaction with CD-80 and PD-1
[00:49:30] but we would not block the interaction of PD-1 with PDL-2. It's really unknown without testing the drugs what the difference might be in terms of efficacy or even toxicity. This slide is only a year old but already the list of different drugs against PD-1 and PDL-1 has grown and my colleagues at FDA tell me that now there are over twenty of these drugs, either already approved or in clinical testing. Why do
[00:50:00] we need so many of them? Maybe we don't need more than twenty, but I would point out that ...

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Suzanne Topalian: I would point out that these drugs are all unique chemicals. Some of them are fully human produced in genetically engineered mice, others are humanized, engineered in a laboratory. And they have different isotypes these are different subtypes of these blocking antibodies which will have different properties. The
[00:50:30] IGG1 isotype antibody will bind very well to Fc receptors on NK cells. Whereas the IGG4 does not. Then the antibodies can be further engineered if they have an IGG1 subtype they can be modified specifically so that they do not bind Fc receptors. But the ones that do bind Fc receptors have the capacity to kill the cells that they are
[00:50:57] directed against. So for instance, this antibody of with an unmodified IGG1 could
[00:51:00] theoretically kill cells expressing PDL1.

So, what are the current challenges? We need to develop a deeper understanding of these mechanisms, develop biomarkers to identify the patients or tumor types likely to respond. Then develop combinations either IO plus IO or IO plus other
[00:51:30] types of treatments to enhance efficacy. And again, as we wrote about it in this recent review, we need to consider mechanism when we're talking about biomarkers. SO let's consider biomarkers for a moment and some common sense questions that we could ask are: what are the antigens being recognized by the T-cells? Does the tumor contain reactive T-cells? And does the tumor or infiltrating immune cells express checkpoints.

[00:52:00] So in 2012 we published evidence for the first time that PDL1 expression on tumor cells might be a pretreatment biomarker to help identify patients who are more likely to respond to anti-PD1 therapy. Further development in other laboratories and by various companies with these drugs lead to regulatory approval for some
[00:52:30] PDL1 IHC tests, but also lead to the coining of a new terminology by the FDA, 'a complimentary diagnostic', in other words a diagnostic that is not essential for giving the drug but might still aid in risk benefit assessment for individual patients. And this is built on evidence that the PDL1 biomarker is not a fixed biomarker it's something that can change over time with the dynamics of the immune system. It
[00:53:00] can be variable expressed at different sites of tumor and even within an individual tumor may be expressed in some spots in the tumor and not others. SO there are uncertainties about PDl1 diagnostic testing which have led to this complimentary terminology.

Just in interested of time let me skip ahead to show you this, which is an example of PDL1 expression in a very specific place within the tumor with is at the interface
[00:53:30] between tumor cells and infiltrating immune cells. Laboratory studies showed us that these immune cells were producing inflammatory cytokines that we know can drive PDL1 expression. This pattern was often seen in melanomas but also in other tumor types that express PDL1 and that have been successfully treated with anti PD1 or PDL1 drugs. Leading us to understand this mechanism that we call adaptive
[00:54:00] immune resistance where tumor cells express PDL1 in response to T-cell attack and the production of inflammatory cytokines. We can use that test to search for tumor types and underserved patient populations where maybe we should be testing antiPD1 drugs.

This is an example of a recent study in patients with anal squamous cell carcinoma
[00:54:30] who either were infected with HIV or not. Showing that the HIV positive patients had the same components of immune reactivity in their tumors and the HIV negative patients. And here you see this immune front pattern of PDL1 expression in a tumor from an HIV positive patient. Suggesting that immune suppressed patients even though they maybe be globally immune suppressed, may still have
[00:55:00] immune reactive tumor micro-environments and maybe should be considered for drug application.

There has been a lot of consideration lately about mutational burden and the intersection of cancer genetics with responsiveness to immune check point

blockade, looking at the frequency of mutations in different human tumor types it appears that the ones circled in red are the ones that we know can respond to anti
[00:55:30] PD1. It appears that they cluster in the area of this graph where we see higher mutational burden. An extreme example of this is MSI-high colon cancers which have a very high mutational burden and are very responsive to antiPD1 therapy. While the garden variety colon cancers which have modest mutational burdens are not responsive. And so this is an example of how a genetic bio-marker may help us
[00:56:00] appropriately develop anti PD1 therapies. But let's not forget that non-mutated antigens can also be important in the anti-tumor immune response.

I'm showing this example of a patient with melanoma. Treated with anti PD1. Who developed vitiligo At the same time he was developing a long lasting complete response to therapy this vitiligo is the result of destruction of normal melanocytes,
[00:56:30] the precursor cells of melanoma cells, that share pigmentation antigens such as Mart and GP100.

The example of Merkel cell cancer teaches us a lot about the nature of tumor antigens and what the immune system needs to see. Because in this case 80% of cancers are caused by the Merkel cell polyomavirus. And they have very, very low tumor burdens, on average 10 mutations per tumor. But the 20% that are virus
[00:57:00] negative are caused by a carcinogen ultraviolet light. And so they have very high mutational burdens on average, about 1500. It turns out that both varieties of Merkel cell cancer respond very well to anti PD1 and this shows that the quality of the tumor antigen, the strength of the tumor antigen may be just as important as the number of available tumor antigens. And so with all of this information we've
[00:57:30] seen a rapid proliferation of FDA approvals. Melanoma studies lead the way but soon followed by lung cancer, kidney cancer, Hodgkin's lymphoma, bladder and head and neck cancer. Although the earliest trials were done in patients with very advanced disease who did not respond to other therapies. Later trials have been done as first line therapy for advanced disease.

Now we need to consider neoadjuvant and I hope this is something that will be
[00:58:00] addressed later in the conference. This is the idea that patients who are resectable potentially for cure but who are at high risk for recurrence maybe effectively treated with anti PD1 drugs or other IO agents. This information was just presented last week at the ESMO Conference from a trial of neoadjuvant anti PD1 therapy in non-small cell lung cancer. Showing that within a 4 week treatment period prior to
[00:58:30] surgery, radiographic responses could occur. Some were quite dramatic, in other cases, it appeared as if the tumor grew, but when we biopsied the tumor, there were almost no viable tumor cells left. And so, actually 41% of these patients in this relatively small study out of 17 studied so far, 41% had a major pathologic
[00:59:00] response, defined as less than 10% residual viable tumor cells. And so this suggests that using these IO drugs at earlier stages of disease may be beneficial.

This is the work of Janis Taube and her laboratory, Showing very complex new
[00:59:30] biomarkers that are being developed that are now looking at multiple markers on a single slice of tumor and, in one of these patients in the neoadjuvant lung cancer

trial, pretreatment we see many tumor cells in orange, may PD1 positive infiltrating T-cells in red. we can look on higher power and see PDl1 positive cells interacting with PD1 positive killer T-cells, but post treatment the tumor is dissolving, there's
[01:00:00] not much orange left and it's flooded now by a very dense infiltrate of these CDA positive...

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Suzanne Topalian: Flooded now by a very dense infiltrate of these CDA positive T cells. Janis Taube and David Rimm can tell you more about how they can measure the distance between cells, the incidents of clustering of cells that are interacting with each other, and how this new level of information might be useful for development of these drugs. I'll leave you with the thought that we need to develop synergistic
[01:00:30] treatment combinations, but they should be based on laboratory evidence. The question that the first panel will discuss is, what level of pre-clinical evidence is appropriate to move a drug into the clinic? This is an example of the combination of the anti-PD-1 and a drug directed against another check point, lag 3, from Alan Korman and others, showing that this combination is very potent in animal models.
[01:01:00] Also, with supporting information from human studies, showing that lag 3 is expressed in the same location as PD-1, PD-L1, and inflammatory cytokines in CDA positive T cells. With immunohistochemistry showing protein expression of PD-L1 and lag 3 in the same location.

I'll leave you with the thought that an understanding of the basics of cancer
[01:01:30] immunobiology is needed to drive effective IO drug development. The unique characteristics of tumor regression and AE's associated with these drugs are consistent with mechanism of action and rational trial design and combination development, should be based on pre-clinical evidence and guided by bio-markers.

Thanks for your attention this morning. I would like to thank the group of collaborators at Hopkins, but also in other trial center, and support from many sources. Thank you.

[01:02:00]

Whitney Helms: All right. Morning. I'm Whitney Helms, I'm a pharm-tech supervisor in the Cedar office of Hematology-Oncology Products. I'm going to introduce our first session on the considerations in the pre-clinical evaluations of immuno-oncology products. Hopefully.

[01:03:00] To begin with, the regulation of cancer of immunotherapy products FDA is regulated by 2 centers, the Cedar group, the Center for Drug Evaluation and Research will regulate the monoclonal antibodies, including many of the check
[01:03:30] point inhibitors. The [inaudible 01:03:30], Pembro, Nevo, and Tocilizumab that was approved earlier this year, as well as fusion proteins like [inaudible 01:03:36], and your older cytokines like IL2, and there's your purine gamma that we discussed earlier. Whereas the Center for Biologic Evaluation and Research focuses on the genetic modified T cell, like the Car T cells and the cancer vaccines and oncolytic

vectors. I've also included here at the bottom some of the relevant non-clinical
[01:04:00] guidance for drug development. The international council of harmonization guidance's on non-clinical evaluation for anti-cancer research and the Q&A document that is currently open for comment, as well as the ICHS6 and its addendum which focus on biotechnology derived products, and the FDA guidance's pre-clinical assessment for investigational and cellular G therapy's and immunogenicity.

The goals of a standard non-clinical program, regardless of which center you are
[01:04:30] going to, are to provide safety data to support on appropriate starting dose and to inform on clinical monitoring. Traditionally this has been based on toxicology studies on healthy animals, and also to provide support for rational and biologic-plausibility of this study. Which relies heavily on xerograph models and in vitro mechanism vaccination studies, but some of the challenges with the IO products has been that the species relevance has been a real issue. There seem to be
[01:05:00] differences in thresholds for immune activation, or maybe FC binding, that are making these models not very predictive of the kinds of toxicity that your seeing clinically. While you may be able to predict the toxicities based on mechanism, it's still hard to figure out what kind of dosing to use based on these models.

Another challenge is translating in vitro data and in vivo data into the human experience. So based on tragedies with some of the earlier immuno-oncology or
[01:05:30] just immunology targets ... there was a recommendation to use some of this data to calculate a minimally anticipated biological affect level or pharmacologic affect level for immunogenicity. This is sort of spread into your immune-modulating agents in general, partly because there are questions about species relevance with some of your more traditional molecules.

Also, an ongoing problem is what to do with the combination. Especially when you
[01:06:00] have concerns about synergistic activity, and calculating MABEL ... inquires a lot of different kinds of data. There's no universal approach for determining a first in human dose based on MABEL regardless of the indication. You use a lot of different inputs, including in vitro pharmacology data from target cells, from human, and your toxicological species. There's concentration affect data from in vitro and in vivo studies. If you are using animal data then caparisons to your human and
[01:06:30] animal differences and your dose exposure responses. So the expectation for a non-clinical immuno-therapeutic packages include a lot of pharmacology. You want to know the pharmacology of your target, and pathway, and whether the target is activating or inhibiting your immune response.

We do generally assess the cytokine release potential, and studies taking into
[01:07:00] account multiply meccas of action of your antibody or other product, as well as receptor occupancy. So some of the points that we want to consider for this session are, are there better models we can use for predicting and understanding the safety of these products? Is there an optimal way to use the non-traditional data sets to find an appropriate starting dose for these products, and how much non-clinical data do we need to support combination therapy? How much can we

leverage the non-clinical data to make decisions about disease selection and
[01:07:30] optimal dosing? Some of this isn't necessarily limited to your first in human studies, but as development proceeds picking your patient population, and maybe smaller trials with more targeted populations.

I think all of our speakers with be touching on all of these issues, and our first speaker for this session is Dr. Kristina Howard, who is working on humanized mice models. I'm going to ask the speakers to go ahead and introduce themselves in the interest of time, and we'll probably hold most questions, unless it's a very burning
[01:08:00] question, until the panel discussion later. So thank. Dr. Howard.

Kristina Howard: Good morning, and thank you for ... I'd like to thank the committee for inviting me to speak, and hopefully I can provide a little bit of information about a different pre-clinical model. So the title of my talk is "checkpoint inhibitor induced
[01:08:30] autoimmunity in a humanized mouse model", and I recognize that there are lots of humanized mouse models out there so I'm going to first explain my model, but first and foremost I have to give you the disclaimer. The findings, conclusions, in this presentation have not been formally disseminated, so they do not represent agency policy or determination. So you can't use them for your submission at this
[01:09:00] point. Sorry. Okay, so I'm first going to talk about the model system that I'm using, and then I'm going to talk about data that we specifically have using the volume [inaudible 01:09:06] in that system, and them some general conclusions.

So the mouse model that we use is what's called the BLT mouse. Now many of you have probably heard of humanized mice before, but these models represent a CD-30 form mouse, meaning it is a severely immune compromised mouse that has
[01:09:30] human CD-34 stem cells infused, and what you end up with is a human immune system. However, it does not have a human thymus, so these cells are educated of mouse thymus, and you do not end up with a re-bust re-population of all of the cellular subsets that you would want to be present to actually evaluate toxicity and potential efficacy of a drug. So the model that we use is a little bit different. It's
[01:10:00] called a BLT mouse, not the sandwich, it stands for bone marrow liver thymus mouse, and the way this mouse works is we use fetal ...

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Kristina Howard: ... thymus mouse and the way this mouse works is we use fetal tissue for these. We get fetal thymus and fetal liver tissue. We give surgery to these mice. These mice are severely immune compromised. There are multiple numbers of models of these mice. There's the NOG mouse which is Techanic's version. The NSG mouse which is Jax's version. There are some slight differences in the genetics of these two mice.

[01:10:30] At present, there are many different knock in and knock outs on top of the NOG and NSG. We currently use the NOG, and I'll get into that a little bit later. What you do is they have surgery and during surgery we implant thymic and liver tissue underneath the kidney capsule. Over time, this will develop into an actual thymus that is human so that the T cells are educated bases on human thymus, not mouse.

[01:11:00] Either the day of surgery or three weeks later they have chemotherapeutic ablation or irradiation of their bone marrow so that we can give them the stem cells in the graft better. Basically, you then wait 8 to 16 weeks. Eight weeks is when we do our first bleed for these animals, and you test them for humanization and eventually you get a little person inside the mouse but it's really the immune system not actually the person.

[01:11:30] Some keys points here, we do not begin testing for engraftment until eight weeks after surgery. You want to have at least two sequential bleeds, preferably three in which you are showing increasing humanization and peripheral blood. Generally speaking if you look in the literature for laboratories that use these models, they generally use a twenty to twenty five percent threshold of humanization.

[01:12:00] We however, do not do that. Part of the reason that we do not is because we want to ensure that we have standardization between our studies and our groups. We use absolute human white blood cells per microliter of blood. That way we get much more consistent results and you can define differences rather than percentages which are always based on a denominator that's changing.

[01:12:30] This is just an example. Twelve weeks post-surgery this is the number of murine and human white blood cells per microliter. Blue and purple in this particular instance represent the human. The red is the mouse, which are mostly neutrophils that remain. This is human CD 45. At this point it's 46%/. Here's your CD 3 and your CD 20 positive cells and they're CD 4 and CD 8 T-cells.

These are all human and they are all functional and they work. This particular slide is based on an NSG model mouse. The NOG humanized slightly slower and with a slightly different balance.

[01:13:00] This is what your thymus looks like, except it's not where it normally belongs. It's underneath the kidney. If you then do flow cytometry on it, you have your double negatives, double positives and you single positive four's and eights, which looks remarkably similar to a human thymus if you look at the flow for it.

We use these models and typically speaking, this is generally what we see but the advantage that you get from these types of models versus a plain CD 34 mouse is that you actually do end up having monocyte and neutrophils in these animals, depending upon what base mouse you use.

[01:13:30] You have a more fully engrafted system that is able to interact between the innate and the adaptive, which Suzanne pointed out so beautifully in her talk. It's critical to have all components there in order to make a full evaluation.

Study design. We were interested in trying to understand how check point inhibitors would show up and whether or not we could identify toxicity in this mouse model. As many of you are aware, non-human primates have not been

[01:14:00] particularly informative in understanding toxicities of these drugs. In some cases, they've been given many fold doses of what humans get and at most they show perhaps some lymphocytic infiltration but they don't actually show auto immunity that's significant.

This was not to try to understand toxicities, this was a pilot study to determine if they could develop toxicity. We had two different base mouse models. The plain
[01:14:30] NOG mouse and then an NOG mouse that had human GMCSF and IL 3 knocked in. This mouse has a little bit more representation of neutrophils and monocytes in the mouse.

In each study we had, at least four mice per treatment group except for the controls where we might have had fewer and in the first study we had four different donors. That means four different individual humans were ... Their tissue was used to make the animals so that we have different people represented in the study.

In the second mice, we only two donors, only because that's all that was available.
[01:15:00] We were trying to determine one, could they develop auto immunity? Two, what type of dosing range were we looking at? Then also looking at strained susceptible. Did it really make a difference what strain we used?

The basic design is to look at a sailing control and we looked at doses of two and a half, five and ten mgs per kg. We dosed them twice weekly IP. We recognized that
[01:15:30] IP is not how they're dosed in the clinic, but since this was a preliminary study, we wanted to make it a little bit easier on ourselves. We also wanted to ensure that if we didn't see any auto immunity, it was not because we didn't try to induce it. It's because it failed.

I'm saying that on the offset, we recognize that we need to repeat these studies using an intravenous route and a less frequent dosing regimen. We looked at PBMC
[01:16:00] pre-study at day 14 and day 28 so we ran the mice for four weeks. We looked at spleen and bone marrow at necropsy as well as histopathologic evaluation of pretty much the entire mouse at necropsy.

These are our survival curves. On the left are the NOG mice and on the right are the ones that had the human GMCSF and bio 3 knocked in. These are not mice that died, these are mice that we euthanized because we had a 20% weight cut off. Once they lost 20%, we euthanized them. We didn't actually have any mice die on
[01:16:30] the study. This represents how quickly they lose weight and reached what we considered a terminal end point. Our goal was to ensure that when we did the study we collected all the data. It didn't do us any good if the mouse died and we couldn't collect any samples. We wanted to make sure we collects the samples.

The high dose group and the NOG's really went very quickly. They were the only group that actually looked fairly sick when they were getting this dose. Even this
[01:17:00] group, they lost some weight and we lost half the mice before the end. Even them,

they didn't look terribly sick at all. The remainder of the mice, while they may have lost weight, they didn't actually look ill. They just lost weight.

When we look at the percentage of PD1 positive T-cells, which is important because if we're not actually depleting the T-cells we don't know if we're seeing any effect at all. You can see in the saline mice that they retained their PD1 positive T-cells where as in each of the dosed groups in peripheral blood they were very
[01:17:30] close to zero if not zero throughout the study following dosing.

If you look in the spleen and the bone marrow at necropsy, you can see that essentially we did very good job depleting the mice. One thing that I would like to point out because when you dose humans obviously the only thing that you can check is peripheral blood and if you can get a biopsy sample that's the only thing that you have objectively to look at. Whereas when you do an animal study we're
[01:18:00] actually able to look at every different tissue that we dissect to determine how good the penetration of the antibody depletion was.

If you look at the literature there are many antibodies that when you give them, you may see full repression of that in the peripheral blood but then when you look at tissues, you find that you really didn't get a good depletion. Certainly for some of these solid tumors that you see in humans, you may not be getting good
[01:18:30] penetrants within the tumor which is why they may not be responding as well.

In looking at the mouse model that we're using, it is humanized. These are human tissues. We wanted to try to understand whether or not we got that level of depletion that we were hoping to get. The fact that we have very good depletion throughout the mouse was very heartening to us.

Looking at activation of T-cells this is ... On the let are PBMC and where we start
[01:19:00] here is at 100%. This is looking at where that individual animal was at the beginning of the study and then where did it go following its own baseline rather than using percentages because that doesn't give you a very good relative understanding since each individual may be different.

What you can see is that the two higher dosed groups are five mgs per kg and our ten mgs per kg group, both of them actually had significant increases in activated T-
[01:19:30] cells and peripheral blood. Whereas our low dose group actually ended up being lower than our saline group. Clearly, the low dose which is two and a half mgs per kg at approximately the dose that humans typically receive in clinical, was pretty similar to saline as far as activation and peripheral blood.

If you looked in spleen, this is the absolute count of human CD 45 RO positive T-cells that were isolated. You can see that in the spleen we had rather significant
[01:20:00] and dramatic increases in activated T-cells at our higher doses whereas our low dose really mirrored our saline group.

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Speaker 1: ... Doses. Whereas, our low dose really mirrored our saline group. And another comment here is that we made sure that each of our donors was present in each group, so that you could actually, essentially, look at them as a set of twins. So, every person got each dose of drug as well as saline, so you can look at that individual and see how that individual responded across a dose range. And so, when you're looking at these, you can actually see that these individuals had a

[01:20:30] much more potent response as you increase the dose of the drug. And in some cases the number of T-cells that were present that were activated were incredibly increased, more than tenfold over where they started. And, the adverse events that we observed: This is just a chart where the NOG strain of mice. And so we identified pneumonitis in pretty much every group. The low dose group ...

[01:21:00] Surprisingly, the low dose group actually, in many cases, had the worst pathology rather than the least pathology. And it's not because of the dose necessarily, it's because they lived the longest so they had more of an opportunity to develop auto-immunity. So the amount of auto-immunity we saw was not necessarily correlated to the dose of the drug, it was the duration in which it was administered. And I have some slides coming up to show you some of the pathology. So we observed

[01:21:30] pneumonitis in all of our dose groups. And that actually the most prevalent. In addition, we also saw hepatitis. Again, very prevalent. Interestingly, if you look the presence of hepatitis, we did not observe significant increases in ALT. But we did see lots of infiltrations of lymphocytes and histiocytes into the liver. We had nephritis. And I found it interesting that in the example that was presented earlier there was nephritis. We saw nephritis in these animals. We had some rather

[01:22:00] significant skin lesions so dermatitis in these animals, as well as adrenalitis in one particular individual, in both the low and high dose group. So looking at the pathology, and I'd like to try to time a little bit going through this, so looking at the pathology of the lung in each of these particular slides I'm going to show a couple of different tissues. The top individual is the saline control. On the left we have our NOG mouse and the dose of that particular mouse, the treatment group it was in. And on the right is the mouse that has the human GM-CSF/IL-3 knocked in. In this

[01:22:30] case it’s a 10 mg per kick. And these are representative, they're not necessarily the worst case or the best case, it's just a representative sample. So looking at this: This is lung. And what you can see, obviously, we have nice normal looking lung, lots of air, lots of alveoli. And we look at both our treated groups we tremendous inflammation. There is a lot of lymphocytic, monocytic, and histiocytic infiltration.

[01:23:00] And you lose a lot of the airways. And it's relatively equivalent between both strains of mice. We had one mouse that at final necropsy was a low dose mouse. And you could almost not detect an alveolus in the entire lung section that we looked at. What was interesting is these individuals looked totally normal. They weren't having trouble breathing. They were running around. They were eating. They did not look abnormal. So even though the pathology was absolutely terrible, they didn't actually clinically look bad. Looking at the skin, our saline control, and

[01:23:30] on the left and the right. And what we observe here is that we have a lot of hyperkeratosis, so that's this pink area here. As compared to the normal single cell layer of skin. There is a lot infiltration and thickening, so we have an epidermal hyperplasia. We have hydropic degeneration, which is a fancy word cellular edema.

[01:24:00] And what you see is a tremendous thickening here. You see a lot of infiltration of leukocytes, of various types into the cellular areas. And overall it really doesn't look good. And the skin on these animals did look ... It was beginning to look crusty and like it had a dermatitis. But it didn't look terrible. Not anything close to what the histopathology looked like. When you look at the liver. In the liver these all centered so that you can see the portal triad here. And this in course is normal. And what you're looking at here is a tremendous amount of inflammation. And it's
[01:24:30] primarily lymphocytes and histiocytes, both in this strain of mouse and this strain of mouse. And we saw quite a bit of this. We actually did see some granulomas. And if you look can see that there is some necrosis within the liver. And there was not a significant increase in liver enzymes in these animals.

[01:25:00] Looking at muscle: We saw this is normal muscle. And we collected muscle associated with collecting bone marrow and sternum. So we collected the femur and we collected the sternum. And what you can see is there is a myositis present in both of these strains. It was also present that we had a lymphocytic infiltration in the bone marrow itself. And it's unclear if that was the muscle going into the bone marrow or if it was the bone marrow going into the muscle. But we definitely saw this infiltration in both places. The animals had no problem running around. So
[01:25:30] again there were no real clinical signs that we could observe. And last but not least, the pancreas. And I do want to point out, these images at all at 10x. This is not a difference in magnification. The reason that these look so different is that this is severe pancreatic atrophy in these animals. And that atrophy in the particular individual affected both the exocrine and endocrine pancreas. And in this individual it's a little bit less far along. It primarily affects the exocrine pancreas first and then
[01:26:00] the endocrine. And the point that I wanted to bring up about this is if you're affecting exocrine pancreas you could develop exocrine pancreatic insufficiency, which can cause diarrhea. And diarrhea is something that is associated with some of these checkpoint inhibitors. And many times we associate it with colitis. But if we're not necessarily looking for EPI it's possible that it could also be associated with damage to the pancreas, rather than necessarily just colitis. But again, these
[01:26:30] particular animals had no diarrhea and they had no clinical signs that we could observe. But as you can see, there was a significant amount of damage. And most of the cells here again, lymphocytes, monocytes, histiocytes.

Kristina Howard: [01:27:00] And one comment that I did want to add there, there is a recent report by Colzer and All that's in the Journal of Immunotherapy of Cancer. And in that, they have an autopsy report of a patient who had originally been treated with [inaudible 01:27:04] followed by Nivolumab. And in that particular individual, they identified pneumonitis, hepatitis, myocarditis. They had been treated originally with [inaudible 01:27:13] then Nivo. And this person died of metastases. Not necessarily of immuneiated pathology. But what was interesting in that particular individual, they did not complain clinically, of really, any problems. And yet when they did the
[01:27:30] pathology and autopsy, they found significant immuneiated pathology in many organs. And the organs which were affected, and if you look at the pathology pictures, they actually look very similar to what we saw in our animal model.

So, summarizing, Anti-PD1 Nivolumab effectively neutralizes PD1 on T-cells in our immune humanized mouse model. They experienced adverse effects in a dose dependent manner. And by that we mean they lost weight and had to be removed
[01:28:00] from study in a dose dependent manner. The T-cells became more activated as the drug was administered, so the longer we gave it to them, the more activated they became. And they can experience profound auto-immunity in response to checkpoint inhibitors therapy. And we still are doing more studies with this. So this is only the opening study. It's not the ending study. And we are looking at other checkpoint inhibitors, as well as combinations thereof.

[01:28:30] And following up, I would now like to initially provide you a segue way to our next talk. So one of the reasons that a model like this is so important is because when you look at drugs like checkpoint inhibitors, the other end of the molecule that's not binding the actual drug target is the FC receptor. And those FC receptors are species specific. And part of the reasons we may not be observing the appropriate toxicity and pathology that we see in humans in these other species is because the FC receptor is not the same. In the immune humanized mice, their immune cells
[01:29:00] have human FC receptors. And that may be integral in understanding that pathology. In our next talk we're going to address a little bit of information on the FC receptors related to how these checkpoint inhibitors work.

And with that, I'd like to thank my colleagues at FDA: James Weaver, [inaudible 01:29:18] (she is the pathologist who read all this), as well as Kathy Gabrielson (she also assisted in reading pathology), Ken Rick and Kathy (who helped process the
[01:29:30] samples). And to Whitney and Payton who helped instigate these studies in the first place. Thank you.

Alan Korman: Good morning. My name is Alan Korman, I'm the vice president of Immuno-
[01:30:00] Oncology at Bristol-Myers Squibb at our California site in Redwood City. I'm going to try and ...

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Section 10 of 46 [01:30:00 - 01:40:04] *(NOTE: speaker names may be different in each section)*

Alan Korman: I'm going to try, in maybe 15 minutes, summarize 20 years of experience on developing antibodies to a variety of negative regulators on t-cells as well as
[01:30:30] agonist antibodies to various co-stimulatory receptors on t-cells and probably breeze through what we think might be a better model for analyzing activity of antibodies. Work on CD40 together with [Ravage 01:30:45] Laboratory where we have a mouse that has human FC receptors together with human CD40 and FC
[01:31:00] modifications of those antibodies.

In general, after a number of years of dealing with many of these issues we recognize that the inbred mouse model really has few toxicities when using antibodies to various negative regulators like CTLA-4 PD1 et cetera. We sometimes
[01:31:30] use autoimmune-prone mice to understand how these antibodies may make autoimmunity worse and that's been particularly insightful using the NOD model. For example, PD1 can induce rapid diabetes in the NOD model, while actually CTLA-

4 does not in that setting.

There are a few rare examples of antibody-mediated toxicity in normal mice. When
[01:32:00] moving to the Cynomolgus macaque studies, they generally have not predicted any of the toxicities that were seen in man with the initial development of ipilimumab and PD1 as well. We really have only one example where, in monkeys, a high-dose combination of anti-PD1 and anti-CTLA4 reveal toxicities that were augmented in
[01:32:30] human clinical trials. As I addressed in a similar workshop in June, the differences between the mouse, Cynomolgus, and human FC receptors, with respect to binding of the different isotypes of the antibodies we use doesn't really allow for a good comparison between mouse and human and Cyno-species. I'll point out a couple of
[01:33:00] examples there.

The next few slides are an attempt to summarize lots of work by former colleagues at Medarex and the disease safety evaluation group at BMS, many of whom are in the audience. We look at both in vitro and in vivo mouse tumor models, evaluate
[01:33:30] the mouse knock outs, and try to develop a surrogate model for efficacy in non-human primates, essentially a vaccine response. Those tests have evolved over the years from simple vaccination with Hepatitis B surface antigen, to newer models where we can follow antigen-specific t-cell responses. Then I have a little arbitrary table of efficacy and toxicity in man.

[01:34:00] What we knew from CTLA-4 was that knock outs in both t-reg, as well as all t-cells, can cause lethal toxicity in 4-6 weeks. However, you never see any toxicity when you give even the most potent CTLA-4 antibodies to mouse. You have a variety of
[01:34:30] anti-tumor effects and we could see vaccine exponentiation in the monkey, but we rarely saw any toxicity. None of the colitis events seen in man, hyper-pituitarism, that I'm sure we'll adjust over the next couple of days were observed in the monkey - some rare cases. Again, an arbitrary toxicity level here for ipi in man.

[01:35:00] With PD1, there are some strains that have a strain-specific lethality, although, this may not be seen in all the knock outs. This is a knockout of PD1 by the Honjo Lab, but it hasn't actually been reported in other knock outs by other groups, so it may
[01:35:30] be unique to that strain. Anti-PD1 can cause autoimmune activation in the NOD mouse and it's not a particular vaccine potentiator [with like 01:35:38] water in non-human primates. I think we now know that there is good, broad efficacy of PD1 and perhaps less toxicity than CTLA-4. When we introduce the combination
[01:36:00] into the clinic we knew that, in mouse models this was a highly active combination of these two different antibodies and we saw toxicity for the first time in non-human primates. We think that that efficacy is better, but at the cost of higher immune activation. Again, an example of that trial is shown here where it was only
[01:36:30] in the high dose group of CTLA-4 and PD1 that we saw diarrhea for the first time at a high frequency in some of these animals concurrent with various pathology in some gut tissues, as well as increases in spleen weight in that high-dose group.

When we began to develop the lag PD1 combination, this is actually the last time
[01:37:00] that we did combination studies with PD1 and another molecule, now we generally

do those testings in the clinic. The second generation of negative regulators, in general they have no phenotype and very little activity on their own, but they do show good combination activity. And interestingly, the combination of lag and PD1
[01:37:30] knock outs, again, using the Honjo PD1 knock out, actually is lethal. In monkeys there is very little toxicity. We did observe some minimal lymphocytic infiltration into the choroid plexus and these trials, using lag mono therapy and PD1 combinations are in progress in the clinic.

[01:38:00] With respect to agonist , one of the most toxic compounds that had been observed in man was anti-CD137 and that was removed from the clinic and came back with a reduced dosing schedule. That actually had no toxicity in monkeys, either alone or actually, an additional study, in combination with CTLA-4. However, we can observe
[01:38:30] some liver inflammation with certain anti-CD137 antibodies in the mouse. In general the mouse knock outs are not relevant for these agonist and there was no testing of the combination of CD137 and PD1 in non-human primates, but testing is going on with low dose and PD1 combinations in man. We've also introduced a gitr
[01:39:00] antibody into the clinic. Those studies are in progress and perhaps it has a modest vaccine exponentiation, but no toxicity in the monkey models.

In general this experience has not been that informative and so we've looked for
[01:39:30] other models to study the role of toxicity and efficacy and this is using this knock in mouse model for CD40 developed in the Ravage Lab. CD40, as you know, is a very potent immune potentiator, it had been in the clinic as an IGG2 antibody developed by Pfizer and that antibody can cause thrombocytopenia, platelet
[01:40:00] reduction, reductions in lymphocyte counts, and ...

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Section 11 of 46 [01:40:00 - 01:50:04] *(NOTE: speaker names may be different in each section)*

Speaker 1: ...counts and cytokine release and reach the maximum tolerated dose, that was quite low.

Let's move on, so one of the important observations in this field was that in the [inaudible 01:40:24] showed that the activity of anti-CD40 antibodies required
[01:40:30] binding to FC inhibitory receptors FCR2B. So, when you either potentiate a vaccine or look at anti-tumor activity in this case mouse IGG1 antibodies were the most potent antibodies.

This particular antibody, this is where both [inaudible 01:40:52] at BMS a very
[01:41:00] commonly used antibody in the mouse anti-CD40 FGK4.5 closes very minimal reduction in platelet counts, minimal toxicity in the liver suggesting that this mouse antibody doesn't completely replicate what might be seen in the human
[01:41:30] experience. So together with Jeff's lab we analyzed a panel of new CD-40 antibodies, he studied variants of the Pfizer antibody as you know they are rarely variations in the activating receptors FCR2A and 3A and that can also impact dramatically the activity of antibodies. So we studied of these antibodies in the
[01:42:00] CD40 transgenic mass.

Some of the variants that we looked at are related to changes in the ability to bind the inhibitory receptor vs. the activating 2A and 2B receptor, these are mutants that are known as B9 and B11 and just to quickly point out, as compared to human
[01:42:30] IGG1 which binds multiple FC receptors, these variants increased the binding to 2B and some of the variants maintained the binding to 2B but alter the binding of 2A changing the ratio binding to the 2B to 2A, there are other subtle changes as well in bindings to human FCR1 like these variant FCs. So what I want to focus on here is
[01:43:00] that we have a panel of different antibodies blocking and non-blocking for human CD40 which are altered in their FC region and which are altered in their ability to bind these different FCR2B receptors, they are all activating DC in vitro but you can't see the effect of those FC receptor changes in that dendritic cell acid.

[01:43:30] So what we showed here along with Jeff's observations on the Pfizer antibody is when you make these variants that increase the binding to FCR2B but most importantly when you increase the binding to FCR2B and reduce the binding of the FCR2A you actually increase the activity of those antibody in the vaccine response,
[01:44:00] I'll show you the anti-tumor response momentarily, but they also cause the most dramatic reduction in platelets.

As you know platelets express CD40, they do express FC receptors, so the goal is actually to make the most potent antibody and then perhaps reduce the level of dosing so that one doesn't experience these adverse events. So, we are studying
[01:44:30] this further and its impact on thromboembolic events. Nevertheless, these antibodies the B11 of the Pfizer antibody as well as these new CD40 antibodies have a higher anti-tumor activity than the human IGG1 or the G2 or other variant of that.

[01:45:00] So I'll leave you with my admonition that I also gave in June, isotype matters, the epitope matters and we need to understand these activities in order to develop the most potent antibodies for our immuno-oncology drugs. Thanks to many of my
[01:45:30] colleagues and I look forward to the next two days here. Thank you.

Marc Theoret: So, we're just going to go ahead and have a break. We are running a few minutes behind here so, let's actually go ahead and... program we get started at 10am and I'll invite Dr. Prell to come up here and begin the second set of presentations followed by the panel session for this morning. Thank you.

[01:46:00] Okay, we're going to go ahead and get started, with that invite Dr. Prell to continue with the presentations in session 1 here.

[01:46:30]
Rodney Prell: So, my name is Rodney Prell and I'm from Genentech, and I'm the principal Toxicologist there and I'm also the therapeutic area lead for non-clinical safety evaluation of our cancer-immune therapy pipeline. So, first of all I'd like to thank the organizers of the sessions, to inviting to give a talk today. I'm going to talk about moving beyond NOAEL as first human dose selection and as was eluded to by
[01:47:00] Whitney in earlier talks, we started to take an approach of NOAEL a long time ago,

and once we got into cancer-immunotherapy we realize that that approach probably isn't appropriate anymore and so I'm going to give you 3 examples, and it's not working, ah there we go.

[01:47:30] 3 examples of programs that we've forwarded gone through the non-clinical safety studies and have entered the clinic and, I'm not going to go over the biologies of these things right now because they were nicely described earlier, but the one molecules I'm going to talk about are: An agonist anti OX40 and antagonist PDL, anti PDL1 and then a bi-specific molecule which you'll hear more about later and these are the ones that actually bring together a T-cell and target cell. In each of these what you'll see is that we used a different approach to select first human

[01:48:00] dose and so, I think that's the key message that I want to get across is that, it's going to be an individualized approach with every molecule.

So first, case that used a Atezolizmuab which is our anti-PDL1 inhibitor and I'm going to go straight into the non-clinical safety program. Suffice it to say that we had set up the pharmacological models, we had great activity, and then we went into our non-clinical safety program and with Atezolizmuab we actually had cross

[01:48:30] reactivity in both mouse and humans so, at first we wanted to see, was there a potential for using both species for GLP studies and to support clinical development. So, we first did a pilot study in 2 strains of mice, one was Black6 mouse and we selected this because it was the strain of mouse that the non-clinical pharmacology programs were conducted in the tumor models and then the CD1 strain of mouse which is the standard mouse, outbred strain of mouse, that you

[01:49:00] used for safety assessment. We did this as a pilot study, you'll see why later on, and then we did a GLP study where we looked at both IV and subcutaneous administration and using a dose range of 5 to 15 mg per kg.

Importantly because it was immuno-oncology or because it was immuno-modulator, we really did a lot more in terms of immuno-monitoring in these

[01:49:30] models. In addition to the standard end points we looked at explanatory endpoints in this and that was Immuno-phenotyping and that was beyond just the TBNK panel, this is activation phenotype of T-cell subsets. So looking at effector memory, central memory, looking at CD2569 on both CD4s and CDAs and looking at serum cytokines. Again, trying to understand, what may or may not be happening with these molecules when you go into your talk studies.

So interestingly the finding that we had in our 15 day pilot study, so this was

[01:50:00] administered weekly for two weeks. We actually did find a neuropathy...

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Section 12 of 46 [01:50:00 - 02:00:04] *(NOTE: speaker names may be different in each section)*

Rodney Prell: For two weeks. We actually did find a neuropathy in the sciatic nerve, and interestingly it was only observed in the Black-6 strain of mouse. We didn't see it at all in the CD-1 strain and when we went back in the literature, we actually saw that if you look, and it was reported by Yoshida et al, that if you actually make it a PDA1 knockout strain on an H2B background, so an MHC that's identical to the C57, they

[01:50:30] actually did notice peripheral neuropathy in that strain, which eventually led to high-length paralysis out at about 26 weeks. Here you can see the sciatic nerve in the normal control animal and you started to see this digestion. The chambers and the mononuclear cell infiltration ... This is right after ... This is two weeks later. You can see in the recovery phase, even after recovery we still had it in a dosage-dependent fashion.

[01:51:00] Now, we didn't go forward with the mouse as a GLP tox study and I'm not going to show the data, but what happened is that this, again was our human candidate, so it's a humanized monoclonal antibody, we had such high immunogenicity in the mouse that even at 50 mg/kg we were losing exposures 1 day after the third administration. We didn't feel it was an appropriate model to take forward to do longer-term studies and so what we ended up doing then is going into [cynos 01:51:24] for our GLP studies and I showed you the study design outline in previous
[01:51:30] slides and again really the major take-home from that was it was very clinically well-tolerated, very similar to what [Alan Korman 01:51:38] just demonstrated before.

Non-clinically, these molecules are very well-tolerated and it was only when we looked histologically that we found arteritis happening in 1 subcu animal that was given 15 mg/kg and then 3 animals that were given atezolizumab at 50 mg/kg and
[01:52:00] that was either by subcu or IV route and the interesting thing is that we had a conversation of was this an ATA-related effect or was this a pharmacological effect? I think from the end-point of ... It's known that arteritis or peri-arteritis or vasculitis, there's a low underlying level that occurs spontaneously in non-human primates and what we observed was that in our study, we just increased the frequency of that occurrence. We didn't increase the severity and we didn't
[01:52:30] increase really introduce novel tissues that were affected by this and so it was very similar to what you saw in the spontaneous control or what happens in controls. What we felt is that this was actually an on-target pharmacology and so therefore we actually used it as a non-target pharmacology and as mentioned here, there actually was not observed at the low-dose or in the controls. We really did feel that this was an on-target pharmacology. What I will mention also is that we have now
[01:53:00] conducted a chronic toxicity study, a 26-week study, and we saw exactly the same thing in 1 animal each at 15 mg/kg and 50 mg/kg. We repeated this finding and so it really, in our mind, was consistent with an on-target pharmacology. The relationship between ATA and this finding is really difficult because pretty much every animal was ATA positive, yet we only had this finding in a few animals.

[01:53:30] How did we go about selecting first-in-human dose when you really don't have a lot of pharmacology in these models and so we looked at a lot of different approaches. Cytokines, we looked at an in vitro cytokine release assay. We saw no indication of cytokine release. We did the in vivo toxicology program, like I said, we considered the 5 mg/kg as our NOAEL which would have given us a reasonable starting dose at 0.3 mg and with a safety factor, but when we also included receptor occupancy,
[01:54:00] what is very common is these particular molecules or this class of molecule, it can become saturated at extremely low levels in the periphery. When we did this

modeling, 0.05 mcg/mL was projected to have serum concentrations sufficient to have 100% receptor occupancy. When you looked at our proposed starting dose of 0.3 mg over on the right-hand slide over here, that would have predicted that we would have had saturation for 2 months at the first-in-human dose.

[01:54:30] We actually had a very nice conversation with the FDA and came to a compromise that said okay, we can go in at 0.01 mg/kg starting dose which would project to be 0 days above our old 90%, but we have some level of receptor occupancy above 50% and the other thing that was agreed upon is that we could actually do single-
[01:55:00] patient cohort dose escalation from the 0.01 mg/kg up to the 0.03 mg/kg which was our original starting dose. This was an example of using a different, a nonstandard end point for first-in-human dose selection for an antagonist antibody in this classification or class of compounds.

The next compound or next molecule I'm going to talk about is MOXR0916. It's an anti-OX40 agonist antibody, so again, it's meant to stimulate the OX40 receptor. Here I'm going to show a little bit of the nonclinical data because as you'll see later
[01:55:30] on, we actually use the pharmacology models to project our first-in-human dose, not the nonclinical safety. We took it all into consideration, but it's really based on this and I'll walk you through this a little bit mores so you get an idea where I'm going. Here we did a very nice dose response in a model of EMT6 syngeneic tumor model where we dosed the animals a single administration of a surrogate molecule
[01:56:00] with 0.11 or 10 mg/kg and you can see that there's an indication that there's a dose response when it comes to tumor killing and when you look at the number of or percentage of complete responders, you can see that 0.11 and 10 again, gives you an indication or suggestion that there's a dose response occurring whereas at 0.01 which we didn't even include in the left-hand part of the slide, but if you look at the overall survival, 0.01 is actually almost superimposed with the control.

[01:56:30] So, here we have a dose-response curve where it looks like 0.01 mg/kg is a single administration is not effective whereas 0.1 mg/kg is effective. Then, again, apparent dose response if you increase the dose levels. When we look at PD effects within this same model, again, 0.01 mg/kg, when you look at Tregs in the blood or in the tumor, you really don't see any effect on the depletion of Tregs which is one
[01:57:00] of the potential mechanisms of OX40 engagement. However, when you start to look at doses in the 0.1 to mg/kg range, you can see again that there's an apparent dose response and a reduction of T regulatory cells in this tumor model and similarly you see proliferation of both CD8 T cells in the blood and in the tumor at dose levels above 0.1 mg/kg whereas the 0.01 mg/kg, again, was not effective. Again, if gives us a range of about 10-fold of where we have that pharmacological effect.

[01:57:30] When we went into the cynomolgus monkey, we selected doses that were within that range or we felt was in a range based on projected PK exposure which is represented by the lines here and what you can see are the actual PK are the individual triangles or squares and other symbols and what you can see pretty
[01:58:00] obviously is following the first dose there was very nice dose dependent exposures,

but after that first dose, you start to see loss of exposure in both the low and the mid-dose and the low dose being 0.5 mg/kg and the mid dose being 5 mg/kg whereas in the high dose of 30 mg/kg we were able to maintain exposures for the entire time. When we look at receptor occupancy in this model, again you can see at the first dose, even at the lowest dose tested, we had 100% receptor occupancy for the first 2 weeks and this was a q 2 week administration, but following that the
[01:58:30] induction of anti-therapeutic antibodies or ATAs really started to impact the receptor occupancy which correlated very nicely with the lack of exposure following the subsequent administrations.

In essence we were able to maintain receptor occupancy at this high-dose level and again in the GLP study where we continued to do this, this was very well-tolerated clinically. Again, you have a model that you have ... And this is an agaonist
[01:59:00] antibody. You have a system here where it was completely well-tolerated. You have 100% receptor occupancy for well over a month and there's no toxicological effect.

In this case, when we took all the information and started looking at it, it's like well what's the appropriate method to project first-in-human doses. When we looked at the different approaches, again, the NOAEL approach, we could've considered 30
[01:59:30] mg/kg or NOAEL and that would've been fine, but when we started thinking about it, OX40 is transiently expressed, we used healthy [cynos 01:59:33], no signal 1 for an immune system to respond and upregulate this molecule and there's really an uncertainty around what's the percent receptor occupancy and what's the pharmacological effect. We ruled that one out. We looked at in vitro again, the cytokine release assay, and again saw no indication of on-target cytokine release,
[02:00:00] so that really wasn't a sensitive model. We did look at receptor occupancy and I just showed the data and again, we had ...

Section 12 of 46 [01:50:00 - 02:00:04]

Section 13 of 46 [02:00:00 - 02:10:04] *(NOTE: speaker names may be different in each section)*

Speaker 1: Look at receptor occupancy, and I just showed the data, and again we had 100% receptor occupancy at the highest dose which is well tolerated. Again, even at the lowest dose during the first administration, we were 100% receptor occupied, so that relationship really wasn't flushed out very well. We went back to the pharmacology model then and said, "Okay, what do we see?" When we actually looked at it, that was the model that actually gave us the PD effect, the dose
[02:00:30] response, and we actually had an indication of where the pharmacological effect level was. It wasn't based on receptor occupancy. It wasn't based on navel, but it was actually, and the term we coined was the MPAD, the minimum pharmacological active dose, it was really based on that dose of .1 mg per kg that gave us some activity. Maybe not the most potent activity but some level of
[02:01:00] activity. Then we related that to the first in-human dose by scaling for the differences in affinity as well as the difference in clarent. We took all the PK parameters, the affinity parameters and modeled that into what projected our first in-human dose. That resulted in a first in-human dose of about 200 micro-gram flat dose or about .002 mg per kg.

Again, if you look back at what we did with the [inaudible 02:01:22] map, that was .01, so now we're at roughly tenfold lower than that with the agonist antibody.

[02:01:30] Now I'll give you the last example of a bi-specific antibody. This is going to be a little bit different approach. These are the ones again that bring the T cell and target cell in proximity and directly activates the T cell. These are ones that are very, very potent. This is the concepts of the molecule I'll talk about today is the CD20, CD3 bi-specific. Again, the idea is that this antibody, your bi-specific antibody bridges

[02:02:00] the T cell and the tumor cell. That proximity sets up the immunological synapse and causes the T cell to de-granulate and kill the tumor cell. That is the concept. Importantly for us, both the targeting arm and the CD3 arm were cross reactive and non-[inaudible 02:02:14], so we could actually use non-[inaudible 02:02:16] as both a pharmacology model to look for B cell depletion as well as a toxicology model.

First I'll show some of the in vitro data that we had in the sense that we looked at a

[02:02:30] panel of B cell lymphoma cell lines and looked at the potency of adding our bi-specific molecule in vitro and basically just looked at a [inaudible 02:02:38] curve. What you can see is that depending on what level of CD20 is expressed, there's a fairly nice correlation with the potency of this. At some of the lymphoma cell lines, it expressed higher levels of CD20, actually had killing activity down to about .1

[02:03:00] nano-gram per mil in this [inaudible 02:03:01]. When you compare that to the depletion of human donor PBMCs, again right here we're just basically looking at peripheral B cell depletion. Again, you can see that some of the activity happens at concentrations down in the nano-gram per mil concentration or sub-nano-gram concentrations, and on the right hand side is just the summary of the data in the sense that the EC50 is really around that two to three nano-gram per mil

[02:03:30] concentration, and this is for peripheral B cells. This isn't the tumor cell line, but this is the B cells that we have.

Again, you can see the potency of this molecule is extremely high. When we went in and did single dose GOP talk study in cymose, because of the cross reactivity of both arms of the molecule, we were actually able to observe both the desired pharmacology. In the upper slide here, we have the B cell depletion, and you can

[02:04:00] see that that remains for the duration of the study in terms of it was a single dose, and we had a follow up period. This gets back to the point I think that Allen brought up is when you look at systemic versus tissue, we're getting peripheral B cell depletion, but we weren't getting complete B cell depletion in the spleen. Again, there's a part that the distribution and penetrations of the molecule that's

[02:04:30] systemically gives you a very high level. In the tissues where you're looking, you may not see that, so again there's that difference and dichotomy of that.

What we did see is that at the .1 mg per kg we did get peripheral B and splenic B cell depletion at day eight. We certainly get a rebound at day 20 whereas in the two higher doses we still had depletion out at day 22. Interestingly again, at .01 mg

[02:05:00] per kg, you can see that we had a depletion of the B cells in the periphery but not in the spleen. When we look at T cell activation, another indication of the PD effect, we saw again very nice activation as indicated by CD25 and CD69 expression in a dose dependent manner. You can see that CD4 positive cells. You see activation

even at the low dose of .01 mg per kg whereas in the CD8, at the CD8, so you don't
[02:05:30] see it in the CD4, sorry. With the CD8, you still see an activation marker of CDC925 even at the lowest dose. When you look at cytokines again, you see a very nice dose response where at the lowest dose of .01, you really don't see much of a cytokine response. Once you increase that dose to .1 mg per kg, you start seeing a systemic cytokine response.

Basically what this says is that each molecule you have to understand the biology, you have to understand the mechanism of action, you have to understand what the
[02:06:00] pharmacological relevance is, and how do you base that first in-human dose. Well in this case, we did use a navel approach because we didn't really feel that the no AL approach ... This was still well tolerated in cymose at the 1 mg per kg in terms of the classical toxicological measurements. We had great pharmacology, and it was well tolerated, but we also didn't feel that it was the most appropriate approach. Receptor occupancy in this case wasn't the most appropriate approach. We did have double transgenic mice that provided some measure of pharmacology, but
[02:06:30] the relationship and translatability of that mouse model is always going to be difficult. We really did use the in vitro EC20 of the T cell proliferation and cytokine production and killing to set that first in-human dose.

In the absence of time because I'm almost on time, it really is looking at this as individual programs and taking the appropriate approach that individual molecule.
[02:07:00] The question moving forward is is this the right approach for every molecule, and how can we differentiate CIT or immuno-oncology drugs as different enough that we can take different approaches and not use the same approach for each one. These were just examples of how we took that approach. I'm sure there are other approaches out there that are just as relevant, so with that I'd like to acknowledge all the people that worked on the [inaudible 02:07:25] map, the mocks, and the CD20, CD3 bi-specific team. Thank you.

[02:07:30]

Tim MacLachlan: Okay. My name is Tim McLachlan. I'm at Novartis, and I'm going to as comprehensively yet succinctly give you an overview of some of the nonclinical safety issues for T cell immuno-therapies. I think on the heels of what Rod was just
[02:08:00] telling you. Here we're talking about a situation where we have no basic approach, so we have to understand what's feasible, and if it's feasible, does it mean we have to do it? We have to then understand if it's translatable.

Nope, wrong way. There we go.

Okay, so I think the first presentation gave you a little bit of an overview of the T cell immuno-therapy field, but just to give you a crash course here. They fall into
[02:08:30] two different flavors generally. Right now you have the first general category that came up several years ago where you're using the T cell receptor that recognizes tumor antigens in the MHC. These are now being genetically modified to more efficiently recognize those peptides, and the more recently you have taking advantage of [inaudible 02:08:45] antibody therapy and taking that variable

domain and latching it onto a chimeric receptor that has different components of the T cell receptor and other co-stimulatory molecules. These we call CAR T cells, chimeric antigen receptor T cells.

[02:09:00] These therapies are generated by taking the T cells out of patients, culturing them, and then introducing these receptors into the cells by MRNA or by lento viruses, and then culturing them further, and then administering them back into the patient. Once they're in the patient, they will then recognize those antigens and then expand, secrete cytokines, recruit additional inflammatory cells, and then kill the tumor. You can imagine this is a very complicated bio-pharmaceutical. You can
[02:09:30] imagine that evaluating this non-clinically from a safety perspective is also going to be very complicated.

I think David Porter is going to talk a little bit about the Novartis Penn cart programs a little bit later on, but just to point out that these are very effective. This is our first program with Penn. This is the cart 19 or CTLO9. As you can see, they expand very robustly. This is in the first paper. The first three patients that were dosed with this expand very robustly. They deplete the systemic B cells as well as
[02:10:00] the B cells in the periphery as well as getting rid of lymphadenopathy.

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Tim MacLachlan: B-cells and the periphery as well as getting rid of lymphadenopathy. The toxicity concerns fall into a couple of different categories and the first of which is where that car or that TCR is recognizing the target and that target is on the tumor. The most classic example of this is cytokine release. Particularly for the liquid tumors that we go after.

Here you can see that we're getting cytokine release not only from those T-cells expanding and secreting cytokines but also from a tumor lyco syndrome of
[02:10:30] depleting the B-cells. This is beginning to be well understood. It's largely controlled in the clinic by treatment with antibodies like tocilizumab and steroids. Although you may have heard in the press that we're starting to see more and more things like neurological toxicities. Things like blinatumomab has been observing in the clinic for some time now. It's possibly linked to some cytokine release and we need to understand this much better as we develop newer forms of carts.

[02:11:00] A second category of this is where that TCR or that cart is recognizing the target but it's off tumor. It's that target that is present on normal tissue as well. We've already hit some of the low hanging fruit. Things like CD 19 where it's not expressed on solid tissue and things like that. We want to go after additional target where that target may be expressed on normal tissue.

This has been seen in the clinic already as evaluated here in a review article recently published. Both for the TCR and the car platforms, this is some of the Mart
[02:11:30] 1 antigen and dermatological toxicity as well as a carbonic and hydrous 9 car which resulted in some liver toxicity there.

A lot of these toxicities are temporary, self-limiting. There have been some deaths with some TCR related T-cell therapies. Some of these characteristics come from another category of off target and you're hitting, or I'm sorry, off tumor and it's not hitting the actual target. You might get cross reactivity to a different antigen in the
[02:12:00] MHC or to a different antigen via the car.

What do we do from a non-clinical perspective in assessing the risk for toxicities, either on target or off target? There's a lot of different ways that we could approach this. We could approach it from a classical sense that we do for other pharmaceuticals but this is going to be exceptionally complicated given the complexity of the therapeutic.

[02:12:30] The first step that we do is a fairly straight forward approach and a lot of the data that we're currently generating and supplementing in our IND submissions for some of these newer targets we're going after. It's quite simple. Understanding where your target is. Having a very deep understanding where your target is expressed such that you know that it's either just going to be on the tumor or are there different tissues that you're going to have to pay close attention to that are off tumor?

You can leverage obviously different RNA evaluation or protein assessment events
[02:13:00] like IHC, ISH and flow cytometry. We're also starting to consider whether or not there's any cross reactivity of the TCR or the car. When the car, this is something we've been doing for a long time with monocle antibodies, evaluating how specific that monocle antibody is to the target.

For TCR's you can do things like MHC petite hematology screens and for cars you do things a lot like we do for monocle antibodies. We're starting to utilize things like
[02:13:30] chip based interaction [inaudible 02:13:28] like those provided by retrogenix. We at Novartis have started to supplement our IND's by taking the SCFV portion of that receptor, purifying it and putting it as a probe across those retrogenix arrays, looking to make sure that the only proteins that we get interacting there is the target we're going after.

In these arrays, they claim to have all of the extra cellular express proteins there, up to 4,500 proteins. Some of our colleagues in the field such as Chris Horvath at
[02:14:00] Bluebird Bio has attempted to take the car itself and use that as a probe. The SCFV in the context of the T-cell and use it as a probe and he was able to find that their CD 19 tool car there was able to very nicely light up the CD 19 dot on that but not in other similar receptor dots.

The gold standard obviously is putting these kinds of materials in animals. We talked a little bit about that this morning for some of the more standard modalities like monocle antibodies. How do we do this for autologous T-cell therapy? Very
[02:14:30] often, obviously, in an efficacy perspective, our pharmacologists are taking these cells and putting them into NSG mice that have a xerographic tumor on them.

It's possible that you could look for some safety events there, although those of who have worked in monocle antibodies for some time know that there's very rarely there's cross reactivity of SCFV's against the human target. Cross reactivity to the rodent target.

[02:15:00] You may be getting good efficacy on that xenographted human tumor but it's not recognizing the mouse antigen in most cases. Of course in these NSG mice you're also lacking any contribution of the host immune system that may contribute to that effect.

Another option is that we do what do with a lot of our toxicology studies which is you put them into healthy, immunocompetent animals. Of course in this case we need to do what we're doing in the clinic as well. You need to create a test article for each individual animal. It has to be autologous.

[02:15:30] In addition, the means by which we put those genes into cells for the human may not be effective for animals. The lentiviruses we use for humans will not infect monkey cells. Will not infect mouse cells. We could even approach from a dog animal perspective. Those reagents won't be useful for that either. We need to come up with new reagents there.

[02:16:00] The conditioning regimes used for humans may not be translatable to animals as well so we have to optimize that. The culturing conditions of the cells prior to dosing and then the dosing regimens as well. This hasn't stopped some of our colleagues in the field from attempting this and publishing and just in the last year, year and a half, there's a paper recently published with immunocompetent mice using cars against the natural killer receptor, NKG 2D where they were able to observe significant pulmonary toxicity with that and I'm not sure if that's moved into the clinic yet but that certainly identified one potential risk there.

[02:16:30] Our colleagues from Stan Ridell's lab at University of Washington last year published a non-human primate model where they're intending to go after the Rora 1 target to create a non-human primate Rora 1 cars. Administer them to the animals got engraftment of the cells and got some measure of pharmacology there and some measure of toxicity as well.

[02:17:00] These are first steps in trying to develop these kinds of models and see if we're going to get any useful information out of them. We at Novartis have taken the first steps as well to implement this as well. We have some of the newer targets coming up that we have that also do have normal tissue liability such as CD 123. Great AML target but also highly expressed on vasculature.

[02:17:30] We generated a couple of different non-human primates samples, car T-cells. Administered them into animals to look for toxicity. We were actually ... We described this this year at the SGCT and we were happy to see that we actually got expansion of the cells and cytokine release from the cells, indicating that these cells

probably saw target and were activated and we didn't see toxicity.

We're still optimizing the model though to definitively see whether or not we saw pharmacology and we're playing a little bit around the conditioning regimes as well to see if we get long term engraftment of the cells.

My colleague Raphael [inaudible 02:17:51] Juno therapeutics in collaboration with
[02:18:00] Leslie Keen's lab in Seattle are also very interested in developing a model to look at this neurotoxicity concern that's secondary to some of the cytokine release we get for hitting these liquid tumors.

What they did was to generate a CD 20 targeting car in non-human primate cells. They administered them into non-human primates and like we did in our CD 123 experience, got very good expansion of these cells after administering and then also, interestingly they got very good pharmacology as well. All of the CD 20 cells
[02:18:30] that they could measure ... They couldn't measure any CD 20 cells up to day seven after administering the CD 20 targeting cars.

Most interestingly as well, not only did they get expansion of the car cells in the blood, but when they tapped the CSF they were also able to see a very broad expansion of the car T-cells in the CSF. This was concomitant with some clinical signs of neurotoxicity including tremor and balance issues.

[02:19:00] This is a really good advance in the field to start to understand a little bit better the nature of this neurotoxicity. Are there different parts of the car receptor signaling complex that are playing more of a role here? Does any of the pre conditioning play a role here as well? This again is just some of the first steps.

We're starting to share some of this information, non-confidential information amongst different companies through a consortium that we've just recently formed
[02:19:30] between companies that are actively working on carts or are collaborating with other companies that are actively working on carts.

The idea here is that this is uncharted ground. We have to identify a way that we could model this in animals not only in the most feasible way again but making sure that it's translatable. There's a number of different gaps there. Understanding the nature of animal T-cells and how they relate to human T-cells and there's going to be mistakes made but we'd rather make mistakes together rather than make
[02:20:00] mistakes separately and then long after the fact discuss them with each other.

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Tim MacLachlan: Then long after the fact, discuss them with each other. Long term we would like to maybe even collaboratively run some studies together so that we can start communicating internally and externally. What we think is feasible and translatable from an animal model perspective for carts.

In summary, what we are really trying to communicate here is that this is really very much an evolving field of safety science. It is uncharted ground. We are really
[02:20:30] waiting through a number of nontraditional options at this point, both in vitro and in vivo. What we would advise, I mean moving forward with an IND for a cart or a TCR therapy right now, is really just utilize platforms and mechanisms that are well understood to determine your clinical path and your clinical monitoring scheme. This really includes a very deep understanding of where your target is and perhaps even if you have the ability to do so, understand and make sure that you have
[02:21:00] specificity of your car against your target.

In the future, and publications will be made over the course of years and collaborations as well, to understand whether or not we can actually extend this to running in vivo studies to understand what the hazards and risks might be. These could be using mouse cross reactive SEFE's on cars. We could optimize our large animal models for CAR-T as well. We are going to have to be playing around with
[02:21:30] various things like the signaling domain, the optimized conditioning regimens.

I finally just wanted to touch on one other thing which is what are we then do with this information. If we did develop a model, how do then inform the clinic. There is a big challenge here as far as toxicology is concerned. If toxicology, and a lot of it means it has to do with exposure. The problem is, I think Carl Jung has said a couple of times, that the human is the bio-reactor. We can administer a certain amount of
[02:22:00] cells to a patient or an animal, in that regard, but then those cells are going to expand, basically have a mind of their own, after they get into the patient or the animal.

At least in the clinic, it is in many ways unpredictable. How one patient may react compared to another patient. We don't, right now anyways, have a lot of control on how those cells ultimately will have the have the final exposure in the individual. As far as how clinical dosing recommendations go, I think clinical dosing for CAR-T
[02:22:30] have been falling generally in the range of a 5E6 to 250E6 CAT-T cells per patient. These aren't really linked up to what we are doing for efficacy. The efficacy is somewhere around the neighborhood of one million cells per mouse and things like that. We are actually dosing at a much lower per keg basis.

There are strategies as far as dose fractionation. You certainly want to employ, for
[02:23:00] example if you were going after a liquid tumor, a new target or something like that, you would want to fractionate 10% of your dose, 20, and then ultimately 70% of your total dose.

Finally, I am sure you have read a little bit about how there is some safety switches being built in to some of these carts. Some of them have shown some level of efficacy. I think Belkim presented a little bit about this last year. Some of this is very promising in the sense that you could treat with a small molecule and then turn off
[02:23:30] the cars. Or treat with an antibody and deplete the cars. Or that the cars will only interact in the context of having two different antigens present, not just one which may give you the risk of hitting normal tissue as well.

There are no large clinical trials that are proving that these are actually efficacy but it does point to the importance of having at least some animal models to test whether or not these actually will reduce toxicity and mitigated our risks going
[02:24:00] forward. That wraps it up. I think we can move on to our next talk.

David Clarke: Thank you. My name is David Clarke. I am the therapeutic elite for vaccines within the drug safety organization at Pfizer. I want to thank the organizing committee for inviting me. This may be a little different because I am going to be talking about
[02:24:30] vaccines but I think it may touch on some of the topics that were raised. I [inaudible 02:24:34] two parts on this. First part is going to be how we design this vaccine based immuno-therapy regimen. Then, the latter half I will talk a little bit about what we have done from a non-clinical perspective.

The objective of this regimen is to reset the immune system to generate
[02:25:00] therapeutic levels of CD4, CD8 T-cells antibodies against the majority, against a particular tumor antigen, in a majority of patients. Idea being that you are going to destroy the tumor cells, high overall response rate. Durable response, perhaps a low side effect profile. The other side of this is you need patients with a fairly competent immune system to be able to do this. And you need to have enough time to generate that immune response.

I am going to go through ... This is sort of a schematic of our thinking in terms of
[02:25:30] how we put this together. You can induce the T-cells, in this case using an adno-virus. You will get a moderate T-cell response, CD4, CD8. What we are trying to do is to boost that T-cell response through the use of an anti-CTLA4 antibody. Now you get a much larger response in CD4, CD8 T-cells. We're going to use DNA plasmid to
[02:26:00] continue to expand that and to maintain that T-cell response. We cannot come back with the adenovirus because you are going to elicit an immune response to it and you will diminish the response in subsequent.

We all know that the tumor micro environment has its own immune suppression mechanisms. The plan is that can we now also come back with therapies, in one instance Sutan against MDSC's or an anti-PD1 to interfere with that check point
[02:26:30] inhibitor. By doing that, kill the tumor, and eliminate the tumor cells. The platform that we are proposing is an adenoviral vector, containing tumor associated antigens that will be administered in combination with an anti-CTLA4 monoclone antibody. We will follow ... That is the priming dose. The boost dose will be a DNA plasmid encoding the same tumor associated antigens. Again, it will be
[02:27:00] administered with electroporation. And again, in conjunction with anti-CTLA4. Then, to maintain it, coming back with an immuno-oncology agent and it could be Sutan or an anti-PD1 to help maintain those T-cells in an active form.

The first program that we are working on here is for prostate cancer. We have
[02:27:30] selected three different antigens to encode. PSA, prostate specific antigen, the prostate stem cell antigen, and the prostate specific membrane antigen. All of which have been associated with prostate cancer. There have been good

expression profile in prostate tumors. Really, they are clinically precedent in other forms and we have shown efficacy and immunogenicity in humans.

[02:28:00] The hope of the multi-antigen approach is that you will get a good polyclonal response to tumor specific response. It will provide a benefit to a broad patient population. And you may prevent the risk of tumor escape because if another one comes up, you already have those T-cells on board to address that. The challenge is, that we are trying to break tolerance to a self-antigen. The classical models to [02:28:30] put the human sequence into a non-human primate, that is not necessarily a self-antigen, that may be viewed as a foreign antigen, at least a portion of it.

[02:29:00] A lot of the work that we did in the early stages is using a Reese's version, and we have tended to use PSMA as the template for that. We have created the adenovirus of the DNA plasmids with the Reese's version of PSMA. Done the studies in Reese's so now we have shown the ability to break tolerance to a self-antigen. This series of experiments, we looked at the ability of an adenovirus with Reese's PSMA on its own. You can see that there is quite a bit of variability in the animals, in terms of the T-cell fighters that we are seeing. If one adds in an anti-CTLA4, you can see that we actually get an increase in the tighter and a larger number of responders within that.

[02:29:30] The next question is, how are we going to administer the anti-CTLA4. Historically the anti-CTLA4 are given IV. We came across the idea that perhaps local administration of the anti-CTLA4, targeting the draining lymph node where the majority expansion of the T-cells are likely to occur, related to the vaccine. This was a study that we conducted again using the Reese's PSMA, adenovirus prime, DNA [02:30:00] boost, and then a second DNA boost, with systemic anti-CTLA4 administration versus a local

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David Clarke: Systemic anti-CTLA4 administration versus a local CTLA4 administration. You can see, for an equal dose, you get a much better response with the local administration. We also looked at exposure levels, both systemic - looking at the proximal and distal lymph nodes. With systemic injection, really as one would expect, no great difference. We do see that with local administration we see a [02:30:30] much higher concentration in the local draining lymph node, which you would expect. Much lower concentrations in the distal lymph nodes, suggesting that we would be able to lower the dose of anti-CTLA4 to still get that robust T-cell response.

That may result in lower clinical exposure - systemic exposure to the anti-CTLA4 and potentially a lower side-effect profile associated with that, compared to what's seen in the monotherapies of the anti-CTLA4's.

[02:31:00] The other question becomes - how durable is the response that we're getting? This was a study that, again, using the [rhesus 02:31:06] PSMA. It was monthly dosing

and it was adenovirus, anti-CTLA4, DNA- 3 DNA boosts, and then we came back at week 16 with the adenovirus, and again running through ... You can see we're getting a robust T-cell response in really all the animals out through dosing, and
[02:31:30] that response is being maintained for at least 16 weeks after the end of that second cycle. One of the questions is, "How often are you going to have to keep going back to boost this immune response in the vaccine world?"

Up to this point, and a lot of the work we did in the design of this program has been based on the immune response that we're eliciting, and primarily T-cell responses, and we're looking at CD4, CD8 T-cell responses. Is there actually efficacy in a tumor
[02:32:00] model? The challenge is, you've got a human vaccine and a human sequence, most of your tumor models are [inaudible 02:32:09] models. In the xerograph models there is no limited functioning immune system.

We actually did, to look at the role of [Suetand 02:32:19] we did conduct a study in a syngeneic mouse model. It was using a [Her-2 02:32:25] expressing tumor. It
[02:32:30] actually is a rat Her-2 expressing tumor. We developed an adenovirus with the rat - expressing the rat Her-2 in a DNA.

We implanted the tumors day zero, a week later we started daily oral Suetand to see whether we could impact the MDSC levels - you have to have the tumor there to get the MDSC's. 3 days later we did the priming dose, 2 weeks later we did a
[02:33:00] boost with DNA. Day 27 we took samples to look at circulating MDSC levels. You can see in the control and vaccine only - no impact on the MDSC's. Suetand alone - we saw a decrease in circulating MDSC's, and then the combination of Suetand and the vaccine saw a marked decrease in the level of circulating MDSC's.

Probably more importantly, if one looks at percent survival, the doses of Suetand
[02:33:30] and the vaccine were in a range that one may not anticipate a lot of efficacy, but one can see ... They're all lumped down here with your control - vaccine alone, Suetand alone - but the combination of vaccine and Suetand gave a significant increase in survival in these mice, suggesting that interfering or impacting that micro-environment in the tumor can increase the efficacy of your vaccine.

[02:34:00] That's the end of the non-clinic. I think some of the challenges we face with this, are that many of the tumor models lack a fully functioning immune system. We're looking at the homologous sequence of the antigens that we're going after. Most of those have poor homology in the rodent species. The non-human primate has a
[02:34:30] much higher homology - you could consider a rodent version of the vaccine, but that's generating a whole new product, similar to what they're suggesting with some of the [car T's 02:34:40], etc.

I think we felt we had sufficient homology with the non-human primates and have shown that we are getting a good response with the human protein in the non-human primate. The other issue, and where this becomes important, is - these are
[02:35:00] self-proteins. So we have to be worried about where else is this antigen being expressed, and do we have to worry about on target, off tumor toxicity, because

we will be eliciting relatively high CD4, CD8 T-cell levels to what could be a self-antigen, and expressed on normal tissues. This whole question of homology and the appropriateness in the non-clinical species was important.

[02:35:30] We did do safety endpoints in some of our earlier studies where we used the homologous antigen, the rhesus PSMA in rhesus, to show that, yes, we do have a sense when you break tolerance that you're not seeing toxicities associated with it. From a non-clinical toxicity perspective, it was primarily related to a non-human primate study. We've used the full human vaccine, both adenovirus and DNA
[02:36:00] encoding the human antigens. We had to go to non-human primates, the anti-CTLA4 monoclonal antibody only had cross-reactivity - or only had activity - in the primate, which was the justification.

We did not included Suetand in this study. A couple of reasons - one is the toxicity profile of Suetand's pretty well understood. Two - Suetand's in there to impact
[02:36:30] MDSCs. In non-tumor-bearing animals the levels of circulating are MDSCs are fairly low, so you really wouldn't be able to assess the impact of that lowering MDSCs in that model.

Typical of a vaccine, we used primarily the human dose. We didn't do a dose response. In the vaccine world, there's always this question of, "How do you relate dose to the immune response you're eliciting?" I sort of view ... You go through this black box of the immune system and putting more into the arm or intramuscular
[02:37:00] site may not necessarily give you a better immune response at the outside of that.

We did a full cycle. We did adenovirus with the CTLA4, three as a prime, three DNA with CTLA4 boosts on a monthly basis. We actually came back and did the adenovirus once more. We've got [inaudible 02:37:18] spots in necropsy, the last necropsy was 28 days after the last dose. The adenovirus we're using is a chimp-
[02:37:30] derived adenovirus, so we did include a separate arm as a single dose to assess the toxicity of that.

Our anti-CTLA4 antibody- this was the first time we'd administered in a tox study Sub-Q, so we put an arm in there to say, "What are we going to see with anti-CTLA4?" Actually, as we were going through [pre-IND 02:37:47] meetings, there was a lot of discussion and concern - because we've demonstrated we're getting very high levels of anti-CTLA4 in the draining lymph node - and concerns about what that would manifest in the animals. So we actually did the vaccine regimen
[02:38:00] with two different doses of anti-CTLA4 antibody.

Endpoints were pretty standard of a toxicity study. Full clinical pathology in life, microscopic path, we did both T-cell responses as well as antibody responses. The bottom line is we saw no evidence of systemic toxicity. What we saw is consistent with what you would see with a vaccine, which is local irritation at the injection site
[02:38:30] - either the IM or the Sub-Q injection sites. We saw evidence of increased germinal [inaudible 02:38:36] in the draining lymph node - which is what you'd expect - but only in the draining lymph node. We didn't see any microscopic pathology in other

draining lymph nodes, which is what you might have expected with - and what had been seen - with IV administration of the anti-CTLA4, supporting that we're getting primarily a local response to the anti-CTLA4.

[02:39:00] This is just the LA spot data. Group one is control, this is the anti-CTLA4 alone, and we've got the 3 antigens - PSMA, PSCA, and PSA. Really no response there. This is the low dose anti-CTLA4, high dose anti-CTLA4. Really no difference between those. We've probably maxed out at the dose we're giving. The effect of the anti-CTLA4 - again, a good response really for all the antigens.

[02:39:30] The last group here is just with the ad C68 alone - the adenovirus. So this is only going out to day 28. We do see a response, probably not quite as robust. One other point - because the adenovirus is the novel adenovirus - had not been in clinical studies. It really has similarities to the human ad virus, serotype-4, so it's a subgroup E, but it is a chimp-derived adenovirus. The reason we went with chimp is
[02:40:00] 50% of the population have pre-existing titers to human ad 5, and so we had some data that showed that that-

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[02:40:01]
David Clarke: ... To and so we had some data that showed that that would diminish the immune response so we went to the chimp. So we did it as is explained in the single dose and in the repeat dose study and then we did a bio-distribution study just to see where they adenovirus goes. Again, similar findings, no systemic toxicity microscopic findings at the injection site and the draining lymph nodes and the bio-
[02:40:30] distribution is pretty consistent with others. We saw highest levels on day two in of course the muscle and the skin that dropped fairly dramatically by 31 and by day 90 there were really no, very low levels of adenovirus remaining following a single dose.

I think from our perspective, we followed a somewhat logical progression, demonstrated the need through nonclinical studies for the various components of this regimen, the dosing regimen, the roots of administration that we are applying
[02:41:00] them. I think we have demonstrated a robust and durable t-cell response to the encoded antigens, to all three encoded antigens. The nonclinical study through a complete cycle plus one, really no evidence of systemic toxicity, well tolerated, no clinical signs.

I think we do have the potential to combine this, not only with [Sutent 02:41:22] up front but other immune check point inhibitors to try to increase the t-cell response
[02:41:30] as well as maintain that t-cell response.

We are currently in a phase-I clinical study in patient populations. One of the challenges here is what is the patient population that you go into? You can't ... Unlike [mini-oncology 02:41:45] where you may be sort of in the later stage of oncology, we have to make sure that they still have enough function left in the

immune system to be able to elicit the response, so it is non-metastatic, castration
[02:42:00] resistant prostate cancer, post-op, with rising PSA. End points will be the titers, CD4, CD8 t-cell, the polyclonal antibody and then PSA, circulating tumor cells and radiographic scans.

This is just a portion of the people, Karen Ellis, Helen Cho and our La Jolla group were our leaders on this program over time but there has been a large number of individuals involved with this program across multiple disciplines and across
[02:42:30] multiple years to get us to this point.

[02:43:00]

Speaker 2: [inaudible 02:43:35]... And in addition to those speakers we have Danuta Herzyk a
[02:43:30] key player in the [inaudible 02:43:19] as well as Janis Taube and Allen Wensky

Speaker 3: I'd like to thank you all again for joining us today. Obviously we held the questions from the session for the panel discussion, so if you have any questions please come up to the mike.

I will go ahead start off by just asking a question about what your thoughts are on how we should be determining the start dose first-in-human clinical trials. I think
[02:44:00] that we have had a lot of discussions about maybe a MABEL is too conservative in some aspects. What kind of target concentrations would you be looking for? What kind of assays are you suggesting? Those sorts of questions are things that we struggle with all the time. And, would you have different suggestions if you have an agonist versus an antagonist in your trials. I think we saw from Dr. [Prells' 02:44:25] presentation that, in some cases, for the bispecifics, a true MABEL approach is
[02:44:30] probably the way to go but maybe in other cases it is a little bit too conservative.

Does anyone have any thoughts on this?

Speaker 4: I agree. I think from the standpoint of, at least the way I started to think about it is, not cancer immunotherapy as a bucket or an umbrella, but can you actually start to
[02:45:00] fractionate, so to speak, the different mechanisms of action, and I think you just touched upon it. It is if you understand the mechanism of action, maybe you can take different approaches to select the first in human dose.

Again, as we gain more clinical experience as well, we might get a better understanding that checkpoint inhibitors antagonist antibodies, starting at low doses that are peripherally ... And I showed that the Atezo ... We went in at a dose
[02:45:30] that was very low when you think of it. It was, I think, a flat dose of about 2 [mig 02:45:32] and yet it projected to be 80% receptor occupied in the periphery. But, what's the receptor occupancy at the tumor site, which is where you really need the mechanism of action. From our standpoint, our clinical dose is 1200 [mig 02:45:49]. So, you look at that difference in terms of where we had to start, to what our clinical therapeutic dose is, it's very dramatic.

[02:46:00] From the standpoint of checkpoint inhibitors, can we start to maybe migrate back

toward the [know-a-L 02:46:03] with some other factors in there and not necessarily just go on peripheral receptor occupancy because it may not be the most accurate reflection. The agonist antibodies and the bispecifics I think ... Again, we don't have as much clinical experience so maybe we have to be a little bit more conservative from that standpoint. I think where people are going are really trying to get away from the MABEL because again, the definition of MABEL can be very arbitrary to a pharmacological effect. If you have a model that you can actually see
[02:46:30] pharmacology and measure that, then maybe you can start to do the modeling in terms of how all of these things interact in a system where you have a lot of variables and then maybe the modeling gives you that minimum pharmacological [acti-bili-tur 02:46:44] ... The term that you just put up there, the pharmacological effective dose where you have some pharmacology and not just an indication of activation in vitro because that can be extremely sensitive and maybe not in vivo
[02:47:00] relevant. Just an opinion.

Male: Can I ask a follow up? What do you do for a combination where you may not have ... One I think could be a combination of two approved products, the other may be a combination of two products in development, or one in approved, one in development?

Speaker 4:
[02:47:30] So again, our approach is that we typically do not do combination tox studies and we really try and get a better understanding of having clinical safety database to understand what the liabilities are and then again, take a conservative approach in terms of your doses. You may do your single agent dose escalation up to a certain point and then when you start the combination, you start back at the starting dose again and do the combination. If it's an approved product you use the clinically approved dose of the second one. If it's not, then if they're both developmental products, again I think there is some discussion in terms of what's the appropriate dose and how do you escalate both of them.

[02:48:00]
Female: I'd like to add to this. I agree with everything but going back to Tim's emphasis. It really depends on the target. We really need to understand the target distribution, target expression, target biology, and the combination. It depends not on the stage of development, clinical approval, this and that, but what we combine with. All
[02:48:30] these aspects are very, very important and from first-in-human, we have very similar approaches. We look at both pharmacology studies, in vivo, in vitro data, toxicology study, if we have relevant species. Everything has to be considered
[02:49:00] together and then we decide which is the most appropriate route and way to take but usually it's not one parameter and one end point that would determine how we go about the strategy of defining first-in-human.

Speaker 3:
[02:49:30] If you have something like a surrogate antibody for a [MOUSE 02:49:25] model, do you give that more weight than you would an in vitro study using human cells typically?

Female: Well...

Speaker 3: Or, does it depend on ... It might depend on binding affinity and other factors?

Female: It depends on the expression and whether this is more localized than tumor and tissue related target versus expressing many other tissues. That is one
[02:50:00] consideration. I would say both. We have to look at all the data together before we decide and, also we need to have good ...

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Section 18 of 46 [02:50:00 - 03:00:04] *(NOTE: speaker names may be different in each section)*

Female 1: ...before we decide, and also we need to have a good surrogate, that's another point, because surrogate can be of different quality.

Speaker 2: So I would just add, really quickly, to the example that I gave, we did do in vitro PBMCs with our clinical candidate and saw no cytokine. So then again, it's not that we even got useful information from the in vitro cytokine release acid with human
[02:50:30] PBMCs we didn't see any activity yet we should expected and again when you look at you need to do in order to get that activity after pre-activate cells you have to do all these other things to manipulate the cells and that's where the approach that we took is using the surrogate as, at least a foundation of what dose the selection we went with.

Female 2: I think Dr. Kermit had a comment and then we have a question.

Speaker 3: We do look at both I think it's important to remember that both may be
[02:51:00] meaningless so, let's take the example of OX40 so you used an antibody that bound to activating FC receptors I think it's 2A and the depletes Treg so if you make the assumption that that mimics human IgG1 and man I think that's still an assumption. So you could've looked at that different isotypes of OX40 and you would've got
[02:51:30] different dose responses in different mouse tumor model, so the anti-6 was sensitive, if you did it in MC38 it would've been less sensitive, if you did it in CT26 it would've been less sensitive so, we can do these exercises but I don't know that it gives us an answer that we can really rely on. There are assumptions made and we
[02:52:00] just have to remember that they are still assumptions.

Female 3: Very nice thoughts, thank you everybody. I just want to echo on what Dr. Pearl said. That data mining at the FDA we also found what you basically presented, CD3 by specifics are very toxic so I set up an approach for antibodies checkpoint
[02:52:30] inhibitors and stimulators actually we found doses that result in saturations are quite safe, unless there is some modifications that changes this CD6 DNA or CD30 to be binding and different conclusion. Maple approaches are all over the place, there is not one single approach and our paper is coming out in 2 or 3 weeks so I encourage you to read it.

[02:53:00]

Ellen Evans: Hi I'm Ellen Evans from Pfizer and I just wanted to comment, I guess this is related to Dr. Howard's presentation, I wanted to comment on the use of the word

autoimmunity because to me the classic definition of autoimmunity is an immune reaction against cells and tissues and what I saw in the photo micrographs was an inflammatory infiltrated mononuclear cell infiltrate.

[02:53:30] I didn't really see and I think that could be termed immuno-stimulation, an immune mediated reaction, something along those lines, but I didn't see overt evidence that it was truly autoimmunity and in fact, the fact that you didn't see increases in hepatic enzymes suggest that you weren't actually attacking, that there wasn't an actual attack on cells and you didn't mention whether you looked at any renal
[02:54:00] parameters but to me it could be explained by a mass of cytokine or chemokine released local or systemic. You have a lot of, potentially some of the tissues are tissues that are normally exposed to antigens every day and if you've got an overstimulated, immune response you could be actually having them more and exuberant response in the tissue so, I just wondered if there actually anything you did that actually characterized it as autoimmunity.

[02:54:30]
Kristina Howard: Okay you asked a lot of questions.

Ellen Evans: Sorry.

Kristina Howard: I'm going to start with one of your middle points which was cytokine release. All of the mice were actually evaluated and there was no cytokine release in any of these animals, so that was not a factor. Going back to really the baseline question, we are
[02:55:00] terming it autoimmunity, and I understand your point as far as clinically validating it as autoimmunity, this was a more of a pathologic identification of autoimmunity vs. a clinical one. As is obvious because it's a chimeric mouse model we don't necessarily have all the tests that we would prefer to have and that may be available in other species to definitely say, "Yes, this is autoimmunity, with those
[02:55:30] very specific diagnostic tests". However, given that we did see necrosis in various tissues that we looked at and necrosis of the actual, for example, hepatocytes as well as necrosis within the skin that was more indicative of autoimmunity.

The other thing I think it's important to understand about this type of model is, the easiest way to relate to how we maintain this animals and the normal level of antigenic stimulation is, we pretty much maintain them as mice in a bubble. So, we
[02:56:00] make every effort, humanly possible so that they have absolutely no antigenic exposure other than what we provide them, specifically in study and that's to try to ensure that we don't get something cross-reactive that may there causing inflammation that we are not looking for. In addition, the other thing that we try to do is make certain that we always have control animals from the same human so,
[02:56:30] that if there was a background inflammatory condition you would see it in the controls, which we did not.

So I agree with you that, perhaps, autoimmunity may not be the best clinical term but from a perspective of the inflammation that we saw, we did see evidence from a micro-pathologic basis that appeared to our pathologist to be autoimmunity.

Ellen Evans: [02:57:00] So I guess we just need to be careful unless we prove it and actually there not sterile mice so they may not have any of the known mouse pathogens but surely they have normal flora and that sort of thing.

Kristina Howard: [02:57:30] They have a very limited amount of normal flora and we actually go through extensive measures to confirm exactly what bacteria are on them so they have a limited cocktail of bacteria when they originally are produced, and we make certain that at necropsy they actually, we characterize exactly how much and what they have in what locations. So, we typically swab their skin, their nose, as well as we do a splenic swab to make sure that they don't have, for example, a sepsis, which is not uncommon in this particular strain of mice, so your point is well taken.

Ellen Evans: Thank you.

Female 3: [02:58:00] I just wanted to make a point in reference to that questions that actually autoimmunity refers to adaptive responses including T-cells and B-cells are immunoglobulins and so, in the clinic, for some patients we do have evidence that specific autoimmune antibody responses have contributed to adverse events. So for instance, patience with myasthenia gravis side effects, anti-acetylcholine in receptor antibodies patients who may develop thyroiditis in some of them we them anti-thyroid antibodies. Patients with other neurological disorders, antibodies against other receptors in the nervous systems, patients with diabetes anti-islet cell [02:58:30] antibodies. So we can't always find these antigens specific responses but when we do I think it's indicative of true anti-self-inflammation.

Ellen Evans: ...agree with that at all and in fact that's a known liability for many of these molecules. I was just questioning whether the model was really showing auto-immunity and unless you did demonstrate any anti-cell anti-bodies, I think you just have to be a little bit careful with the terminology.

[02:59:00]

Female: [02:59:30] Could I just pose a panel question related then to animal models of adverse events? So the very elegant humanized model that Christina presented it seemed as if maybe it overshot the mark a little bit in terms of showing inflammation and multiple organs. We don't normally see that in patients and some of the patients that have come to autopsy, we've actually studied, but maybe that's something that we need to look for, more intensely. Other models underplayed what we actually saw in the clinic so, where does the panel think would be the set point for animal model for IO agents? I think we're still not there yet.

Kristina Howard: [03:00:00] I guess what I'm going to say to address this specific concern, and you are absolutely correct we overshot where we intended to go with it, but our biggest concern with this particular...

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Section 19 of 46 [03:00:00 - 03:10:04] *(NOTE: speaker names may be different in each section)*

Speaker 1: Intended to go with it. But our biggest concern with this particular humanized mouse model was that we didn't want to miss pathology. Since if you look at non-human primate models, they've been dosed in many cases up to 50 [migs 03:00:12] per [kig 03:00:13], and very limited pathology we've seen with single agent dosing. We wanted to dose high enough we saw something. we did not anticipate anything like we saw. We were just hoping to see something. What we planned to do was back off that dosing quite a bit so that we are more in the range of seeing the type
[03:00:30] of clinical signs, not clinical signs, the pathology that you might see in a patient. But, from a perspective of the models, I don't think that there is ever going to be one model that will answer all the questions for these types of drugs.

From my personal perspective working with these animals, I think they can be very informative from a pharmacologic as well as a toxicity stand point, but not every drug will bind in them, not every drug will work. There are issues even with this
[03:01:00] type of model. They're not easy to work with because of the sterility aspect in which you have to maintain them. I think that some of the other models that the other presenters showed us, each of them seems to have certain benefits and I think it comes back to a point that many of the speakers made, which is we really have to look at what is the molecule that we are evaluating and what is it's biology? Based upon that, then look at what models might most appropriately answer those questions.

[03:01:30]

Speaker 2: I would add too, I mean, you talked about maybe before some of the checkpoint inhibitors, going back to some of the [tox 03:01:37] models and looking at new [ALs 03:01:38]. That could be a strategy going forward, but at the same time, some of these models you have no [ALs 03:01:46] that are 150 migs per kig, and even if you go a ten-fold dilution, or a ten-fold safety factor, for that type of molecule, you're
[03:02:00] above the approved doses for some those drugs if you look back historically. Maybe not for [inaudible 03:02:02] in this case, but for some of the other molecules.

Speaker 3: I was just going to comment, this is always the issue in departments of pre-clinical safety, because if we use a trans-genetic mouse and it completely overshoots, then we end up in discussions about well is it relevant, or is it not? If they don't generate anything they look at us and say, what did you do? What's wrong with your
[03:02:30] models? I think particularly in this therapeutic category of immuno-oncology, I think we need to, a few different categories aside, I think we need to be in the mindset of hazard identification at this point, and I think that that might be where we should shift our mind set, if we're using human immune system mice. I think we should probably at least get away a little bit from using those mice and thinking this is the dose at which it will happen and this is a safe dose. I think that's why we're
[03:03:00] here, that's why we had this session here today. We need to reset what we're thinking as far as non-clinical safety, as related to this. It applies to the carts, for example. By no means are we ever going to define a safe dose of T-cells in those models. What we'd like to try to do is to develop a model to identify what a hazard might be, and then work backward from there.

Speaker 4: [03:03:30] I couldn't agree more with this, because we need to shift our thinking, typically for toxicologist study we used to do margins, exposure margins, risk assessment based on dose and exposure. Here, I think we need to focus on Hazard identification, based on biology and this [inaudible 03:03:43] all kinds of systems, if they give us some signal, we need to think about it and be prepared to monitor in the clinic, but we cannot really predict exactly what will happen based on annual study. I think [03:04:00] this is ... I totally agree, we need to accept that we actually don't have very good models for classical risk assessment which we've done for so many decades in direct development. It's much more about hazard identification based on biology and putting this in perspective and trying to figure out, well focus on defining starting dose, because then, a lot really depends on clinical data. I think that's the [03:04:30] important point.

Speaker 3: I think in [Cbear 03:04:36] where we handle the [car t cells 03:04:38], like Tim was saying, we already do that, we do that a lot, we don't ask for the standard assays for PK/PD, no [AL 03:04:47]. We look for hazard assessment, we look at these animal studies, and especially in vitro studies, and the science behind what the [03:05:00] molecule is, what the target is, what the vector is, what the cells are, and we use all of that to help inform a clinical study, to help inform what risks may pop up and what we need to look for in that sense. Less of a focus on starting dose, for those particular products. Whereas, he pointed out, they're being manufactured in [vivo 03:05:25]. They're proliferating at a very great rate and every patient is different. [03:05:30] Every patient has a different dose.

Speaker 5: [inaudible 03:06:09] independent. To make things even easier, and in view of the utilization of this [novel 03:05:43] agents in a pediatric population, I'm thinking of [t car 03:05:47] cells but also of other agents. Can any of you comment on the reliability, availability of pre-clinical models that would predict of a population [03:06:00] who's immune system may be different than the one of adults since they're under development?

Speaker 1: I will say that, in CDER, it's rare for us to request a specific juvenile study, unless there's a liability we don't feel has been addressed. We don't do a lot of that. We see a lot of in vitro cell line data to support specific pediatric trials. I don't know if [03:06:30] Dr, maybe Dr. [Tab 03:06:32] has some ideas about bio markers that you could use to sort of choose pediatric populations.

Speaker 2: We do archival studies on underserved populations, and Dr. [Topalian 03:06:46] gave a nice example of the anal [inaudible 03:06:48] cell carcinomas in the HIV positive patients, and where we compare them to patients who are [03:07:00] immunocompetent. You could take a pediatric population and compare their tissue specific distribution of their marker of interest, right, and infer from that as long as it parallels what we see in adults. That you should be able to make a case for a similar activity, and I think that's a good use of some of the human tissue studies in this scenario.

Speaker 6: [03:07:30] That's kind of non-clinical development, but it's a little later than what you're typical pharm-tox reviewer is looking at because by that time you also have some clinical data so it becomes more interactive process, I guess.

Speaker 7: [03:08:00] Thanks, Dan Chen, [Genentec 03:07:42] and [Rosch 03:07:42]. I think the speakers did a wonderful job highlighting the kind of challenges we face in this space in terms of translating our pre-clinical models to our experiments in humans. That appears to extend from both the safety and the ethicascy side. Suggesting just the kind of differences that exist between models and human immunity. When we extend that to how we look at dose escalation in human experiments, it's not even clear from a safety standpoint how well that dose escalation is de-risking this class for [inaudible 03:08:22] human toxicity.

[03:08:30] One of the questions I have for the panel is, as we evaluate potential safety issues, and I like the comment on resetting and really focusing on identifying the things that we should be looking for in the human experiment, do you think that we can get to a point where we are less focused at starting on very conservative doses, really targeting at starting at more biologically relevant doses, and then focusing those phase 1 experiments on really going slow in terms of evaluating single [03:09:00] patients at a time and monitoring very closely for the kind of toxicities that we know can occur acutely with immune based therapies. The one thing that I would throw on the table is that this is one field where, in many ways, we have the tools, if we can recognize those immunologic events early to be able to shut down that immune response, and hopefully mitigate really severe immune toxicity. We'd love [03:09:30] to hear the panels' thoughts on this.

Speaker 3: [03:10:00] I think you hit it on the head. We're all kind of getting back into that idea that, if we can look at pharmacologic ally active doses, pharmacologic ally relevant doses, and what can we do, to Tim's point, what can we do for hazard identification? Not necessarily set it, and I can't remember who brought this up, but the Mabel approach ... it's interesting because it's the minimum biological effect, and that's to de-risk it, but who's to say that the next dose up won't give you your maximum pharmacology? Is your Mabel de-risking the next dose level?

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Section 20 of 46 [03:10:00 - 03:20:04] *(NOTE: speaker names may be different in each section)*

Male: [03:10:30] So is your mabel de risking the next dose level and I have a question around that, and so, the idea is you have to go slow and you have to escalate very cautiously and that's to your point. So is there an area that you can, using all the information, and non-clinically predict what a pharmacologically active dose may be and then take that very cautious clinical approach because that's more, potentially a lot more relevant than what we can define in the non-clinical space. So again, just thoughts on that?

Female: I think from the FDA perspective, or some of the reviewers perspective, we are trying to take that into account, and we are looking more at things that are closer to EC50's in vitro than receptor occupancy 10's. That may still be a bit low, we are

also, if you'll take a look at Dr. Saber's upcoming paper, thinking more about allowing more single patient escalation, especially at the lowest doses so that you
[03:11:00] have some sort of idea that you're not blowing people out and causing massive problems with your first dose, but also, not dis servicing patients by not allowing them to be dosed at a relevant concentration, so you know, these are discussions that we're having internally as well as to where is the balance between safety and activity.

Male:
[03:11:30] Yeah, and I was just going to add, we had a really great discussion with the FDA with dicentric in terms of how could we get up to what we considered a reasonable starting dose, but yet also saw some of the liabilities, or potential liabilities with that, and, you know, allowing us to have those single patient cohorts and that was one of the earlier, I think, allowing single patient cohorts with these molecules starting at very low dose. You know, starting at what we consider pretty low doses, so again, I think with that interaction to get the agencies and the sponsors on the
[03:12:00] same page might actually help us again bring this pendulum back more toward the middle, versus one extreme or another.

Female:
[03:12:30] I'd like to add that especially for adaptive immunity it seems like we don't have examples of very acute toxicity. It's really about cytokine mediated acute toxicity, and for that I think we have chosen to evaluate dose response, even in vitro dose response. The shape of the dose response is quite informative, so it really depends again, which arm of modulation we are talking about, but it seems like ... well, so far at least ... we've been on the right track trying to characterize and define these
[03:13:00] doses so hopefully, despite the limitations of all these systems we still are able to figure out not only the starting dose, the recommended starting dose, but also the dose escalation or slope of the response.

Male:
[03:13:30] Good morning, my name is [inaudible 03:13:18], I'm a statistician at [inaudible 03:13:20], and I think my question ties in very well with the discussion we're having now. With how, it's not only about the starting dose, but also about the increases we can have in the dose escalation studies, so my question is, instead of just looking back at past studies and past basic experience and then linking back to what have we actually seen in the pre[inaudible 03:13:40] stage, could we actually go a step further and say when we are actually having our first patients on the study, let's look at the responses we get in terms of safety and let's link that back to all the models that we have done in pre-clinical stage and then maybe re-weight evidence we have from the pre-clinical experiments, and then loop that back to the
[03:14:00] clinical stage, for example, adjusting the increases we can make in order to get more relevant doses in a quicker stage. So what's the panel's thought on this?

Male:
[03:14:30] It might be different from target to target. I mean, we may learn quite a bit on one particular program retrospectively, but I'm not sure we can apply that to a different, you know ... different IO target. So it'd be tough. Perhaps we ought to do a retrospective analysis of like, you know, 4 different IO targets and see if the all line up, but my suspicion is that they would be different.

Female: I think that's going to be a hard process to figure out exactly what those dose increments should be. We typically use a half log for most of your therapeutic

[03:15:00] biologics, but in some cases you might want to go lower. We're about to run out of time and I wanted to get to one last question from the audience maybe too if it's really fast.

Male: Okay, so my question is about the mabel dose calculation for tazo, and I was just wondering if you could shed light on what's the pharmacological basis for selecting 80% [inaudible 03:15:17], and what was the FDA discussion like to come to that conclusion?

[03:15:30]

Male: Calling back some history there. So we actually proposed a 0.3 mg/kg and that was really based on the experience at the time when we went into oncology which was 2010, 2011 I think it was where there was, you know, again a lot of history with molecules that inhibited that pathway, other checkpoint inhibitors, and based on the lack of toxicity in our own clinical models.

Again, we got response saying you should take a mabel approach from the FDA and

[03:16:00] then on the TC, you know, they also said we kind of, we may have overreacted, but we don't, we aren't comfortable with what you have proposed as well, so it really just came down to a conversation in terms of, well, what would you like to see and given that this is an antagonist antibody, they again, more willing to say, well you don't need to have an EC20 or an RO20, let's, you know, what's above 50% and what would the dose be? And so, when we showed them our PK modelling and our receptor occupancy modelling, we both kind of came to an agreement again with

[03:16:30] that 0.01 mg/kg dose, starting dose and again, they were the ones that actually said we're comfortable with you going single patient doses. Single patient cohorts up to the point 3 mg/kg where again if you looked at the modelling, that 0.3 was going to have 100% peripheral receptor occupancy for 2 months. So, you know, we could get there in 3 patients and then using that safety database to really drive it, so it was a really nice example of where the conversation started and where it actually

[03:17:00] ended up, in what was reasonable at that time.

Female: One last question.

Female: Hi, my name's Lori. I'm wondering if any of you would like to comment on the length of the studies we do in animals and how long we monitor in the clinic with regard to some of the changes in the adaptive immune response that often take weeks to months to develop?

[03:17:30]

Female: Well the standard tox studies are for, to start a trial are 28 days and we'll see weekly dosing or twice weekly or every two week dosing typically for a small molecule, so you do have some time to build a response, and a lot of these programs also have recovery animals which are un-dosed so you have a little more time to see what happens with exposure. But of course you also have issues with

ADA in a lot of animals because of the humanized molecules, but I don't know if anyone else has any comments on this but ...

[03:18:00]
Female: So, yeah, typically we use, we add additional animals to follow them in the so-called treatment free period because we don't know if they will have any toxicity or not whether they'll need to be recovery or not, we cannot predict this before we do the study, but we do this from experience working biologics based on long half-
[03:18:30] life[inaudible 03:18:24] and this adaptive immunity response. So typically our studies do have cohort of animals that we monitor typically at least twice as long as the dosing period. If we dose for one month, we monitor for two additional months later on, so we do have some insight into this.

[03:19:00]
Female: I think we're out of time and we didn't get to any of the combination talk, which I think everyone is very interested in, and how we're using some of the pharmacology to try to inform on dosing for combinations early in development, but maybe we'll get to that later and some of the maybe bio markers for what products you should put together if there's any rational design for that, so we've got lots to look forward to. Thank you.

[03:19:30]
Male: Okay, we're going to get started here in a minute. All right so we're going to kick of the afternoon here with session 2A, which is considerations for dose: dose finding
[03:20:00] within the oncology[inaudible 03:19:59]. I just wanted to ... one housekeeping issue ...

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Section 21 of 46 [03:20:00 - 03:30:04] *(NOTE: speaker names may be different in each section)*

Speaker 1: On a housekeeping issue, I just want to remind the speakers and the panelists before speaking, if you could just announce your name so that the folks on the webcast can identify who is speaking. At this point, I'd like to invite Dr. Geoffrey Kim up to the podium who's going to moderate this next session.

[03:20:30]
Definitely have to lower the mic. One more housekeeping request. In honor of his receipt of the Nobel Prize, we would like to request that at the next intermission Bob Dylan's music be played.

Geoffrey Kim:
Thank you for having me. My name is Geoff Kim. I'm the Director of the Division of Oncology Products 1 at the FDA. For those that don't know how we're structured, DOP1 does solid tumors and we do genitourinary, gynecological and breast cancer.
[03:21:00] We also do what remains of the supportive care products as well. I've been privileged and honored for the past couple of years to be part of the planning and implementation of two dose finding workshops.

[03:21:30] The impetus for these workshops was initially to start looking at the dosing of our small molecule kinase inhibitors in particular and to engender a really multidisciplinary approach to looking at dose, looking at, too, how we can optimize dose early in development but also in the whole life cycle of the drug.

[03:22:00] Two years ago we held Dose Finding Workshop Part 1. That was an interdisciplinary discussion cosponsored by FDA and AACR. It was a tremendous opportunity to have multiple disciplines come together to discuss how integrated data from nonclinical toxicology, pharmacology studies can be integrated with novel statistical designs of dose finding trials. In addition, the PK and pharmacometrics characterization of the drugs, how that contributes and then taking a step back and looking at the whole life cycle development of the drug, how things can be improved for future studies including combination studies.

[03:22:30] The real take home message from the first dose finding workshop was we need to move past the 3+3 traditional dose escalation, a model in oncology where dose optimization stops after the first in-human study. In addition, we also learned valuable lessons about the reintegration of what we call nonclinical models

[03:23:00] because as I am reminded by our nonclinical colleagues that it's not just in the preclinical settings. Their work does not stop before the drug is introduced into humans. After developments and new safety signals appear, people could go back and look at these models, look at focus models, too, to inform drug development.

[03:23:30] Last year we held another workshop, Dose Finding Part 2. Here, we focused on many different topics but one of the main themes that came about was the interdisciplinary conversations and need for interdisciplinary involvement in determining dose. We had great talks across the board from, again, nonclinical pharmacometrics, statistical clinical participation, and clinical pharmacology participation, and we really were able to discuss thinking forward to combination

[03:24:00] studies and novel methodologies for dose optimization. We consider this session to be more of a dose finding 2.5 because I think some of the same principals are going to be discussed in this session.

I do want to give you the teaser for Dose Finding Part 3 which we are planning to hold during the annual meeting at the AACR which is held in DC this year. There, we will exquisitely be focused on combination studies but also one other topic would be the inclusion of special populations such as geriatric oncology that needs to be addressed.

[03:24:30] Without further ado, I would like to start by bringing Eric Rubin to the podium, and we'll ask that we continue the tradition of having the speakers introduce themselves. Thank you.

Eric Rubin: Thanks, Geoff, and I'd like to thank the organizers for inviting me to speak. My name's Eric Rubin. I'm a medical oncologist, and I oversee early oncology clinical

[03:25:00] development at Merck. I'll spend a few minutes this afternoon talking to you about dose finding approaches for both monotherapy and in combinations.

[03:25:30] I'll start with a brief summary of our approach to monotherapy dose finding for pembrolizumab. Our first in-human study known as KEYNOTE-001 started with a fairly traditional approach of looking at ascending doses of 1 mg/kg, 2 mg/kg and 10 mg/kg given every 2 weeks. There were no dose limiting toxicities at any dose. Based on initial pharmacokinetics that demonstrated at 26-day half-life, the dosing interval was changed to every three weeks.

[03:26:00] We then used, and I'll provide more information on this in the next few slides, an interpatient dose escalation approach and ex vivo IL-2 assay and translational PK/PD modeling to select a recommended phase 2 dose of 2 mg/kg every 3 weeks. Subsequently, we used randomized cohorts in both melanoma and lung cancer to show equivalency in terms of efficacy for both the 2 mg/kg and the 10 mg/kg doses. Ultimately, this study was expanded to 1,235 patients, and this has been discussed in other settings and was used to support regulatory approvals in previously treated melanoma and lung cancer as well as PD-L1 immunohistochemical companion diagnostic assay.

[03:26:30] This is the interpatient dose escalation approach we used to evaluate dose response with regard to pharmacodynamics. Patients were escalated in 3 steps, at days 1, 8 and 22 from low doses down to 0.005 mg/kg and up to higher doses including 2 and 10 mg/kg. We use an ex vivo IL-2 assay, so the way this works is

[03:27:00] that staphylococcal enterotoxin B induces lymphocyte IL-2 release. If you have an active PD-1 pathway in these lymphocytes, this will block the IL-2 release. In turn, if you administer an anti-PD-1 agent such as pembrolizumab, this will inhibit the PD-1 pathway and thus allow IL-2 release. If you can construct an assay where IL-2 stimulation is measured in the presence of absence of exogenously added

[03:27:30] saturating pembrolizumab, and this can be used to provide stimulation ratio as shown on the slide where you look at IL-2 produced in the presence of saturating pembro over just the IL-2 produced just in the presence of enterotoxin B alone.

[03:28:00] If you do this and look at the patients that were treated in this interpatient dose escalation as well as other cohorts, you can derive the graft shown on the right which plots IL-2, the IL-2 stimulation ratio as a function of estimated pembrolizumab concentration. You can see there's a plateau that occurs where at 1 mg/kg every 3 weeks you achieve 95% saturation and, therefore, that 1 mg/kg every 3 weeks was considered the lower boundary for clinical efficacy.

[03:28:30] Similarly, if you're looking towards the upper side, we ... Our pharmacokinetics folks looked at the derived probability estimation shown in this graph up here of the probability of achieving full target engagement as a function of dose and you can see this curve also plateaus approximately at 2 mg/kg. At 2 mg/kg the

[03:29:00] probability is 90% or higher of achieving full target engagement and again you can see with competence intervals down here that the 2 mg/kg dose again is near this plateau of the underlying exposure response relationship.

Based on these data, we proposed a recommended phase 2 dose of 2 mg/kg every

2 weeks. This was supported by additional analysis including an exposure response
[03:29:30] analysis shown on this slide where we looked in this case at tumor size change over time, so in the Y axis here is the sum of the longest diameters changed from baseline. This is actually different than modeling response on the basis of just resist which just uses categorical information.

When we looked at this as a function of exposure at 6 weeks, we saw that the
[03:30:00] exposure response curves were flat across concentrations that were achieved at these various dose levels. This again supported the selection ...

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Eric Rubin: - ... at these various dose levels. This supported the selection of 2 milligram per kilogram as the recommended phase II dose. Finally, when we looked at exposure AE relationships, (this is adverse events of special interest, these are basically immune-based adverse events) we also saw a flat exposure AE relationship over
[03:30:30] concentrations at six weeks. You can see a flat dose response relationship here, this again supported selection of 2 milligram per kilogram as a recommended phase II dose.

Now I'm going to switch gears and talk about combinations. I think many of you know that clinical combinations of immunotherapy agents is a very large and growing effort, so this is data from ClinicalTrials.gov over time, starting from 2014
[03:31:00] to when I put the slide together, was September 20th. You can see that among the anti PD1 agents that are furthest advanced, the total number of such studies is actually 456. Merck is right at around the 200 mark with pembrolizumab, so I'll say that many of our combinations are sponsored by a collaborating company.
[03:31:30] Although we're not in the decision-making for how these studies are done, we do get to see the studies. One of the things we do insist on is that we fix the pembrolizumab dose at 200 milligrams every three weeks, which is basically our current recommended dose, it's the 2 milligram per kilogram dose, adjusted to be a fixed dose. One of the things that we've noticed is that there are multiple variations in the approach to recommended dose for agents combined with pembrolizumab.

[03:32:00] I'd like to take you through some examples of things we've seen, and this is something we can discuss during the panel discussion. I'll start with Company A, which has a small molecule A. In this case, that drug A, there's not been an MTD identified with monotherapy administration of this drug. The same is true that there is no recommended phase II dose yet for monotherapy for this drug, so it's a
[03:32:30] relatively new drug. There is interest in combinations with a check-point inhibitor. This company proposed 3 + 3 up and down dose-limiting toxicity approach with standard dose-limiting toxicity criteria. I'll come back to this a little bit later. The starting dose of the drug was based on clinical safety and pharmacodynamic data. There was also a maximum administered dose that was specified in the protocol, in
[03:33:00] case there was no MTD identified during dose finding, although the rationale for the selection of the maximum administered dose was not provided.

This is a quote from the study. It says the recommended phase II dose will be based on all available data, including DLT data, in an assessment of ... There's a gene expression signature that's being used, as well as safety and tolerability data. There is also some flexibility in the protocol, which is commonly done, in the statement that the sponsor may also choose to investigate lower dose levels, and enroll three
[03:33:30] or more additional patients prior to phase II.

Now, as Geoff alluded to, this approach has the usual risk of selection of a non-tolerable recommended phase II dose, because of the small numbers used with the 3 + 3.

Here's a second one, Company B, with small molecule B, in this case also, there has been no maximum tolerated dose identified with monotherapy administration of
[03:34:00] this drug. However, there is a recommended phase II dose and the starting dose is based on that, and the dose-finding approach here is a 6 + 6 up and down approach, again with "standard DLT criteria." This study also included a dose level -1, in case the recommended monotherapy dose of drug B was not tolerated in combination with pembro, and there was no dose escalation here. Somewhat simple study, in my view, better than 3 + 3, but still at risk in selecting a non-
[03:34:30] tolerable dose, based on a relatively small number of patients, in this case, six.

And the last example I'm going to give you is Company C. Company C has a monoclonal antibody, drug C. No maximum tolerated dose identified with monotherapy administration of drug C, and there is also not yet a recommended phase II dose known for drug C. The starting dose is based on pre-clinical data and data that's coming from a preceding monotherapy cohort that is also part of the
[03:35:00] study. We are seeing this commonly, in combination studies for newer drugs, where there is a preceding monotherapy cohort that is a dose level above the combination, and so that can provide ongoing data that can be used for the combination cohort. In this case, the dose finding was based on a toxicity probability interval design, with a target DLT rate of 30%, and this would be applied
[03:35:30] to identify an MTD of drug C, in combination with pembro. This study also included a maximum administered dose, in case there was no MTD, but there was no rationale for the selection of the maximum administered dose. In this study, a quote from the protocol was that "the totality of the date will be considered before deciding on the doses to carry forward to part B, which was an expansion cohort, and the escalation schedule may be adjusted, based on pharmacodynamics, PK and safety data.

[03:36:00] We actually like the toxicity probability interval design. This is an example of a table that's typically generated in protocols that use this. How we can use this is that on the left here are the number of toxicities; on the right here are the number of patients treated at the current dose, so you can see that at any number of subjects, depending on the number of toxicities, there is a letter in the cell, and S means stay at the current dose, E is escalate, D is de-escalate, and DU is considered
[03:36:30] unacceptably toxic, and that dose would not be revisited. This is based on a paper published in clinical trials a few years ago, from G. and Becca Lee and colleagues,

and we can like this because it's a relatively large number of patients that is usually used here in this case 14, and I think the likelihood of identifying a dose that is actually not tolerable here is less than in the other up and down type cases that I
[03:37:00] mentioned before.

I want to move out now to a related topic, which is DLT criteria in combination studies. One of the issues that's come up in discussions with companies as we collaborate on these combination studies is this one. We're combining two drugs
[03:37:30] here. Let's just say, for sake of example, that drug A is pembrolizumab, and drug B is another agent. What about severe toxicities that could be attributed to drug A, pembrolizumab? After all, every drug has side effects, and sometimes they are severe. Sometimes, what we get is ... The question is should those not be considered as dose-limiting toxicities? Let's take, for example, a pneumonitis event or something. So, rare, but they can be severe with pembrolizumab. There's a question is that if a patient has a pneumonitis event and the combination, maybe
[03:38:00] that's coming from pembrolizumab and really isn't part of the combination, so it shouldn't be counted as a dose-limiting toxicity, and the point that's made that maybe if you've enrolled a patient that's uniquely susceptible to pembrolizumab pneumonitis, that this patient could actually skew dose finding in a negative way.

The problem with this is that, other than an infusion reaction that occurs immediately after drug A, can we really be sure that an observed DLT originates in a
[03:38:30] combination setting, originates only from drug A, and I would argue that's no, that toxicities that are well-known for drug A may still be enhanced, including greater frequency or severity in the presence of drug B. But how do you deal with this issue? This is another reason to avoid small numbers, so that if you happen to enroll a patient that might be uniquely susceptible to one of the drugs, that patient is not skewing your dose finding in an inappropriate way, and it goes back to
[03:39:00] approaches such as the one I mentioned before, the toxicity probability info method, can account for this chance enrollment, because you've got larger numbers and, as I mentioned, typically you go up to 14 patients enrolled at a given dose, that meets or below is where the toxicity probability is at or below the targeted probability rate, and this also gives you the freedom to actually set what
[03:39:30] you would like that rate to be. This can be set based upon the expected rates for each drug, when given as monotherapy, and in the combination setting. It's usually below 35%. So I'd like to thank the people at Merck who helped with both the monotherapy dose finding, as well as some of the discussions I've had with you related to combinations. Thank you for your attention.

(applause)

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Section 23 of 46 [03:40:00 - 03:50:04] *(NOTE: speaker names may be different in each section)*

David Feltquate: Good afternoon. My name is David Feltquate. I'm on oncologist, and I work at Bristol-Myers Squibb. I work as the head of the early clinical development program.

[03:40:30] What I'm going to do today is, I'm going to talk about a real world example. I'm

going to talk about the lessons learned as we were evaluating the combination of two IO agents. Ipilimumab and Nivolumab in non-small cell lung cancer.

To start, when we talk about any kind of combinations, you have to have a strong rationale of why you're combining these agents. In the case of combining these two
[03:41:00] IO agents, anti-CTLA4, and anti-PD1, we know that, although these are both checkpoint pathway inhibitors, they work in complimentary fashions. Anti-CTLA4 helps to stimulate the activation of T-Cells and their proliferation. Opdivo, or Nivolumab anti-PD1 agents help to reverse exhaustion, and also to continue the activity of these T-Cells.

In addition, something that Alan Korman was speaking about earlier today,
[03:41:30] Ipilimumab has a specific FC receptor that may also lead to the depletion of T-regulatory cells, and may also have an additional way that it's working effectively in combination.

A little bit of background before we get to lung cancer. We did the initial explorations of this combination in melanoma. Eventually we were able to successfully show that the combination improved outcomes in patients, versus either agent alone, and received an approval for this combination in melanoma.

[03:42:00] But I want to take everyone back to what we knew at the time we started these investigations. The first thing was Ipilimumab was already approved in melanoma, at a dose of 3 milligrams per kilogram every three weeks, for four doses. Going into this trial, that was our base. We knew very little about anti-PD1 at that point, so we were carefully escalating the anti-PD1.

That's shown here in this schematic. As Eric was describing, we actually took the
[03:42:30] more traditional approach of the three and three, the six and six design, in doing this at that time.

We had started again with a fixed dose of Ipi, and we were doing cohorts. We were escalating the dose of Nivo. What we subsequently learned is that Nivolumab, or other anti-PD1 agents as Eric was describing, as a mono-therapy it's a flat dose response curve. Whereas with anti-CTLA4, there actually is a pretty decent dose response curve.

[03:43:00] As such, you would think by going up with higher doses of the anti-PD1 agent, this would be tolerable. But in fact we found something different. When we got to the three and three dose core, we had exceeded the pre-defined toxicity.

Then we went back and we added a cohort 2A, because you can actually, when you think about it, we've established what the MTD is at Ipi of three, but we wanted to ask the question about Ipi at one and Nivo of three, because at that point we
[03:43:30] started to learn about how active Nivo was at that dose. We did this in a serial fashion.

Later, and I'll show you some of this data, but later we ended up dropping what was part of the maintenance part of this, which is shown on the right hand side of this figure. We just did continuous PD1 mono-therapy.

A couple of things to note, beyond unrolling these cohorts sequentially. You'll notice these are very small cohorts. The numbers of patients are in the teens. The
[03:44:00] other thing that's not shown here, but I will tell you is, although we were seeing toxicity with this combination, in patients who did get toxicity and had to discontinue, in melanoma, we found that the activity of these patients was very similar to patients that had continued taking the drug. The effect of discontinuing was not evident that it was leading to necessarily a major difference in the outcomes in these patients as measured by response.

[03:44:30] I'm only going to show you select information, and I'm going to do this for multiple tumor types. But I want to have a consistent pattern, so you can relate one study to the next.

For melanoma with these two different cohorts, we found if you look at different measures of toxicity, that in general there was similar toxicity to the Ipi three Nivo one, and the Ipi one Nivo three cohorts. Maybe a little bit lower toxicity in the Ipi one Nivo three. If you look at the amount of discontinuation, about 20 percent of
[03:45:00] patients were discontinuing these treatments. If you look at activity as measured by response, it was about 50 percent of patients were responding.

As I mentioned, discontinuing early or late seemed to have no bearing on the outcome.

I mentioned that we then took the Ipi three Nivo one dose forward into randomized studies, and that's what was eventually approved.

While the registrational studies were being build and executed, we started to ask
[03:45:30] the question about, "What is the activity of this combination on other tumor types?". We took existing studies for both renal cancer and non-small cell lung cancer, and started to evaluate those. In renal cancer, we were able to then do a randomized evaluation of the 1331. Following four doses, that same paradigm I mentioned before, we then reverted to continuous PD1 treatment.

[03:46:00] This is what the data looks like. In terms of toxicity, there clearly was a better tolerability with the lower dose of Ipi, so the Nivo three Ipi one combination, than with the higher dose of Ipi, lower dose of Nivo. That's measured by both the 50 percent difference in the grade 3-4 related adverse events, as well as in their rates of discontinuation.

Looking at response as a measure of efficacy, these two combinations were very
[03:46:30] similar. Based on this data, we move forward in renal cancer. The higher dose in Nivo, lower dose of Ipi regimen. So it's different than what we did in melanoma.

Again I point out, what was nice about this was, we did this in a randomized fashion, not unrolling the patients serially. You can see by the sample size, this was a decent sized expansion with which to better estimate the activity and tolerability.

[03:47:00] While the renal was going on, we also in parallel were doing the same thing in lung cancer. It looks a little more complicated, but at the time, we weren't sure whether there would be difference in activity in squamous and non-squamous cancers, so we had created distinct cohorts for these histologies. But you can think about lumping these together. This is the Nivo one Ipi three cohort, and then on the right is the higher dose of Nivo, lower dose of Ipi cohort. Again, four doses, and then they move onto PD1 mono-therapy.

[03:47:30] I want you to focus first on these first two columns here, and what we found was something quite dramatic. We found that in both of these cohorts, there was a fair amount of toxicity. In fact, too much toxicity. If you look at their rates of discontinuation, a third of patients were discontinuing, and I'll show you data in a moment, but the discontinuations were occurring quite early. They were occurring within the first one or two treatment cycles.

If you look at the efficacy, very little efficacy in terms of response, probably because these patients were discontinuing so early. Which is different than what I was told you about melanoma.

[03:48:00] If you compare this to a separate cohort that was unrolled previously with Nivo mono-therapy, with lung cancer patients, you see that the discontinuation rates were one third. About ten percent of patients, and again that activity was in the 20 to 25 percent range. With this combination, we're seeing lower efficacy, greater toxicity. Obviously this is problematic. It also sets up a number of questions as to why this may be happening.

[03:48:30] One of the things we did immediately was just look at a lower dose combination. We dropped the dose of Ipi, trying to understand whether the concurrent administration of these two drugs was even feasible. You can see that with these lower dose cohorts, it is indeed feasible. It's safe, but you'll also notice that the overall activity is really not better, and maybe even still a little bit less than what you're seeing with the PD1 agent as a mono-therapy.

[03:49:00] Just a little bit more detail around what we were seeing. This is the high dose Ipi, and the low dose Ipi cohorts. Again, both of them we felt had too much toxicity to move forward. You'll notice that with the higher dose Ipi, there's generally more of these events. The different colors denote the different cycles where the events are occurring. You'll notice most of the events are occurring with the higher dose of Ipi in the first cycle, but there are still also meaningful events occurring in the second cycle. And a little bit less in the higher dose of Nivo, lower dose of Ipi.

[03:49:30] I do want to call out something interesting. There were actually two events in those first cycles that led to discontinuation, that upon reflection made us consider

whether the Nivo three Ipi one might still have some measure of tolerability. One of these events that ultimately led to death was a patient that had a history of all sort of colitis, and was inadvertently enrolled to the trial. This is someone you would not have put on the trial, it was part of the exclusion criteria, and it's not a surprise given these kinds of drugs that they develop rapidly, the recurrence of their auto-immune disease.

[03:50:00] The other was a grade three plural diffusion that was not part of the discontinuation criteria, and so ...

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David Feltquate: ... Profusion that was not part of the discontinuation criteria and so this patient actually continued on treatment. So it was considered slimming, but the way the protocol was written, but rules, they were able to continue on treatment.

[03:50:30] The other thing to be aware of is what do we know about some of the pharmacodynamics? With pd 1 agents you see very little in the periphery in terms of the activation of ... Or changes in the characteristics of immune cells. If you look at certain subsets such as cd4, cd8 positive ki 67 positive t cells looking for evidence that you're leading to proliferation, you don't see very much with pd1 alone. I know this is saying sequence, but I can tell you this is also what you see with just pd1 alone.

[03:51:00] When you give ... Concurrently with an anti ctla4 agent you a massive rise in the numbers of these cells. It drops back down prior to the next dose, I don't have the dosing in-between, but you can see a sustain number of these cells in circulation. Arguing for, it's important to give these drugs concurrently and to try to do this early in the treatment regimen.

[03:51:30] So what was the piece of information that we had available to us to make the next move? So when we thought about it, everything that we had built around this combination was built around the premise that ipi is the foundation. That makes sense for now in a historical sense of when we all started this, but for lung cancer, there was no monotherapy data with anti ctla4. Where we did have good activity was with nivolumab. We said "So maybe that's the way to do this" and based on looking at the data, it looked like ipi was really driving this toxicity.

[03:52:00] As I showed you, there was data at even one-on-one, you could put the two together concurrently, it just wasn't optimized. There's data from pharmacodynamics of putting the two together could lead to meaningful biologic activity. And we felt, when we really looked at the individual patient data, it was feasible to give at least one dose of nivo3, ipi1 concurrently. So really the question for us was, how much of a dose of ipi should we be giving? And how far apart? What should the ipi schedule be?

We went back. We went back and devised a second generational look at this. We

took the existing study, and what's seen on the left here is those cohorts I already told you about, and we added three more cohorts. We enrolled these in a
[03:52:30] randomized fashion. We evaluated now, on the right in yellow, same dose of nivo ... Same dose of ipi, but looking at different schedules of ipi in this concurrent regimen. And then in grey is showing what I would call the lower bar here. It's looking at, compared to the middle column, the same schedule of ipi and dose, but now looking at a lower dose of nivo.

So based on our pharmacokinetic modeling, this is going to really flank the different scenarios of what we deem to be tolerable and to get a better idea of whether this
[03:53:00] would be not only tolerable, but adventatious . And this is what the data shows. So if you look at both the concurrent arms, I'm not showing here the lower dose of one-on-one. I can tell you that it is tolerable, but it has less activity. If you look at both the nivo3 arms with different schedules of ipi, you find much more tolerable than the other schedules we had shown you before. Particular if you look at the discontinuation rates, it's single digit and it compares similarly to what we had
[03:53:30] shown you before with nivo monotherapy.

There is more, probably a doubling, in the grade 3/4 events. We're going to talk about in the session after this, what is the nature of these events. A number of these are laboratory based and these actually are pretty well tolerated which is why the discontinuation rate is so low.

If you look at the efficacy now, which before we had 10-20% response rates, we are
[03:54:00] now on the order of almost greater than 50%. Almost 60% ... I'm sorry, in the order of about 40-45% response rates in all comers. If you look at the pdo1 population, where we know there is a bit more activity, you're seeing upwards of almost 60% response rates. And this compares, again, favorably to nivo monotherapy.

So basically what we've done in lowering the anti ctla4 and extended out that schedule, is we've found now a way to have a very similar and quite tolerable
[03:54:30] safety profile. But giving a chance now for that clinical activity to be observed and in this case, it's quite significant.

I just want to show you one other piece of data. Just another way to look at the breakdown of these kinds of events. I want you to focus in particular on the yellow which represents the high grade events. And you can see with the two different profiles, Ipi Q12 and Ipi Q6, very, very similar. And if you compare that to the monotherapy. Again, the nature of the events is the same. The relative frequency, the frequencies within a category's the same. It's just a little bit high degree of
[03:55:00] these high grade events that you're seeing with this combination.

In summary, the combining IO agents such as ipi and nivo is feasible. And this is obviously of great interest to all of us as we move this forward. The evaluation of the different doses and schedules of these combinations do benefit from larger sample sizes and also in doing this in a randomized fashion so you're able to make
[03:55:30] more appropriate comparisons. The systematic evaluation of these combinations

may need to be looked at tumor by tumor if we want to optimize and try to achieve the maximal effect. Making assumptions about what we're going to see from one tumor to the next, may not be valid.

Just like to acknowledge the organizing committee for inviting me here. I really
[03:55:58] appreciate that and all the people at and our investigators that have worked very hard on all those trials to get us as far as we are right now.

Thank you.

[04:00:04]

Mark Ratain: Well thank you. I'm Mark Ratain from the University of Chicago and I want to build on what the previous speakers have conveyed. I'm a medical oncologist as well and
[03:56:30] I also ... Have some ... Do some work in clinical pharmacology. My title is "Randomized Dose Escalation and Dose Ranging Trial Designs." I think you've seen from the previous speakers the importance of randomization in their developing plans. And I would like to put this into a more generalized viewpoint.

[03:57:00] Here's the historical clinical ... Oncology clinical development plan. More is better. This is what we teach our fellows. Phase 1 we should escalate in cohorts of 3-6 patients. The highest dose, the results in less than 33% instance of dosing toxicity. And then treat 6 patients at the final recommended phase 2 dose. And then phase 2 we should treat a sufficient number of patients the single dose to either prove
[03:57:30] the drug is inactive or to estimate the response rate to the desired level precision.

It's not surprising that a lot of these developing plans fail, as they have historically. Now, some that is that the drugs haven't been that great. I think that we are now blessed with much better drugs, and so I would say as a community, we should give it our best shot from a development perspective. And here's what I want to convey as my recommendation, particularly in the context of immuno-oncology
[03:58:00] combinations, which is what I was asked to do.

That for phase 1, we should do randomized dose escalation trials where a subset of each dose cohort is randomized to monotherapy. And for phase 2 we should do randomized dose [inaudible 03:58:15] trials which is also appropriate for monotherapy, as well. This is the way we've looked at the world. This is actually
[03:58:30] from a Multiple Sclerosis research organization in Australia and so this is not just a oncocentric view of the world. Pre-clinical lab and animal studies, we then do phase 1. A safety study, 20-80 people. We then do phase 2, both a safety and efficacy study in 100-300 people. Then we do phase 3; measure effectiveness, monitor side effects, 1,000-3,000 people. And then phase 4; monitor long-term side effects.

[03:59:00] And this is the way we've been looking at it and you put this view, this traditional view into the design of oncology combinations. And you've heard a little bit of this in the context of previous presentations for phase 1, and the two drugs here are BW. "B" stands for "blockbuster" and "W" stand for "wonder drug." And you can fix

[03:59:30] B and escalate W. You can fix W and escalate B. You can fix your W to be ratio. You can escalate both B and W ... We see many, many proposals like this. We see many presentations like this at ACR and ASCO meetings.

And then, phase 2. There's a couple of basic choices. We can compare the combination at the recommended phase 2 dose to monotherapy alone. Usually
[04:00:00] based on historical control, sometimes in a perspective comparison. Or one -

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Mark Ratain: Sometimes in a prospective comparison. Or one can test the activity of the combination disease resistant to be. And then Phase Three, compare the combination to, who knows what. Traditional view people say "I want to do a Phase One trial, a B plus W", and you go "Well what are you going to do with it?" "Well I'm not sure, I'll figure it out as I go." Well that has not worked all that well, that general strategy.

[04:00:30] This is an analysis that we did and published in 2010, where we looked at all Phase Two trials published in the medical literature during the period 2001 and 2002. And looked at the impact of those studies on the subsequent changes in the standard of care. We defined something called positive predictive contributory value. You see
[04:01:00] in the figure that we looked at 363 trials. The vast majority were non-randomized, three hundred forty-one. And you see the two hundred sixty-two of these Phase Two trials, two hundred sixty-two of three hundred sixty-three, were deemed positive by the authors. And yet, the table there on the right shows the number of those regimens that eventually changed the standard of care. In other words, four percent of Phase Two trials deemed positive actually had any impact. And these
[04:01:30] trials involved more than sixteen thousand patients. And so, this approach is fairly inefficient to say the least. So we really need to think a lot harder.

You've seen the number of combination trials, for example, Pembro. Eric showed two hundred with Pembro alone. And the recent issue of the cancer that are also illuminated this story, with the vast number of clinical trials of immunotherapy
[04:02:00] ongoing globally. So, I think we need to rethink it. I have said this before in a Nature Reviews Clinical Oncology paper, that we need to redefine the primary objective of Phase One trials, and to stop trying to define an optimal dose in phase one. So just forget it, it's not worth doing. We can gather experience. We can gather information.

[04:02:30] Phase One studies are clinical pharmacology studies. To do them well requires an understanding of pharmacokinetics and pharmacodynamics. That's not what we teach our fellows. And that we really need to do these well, and to define the range of Phase Two doses as an outcome of a Phase One trial. Whether one is dealing with a monotherapy, or a combination. So, here's my proposed view of the design of oncology combinations. Rather than starting with Phase One, one should start
[04:03:00] with Phase Three. And one should think about "What am I going to do with this combination? Where do I see it having an impact?" and to think about the

combination versus a control arm, which you should be able to think about. At least, recognizing that the standard of care may change, but at least at the time one is beginning development of the combination, to have a view as to what that
[04:03:30] Phase Three is going to look like. If you don't have a plan for Phase Three, don't bother with Phase One. It's not going to be fruitful.

Once you've defined your control arm, you can then think about what experimental arm would be optimal, and to think about what that Phase Two trial would look like. For example, are you going to have a Pembrolizumab as the control arm? Are
[04:04:00] you going to have Paclitaxel as the control arm? Are you going to have Erlotinib as a control arm? To really think about the control arm and then you can think about the design of the Phase Two to obtain that potential combination. And it should really be a randomized dose ranging trial, to find the optimal experimental arm or arms appropriate for Phase Three. Again, the concept being that Phase Three may have more than one experimental arm. And then, you can think about "What does
[04:04:30] the Phase One need to look like, to define the arms for the Phase Two?"

So we really need to rethink the way we're looking at development and there's just way too many combinations going into the clinic without a plan. And that's why we're going to spend a lot of money on clinical trials, and then the industry will say it costs us too much money to develop drugs, and we're going to have to keep raising prices. So, let’s be more efficient and the world will be a better place.

[04:05:00] All right, now just to give you some examples, we have done trials using these types of designs. This is a trial that one of my colleagues conducted, Dr. Rita Nanda. A randomized Phase One trial of nanoparticle albumin–bound paclitaxel, with or without Mifepristone for advanced breast cancer. Mifepristone is an antagonist of the glucocorticoid receptor. And has been demonstrated in pre-clinical models to
[04:05:30] overcome taxane resistance. So the thought was, "we can combine these two". It's also known that if you antagonize glucocorticoid receptors, you're likely to have a lot of PK and PD interactions with a taxane. And the starting dose was one hundred milligrams per meters squared, and with a plan to deescalate as needed, we expected that we were going to run into increased toxicity.

Patients were randomized to the taxane alone versus, in fact we used a placebo
[04:06:00] taxane, plus placebo versus taxane, plus Mifepristone. And we used a three to two ratio with a plan minimum of five patients per dose level. And the plan was to potentially escalate the Mifepristone dose up to as high as twelve hundred with a starting dose of three hundred. So, what happened was, not surprisingly, we ran into toxicity. And the toxicity was technically dose limiting, but it was really
[04:06:30] myelosuppression that was manageable. And the toxicity was clearly predominating in the experimental arm. It clearly support the hypothesis of increased toxicity with the mifepristone. We have PK data to go with this, to support that. And basically the conclusion was that the strategy was feasible. There's going to be increased toxicity, but it was manageable. There was a clear plan to move forward, in fact, this strategy is moving forward, just with a different
[04:07:00] glucocorticoid receptor antagonist. Now, this strategy is used all the time outside of

oncology.

So, let's turn to a different disease model. Inflammatory Bowel Disease. Here's an example, 2010 Phase One, double-blind, randomized placebo-controlled, dose-escalation study of NI-0401. Which is a humanized anti-CD3 monoclonal in patients with moderate to severe active Crohn's Disease. You can consider this either
[04:07:30] monotherapy or combination depending on definitions.

Patients were allowed to be on other drugs, as long as the other drugs were stable. corticosteroids, salicylates, diapurines, methotrexate. Things that we have some familiarity with. And then, this drug was put on top of that stable backbone therapy that the patients were obviously not doing terribly well on. And it was a
[04:08:00] randomized trial, they actually started at ten, and had to go down. And you note that the lowest dose is placebo. So that there was prospect of randomization to placebo across the entire study. Forty patients were randomized. Seven of them ended up getting randomized placebo. And of course, if you're only randomizing one or two per dose level to placebo, you can still combine all those placebos into a single placebo cohort. And so, they started at ten and actually ended up then, had
[04:08:30] dropped the lowest active dose to .05 so to sequential randomization to higher and higher doses of the active drug. The readout was CD3 modulation, and there was clear evidence of dose response. And the conclusion was the drug was tolerated, doses less or equal to one milligram with manageable side effects, with dose dependent modulation of their biomarker. And this allowed them in a forty patient
[04:09:00] randomized trial to really hone in on a range of doses appropriate for future development.

Here's another example, a drug called sifalimumab a humanized anti-interferon alpha monoclonal that was developed for lupus. And these patients again had active lupus and they were randomized two to one, for an active dose ranging from
[04:09:30] .3 to 30. Again, being escalated, versus placebo, so sending dose blinded cohort. So, this is actually a placebo controlled study. And in each cohort, six to eight patients received active drug and three to four received placebo in the study. Here again, you see the relationship between dose and their biomarker. Clear evidence of a
[04:10:00] drug effect. They then took three of these doses into a randomized Phase Two trial. Two hundred, six hundred ...

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Mark Ratain: ... in my phase 2 trial, at 200, 600, and 1200 milligrams, the previous dosing was per milligram per kilogram but these are [inaudible 04:10:09] approximately to three highest doses. And again, you get a read out showing activity. The three active doses look about the same. And for a variety of reasons and my understanding is the development of this drug was paused but this was a positive trial.

[04:10:30] Here's another example: cirrhosis. Double blind, placebo controlled, dose escalations study, Pfizer compound CP690, 550. A phase one randomized dose escalation, double blind study, administration of 5 to 15 milligrams, BID, as well as

a 60 milligram once a D, with a concurrent parallel placebo control.

[04:11:00] Again, read out, this happens to be a clinical read out. And clear evidence of dose response. 13 placebos patients. And then cohorts of 5-9 patients.

So these are not big studies to understand relationship between dose and activity, or dose in a bio-marker. They're not definitive but we can certainly distinguish dose levels that are clearly inactive from those that are clearly pharmacologically active. So, randomized dose escalations studies are used frequently outside of oncology,
[04:11:30] either as mono-therapy or in combination. Ideal includes a zero dose group pulled across active dose levels. And there's no reason not to cross over to an active dose after evaluation for the primary toxicity or bio-marker in pointe with an aim to identify a range of doses for randomized dose ranging phase 2.

Randomized dose ranging trials are the norm outside of oncology. You will never
[04:12:00] see a non-randomized trial, at least I haven't, outside of oncology for phase 2. And not always dose-ranging, they're always randomized and importantly, the concept of counting dose [inaudible 04:12:11] toxicities should constrain the dose. But not define the dose. In other words, we can't be giving doses that are absolutely unacceptable. We should never be defining a dose on the basis of the number of
[04:12:30] DLT's divided by number of patients treated. The concept of NTD defining the dose should go away. And by the way, MTD's with BSA, hopefully. So, randomized proof of concept studies can also be done using bio-markers for combinations and in this context, you need a clear hypothesis that is testable and if disproven, should lead to discontinuation of the combination development. What one could call a pivotal
[04:13:00] study. One needs a bio-marker assay that is suitable for serial sampling and patients. Ideally, blood based bio-markers. And a trial designed that's robust enough to compare the effect of a combination versus mono-therapy.

And once such example, this is not an immunotherapy trial but it's a study we did of Sunitinib and [inaudible 04:13:22]. And Sunitinib, I think this audience is familiar
[04:13:30] with its role as an inhibitor of KDR VEGFR2 and VEGFR2 is measurable in plasma and goes down with dosing. The concept was [inaudible 04:13:42] a putative anti-angiogenetic agent, if it's really active should be modulating VEGFR2 and so VEGFR2 was the read out here.

We originally conceived this as four weeks on Sunitinib, followed by two weeks of
[04:14:00] [inaudible 04:13:57] versus four weeks of Sunitinib plus nothing. In fact, we couldn't get patients through the four weeks Sunitinib at the labeled dose so we modified it to two weeks on followed by two week break. A relatively small study because even though we enrolled 41 patients, we ended up only being able to only randomize 14 because we had to amend the protocol to get these patients
[04:14:30] through. But we had 14 patients, 7 who got [inaudible 04:14:28] and 7 who didn't. And basically we couldn't see anything resembling a difference and we concluded therefore that it was clear evidence against proof of concept using this bio-marker in pointe. Again, small study using a bio-marker, if you have a concept, it should be clear and it clearly wasn't there.

So in conclusion, combination development is difficult. It's particularly difficult for IO combinations, where we have significant efficacy without regression. We have
[04:15:00] delay in manifestation of efficacy in many patients and I would say randomized trials are necessary throughout the development of IO combinations and being from Chicago, I will say randomized early and often.

[04:15:30]
Hong Zhao: Hi. Good afternoon. My name is Hong Zhao, I'm a clinical pharmacologist from the FDA. I would like to thank the workshop organizer for inviting me to give this talk. My talk will be focused on regulatory consideration, optimize dose selection for immune-oncology products.

[04:16:00] So first, I'd like to say the views of this presentation represents my personal perspectives and do not represent the official position of the US FDA. My talk will focus on the importance of dose selection and factors to be considered and recommendations. I will also switch gears and talk about communication with the FDA and conclude my talk with a take home message.

[04:16:30] First I want to lay out the FDA mission statement not only saying protect the public health but assuring the safety, efficacy and security of FDA regulated products. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicine more effective, safer, and more affordable.

[04:17:00] So first I would like to talk about the importance of dose selection as the FDA mission statement, saying that FDA promotes and helps innovative and efficient drug development. We at the FDA are striving to give the right drug at the right dose to the right patient at the right time. And this way, to increase, to maximize
[04:17:30] the efficacy and minimize the toxicity, ultimately to increase the success rate of drug development to make more efficacious and safe drugs to the American public.

Here I listed 6 major factors to be considered in clinical dose selection. They are
[04:18:00] pharmacokinetics and pharmacodynamics, levels of targeted expression and incubation or stimulation, body size based versus flat dosing and exposure response or dose response relationship. Also need to consider tolerability and safety profile in the product and the patient population and study.

[04:18:30] In theory, my talk, I'll be focused on three factors: the body size based approach or flat dose approach and also whether in a cancer type or specific patient population needs to be specifically considered and supported by exposure and dose response analysis. For the level of targeted expression or inhibition, this morning my
[04:19:00] previous people have already covered and later this afternoon for the safety, other session will be covered also.

So first, let's see, body sized based dose or flat dose. This is a dosing approach. I want to talk about this, to use two examples, illustrate the point. One is the aflibercept and the other is TDM1. So when we think about body sized based dose,

[04:19:30] in other words, is per body, per kilogram or body surface area versus flat dose, in other words, a fixed dose. So when one choose one of the approach is more appropriate, we first have to look at the PK, pharmacokinetics of the product. If the
[04:20:00] clearance is independent with body weight, that means flat dose is maybe more appropriate to give ...

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Hong Zhao: That means flat dose may be more appropriate, give you less intersubjective variability. On the other hand, if the clearance in body weight based, then body weight based dose make more sense. This is a case, actually, of aflibercept, it's clearance is not body-weight based, dependent or related to body weight.
[04:20:30] Therefore, when patient was given body-weight based dose, we can see clearly the slope that suggesting the body weight, the exposure increased with body weight increase.

What this means here, we compared the two approach, one is a body weight based
[04:21:00] dose. One is a flat dose. Let's see how it come out. The intersubjective variability with body-weight based dose is much, much larger than the flat dose. Also, please note that these two approach give you two different patient populations with higher exposure or lower exposure. In other words, for a flat dose if you give-, for
[04:21:30] the lighter patient they will have a higher exposure. The heavier patient has a less exposure. If a body-weight based dose, of course, the dose increase with body weight. Then, the heavier body weight patient has a higher exposure and the lighter patient has a lower exposure.

This is what we observed for exposure, whether this is have any impact on clinical
[04:22:00] outcome. Let's take a look of that. Based on exposure response analysis, it suggests the possibility of improving survival benefit in patients with lighter body weight. How is that? Let's look at the left panel, this plot. We plotted the survival based on
[04:22:30] 4 exposure quartile from the lowest quartile, Q1, to Q4, highest quartile. We can see very clear separation in terms of overall survival, Lower quartile, exposure quartile, has less survival benefit. We further plot this curve based on body weight. We can see patient with less than 55 kilogram body weight has less overall survival
[04:23:00] benefit than patient with a body weight of greater than 80 kilogram.

We also know during the-, during aflibercept drug development, maximum tolerated dose was not reached. How much evidence difference is due to poor dosing we don't know. Here we take the consideration of other factor, confounding
[04:23:30] factors into consideration, then we may be able identify or-. In other words, it's saying even consider the other factors we still think there is a possibility to improve the survival benefit in the lower-, lighter patient with a better dosing.

[04:24:00] The next case-, oh sorry. The second case I'd like to discuss is T-DM1. Also, our exposure response analysis suggests that increased efficacy with the increasing exposure. On the left panel, you can see the Q1 is still full quartile based on exposure. There's a clear separation between Q1 and the rest of three quarters of

[04:24:30] patient population. Lowest exposure quartile it's in-, almost no different from control. This is the same thing for PFS, for the progression-free survival.

Now, let's take a further look to see how much the exposure contribute to this difference. Based on the multivariable Cox regression analysis, after adjusting for
[04:25:00] co-variants - those are ECOG, number of disease site, prior [inaudible 04:25:04], prior trastuzumab treatment, physical disease, measurable disease in Her2 shed antigen and the tumor burden - all those confounding factor, all co-variants, were taken into consideration. This is the hazard ratio compared to control. For the
[04:25:30] lowest exposure quartile, the hazard ratio is almost, it's 1, compared to the highest exposure quartile the hazard ratio is .35. This one it's clearly demonstrated that the lower exposure quartile patient has no benefit from the treatment.

Another question is whether one dose regimen fits all cancer types, whether
[04:26:00] disease has some effect on exposure then leading to different clinical efficacy. Now listen, I want take to example two. One is a trastuzumab and another one is ramucirumab. We observed a similar phenomenon. For trastuzumab, based on population pharmacokinetics analysis we noticed that in the patients with GI
[04:26:30] cancer, their exposure was lower - between 24-63% lower trough concentration - than the breast cancer population. They both-, both population used the same dose regimen, 8mg/kg initially then the maintenance was 6mg q3 weeks. We also
[04:27:00] look at the covers in terms of, in fact of the exposure. The gender and the race did not lead to clinical relevant change in all exposure parameters at a steady state. Body weight did have some effect, cannot be excluded.

Let's see the clinical impact. The left side is also plot with 4 distribution quartile in
[04:27:30] terms of exposure. We can see the red one is the lowest quartile. It's clearly separated from the rest three quarter of patient population. We did a further analysis by matching, you know, control for the lowest quartile and also the rest patient with matching the case also. Here, we can see for the lowest quartile the
[04:28:00] overall survival compared to the control, they're overlapping. That also clearly demonstrate in the case-control analysis showing that no benefit from the lowest exposure quartile and the current dose regimen.

Ramucirumab, same exact case for GI cancer compared to colorectal cancer. GI
[04:28:30] cancer patient has lower exposure than colorectal cancer and those lowest exposure quartile did not benefit from the treatment. Therefore the sponsor currently is conducting post-marketing [inaudible 04:28:44] study to explore to see whether a higher dose can improve the clinical efficacy.

[04:29:00] Here, I want to present one good example of dose selection. This is the nivolumab. Nivolumab, the company did a very good dose exploration and they used a wide range of dose from .1 to 10. Also, they enrolled a good number of subject in each dose cohort to come up with, how I can say, as a reliable activity, reliability, in the
[04:29:30] melanoma. From this dose, it responds. We can see it's a flat dose response relationship for nivolumab in melanoma indication. The sponsor choose this 3mg per kg dose to move forward for the clinical efficacy and safety trial. We also-,

[04:30:00] sorry. We also did exposure response with 3mg per kg q2 weeks dosing schedule.

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Hong Zhao: ... Per kilogram to cure two weeks dosage schedule, and identify the flat relationship for the ER ... ER relationship also acknowledge that the exposure range is limited due to one dose level. The meantime, we also did a safety evaluation. There are also flat relationship exposure response for safety.

[04:30:30] Now, let's move to dose funding and immuno-oncology combination therapy, what the regulatory considerations. FDA has a guidance published on this combination use, developer to a more ... Drugs, new drugs in combination. It has to have strong rationale for the combination. The combination of drug directed at the multiple
[04:31:00] [inaudible 04:30:58] targeted to either improve treatment response or minimize development of a resistance or minimize adverse events. We have to have a plausible, biologic rationale for combination use ... Supported by non-clinical model demonstrate the improved clinical outcome either additive or synergistic, in other words, there's a one plus one equal two, or one plus one greater than two.

[04:31:30] It is optimal if we know effective dose for each monotherapy, and also optimal to know dose response or exposure response for each monotherapy for efficacy and safety. We need to know that safety or efficacy profile may be tumor-specific as illustrated by previous speakers also. Also, safety and efficacy profile may be
[04:32:00] different for different dose combination. Actually, I also list [Nivolumab 04:32:09] and [ipilimumab 04:32:10] combination for melanoma as a good example, but I don't need to say more here because my previous speaker covered very well on this one. The efficacy showed more than the monotherapy, this is very successful case.

[04:32:30] During those funding for those IO product combination ... We also need to consider whether the drugs can be given concurrently administered or sequential dosing is better to have a better clinical outcome in term of efficacy or safety. We also need to consider whether combination has a different ER relationship, or is the same as a
[04:33:00] monotherapy. Most of time, combination use as we mentioned either sensitized to overcome the resistance or reduce the toxicity. Sometimes combination may potentiate the toxicity ... We have to pay attention to that. Specific tumor type may
[04:33:30] need a different combination, and also different dose of combination ... That was well explained by EP and nivo combination in melanoma, and renal cell carcinoma, and non-small cell lung cancer cases.

Here is a regulatory current recommendation in terms of dosage selection for clinical trials. We recommend identified optimal systemic exposure of the immuno-
[04:34:00] oncology product in the general population. We also need for pay attention to special population to assess the effect of the intrinsic factors exposure, systemic exposure of IO product. Intrinsic factors including age, sex, body weight, organ
[04:34:28] impairment, disease, immunogenicity , et cetera. The intrinsic factors as many
[04:34:41] concomitant medication as lot of immuno drugs may cause cytokine release that

may pose a potential for drug interaction.

Then we recommend before commencing trials to support [inaudible 04:34:52] optimize the dose regiment, conduct the adequate dose exploration, and
[04:35:00] investigate more than one dose, and more than one dose schedule for efficacy and
[04:35:07] safety. For example, for pembrolizumab , they studied the two milligram per kilogram and 10 milligram per kilogram to see which dose give better clinical outcome.

We highly encourage collection of [inaudible 04:35:19], in all clinical trial in order to
[04:35:30] do exposure response or dose response analysis for efficacy and safety to help better clinical dose selection. Also, don't forget to evaluate whether body weight, base dose, or flat dose is a better approach based on the body size and the drug clearance relationship.

After completing the registration trial, we also recommend conduct the analysis to
[04:36:00] confirm ER relationship support the recommended dose and dose regiment for marketing. We always ask for this because the clinical phase three data is the more rich data to confirm that.

Now, allow me to switch gear to talk about the communication with the FDA. FDA
[04:36:30] and the drug developers have shared the public health goal of early availability of a safe, effective, and high quality of drug to the American public. FDA provides valuable scientific and regulatory advice resulting in more efficient and robust development programs. FDA helps sponsor define adequate evidence of effectiveness, safety, and product quality. With enhanced communication will
[04:37:00] enhance regulatory science and expedite drug development. FDA has best practice for communication drafted guidance published.

Here, those funding and a selection for future clinical trials, we encourage early, frequent communication with FDA. You can request meeting with FDA in early stage of drug development, and consult FDA as needed throughout the drug
[04:37:30] development. There are milestone meetings you don't want to miss. One is a pre-IND meeting, end of phase one, end of phase two, and the pre-BLA for drugs will be pre-NDA meeting. You also can request discipline, specific type C meetings. We usually give you written response back.

There's a pre-BLA or pre-NDA meeting ... At this meeting we'll discuss what
[04:38:00] constitute a complete application. The take home message is use of optimal, biological [inaudible 04:38:04] dose and dose regiment ... Better utilize of target interaction biomarker data for dose selection. I didn't talk about this, but other speakers in the morning talked about this point. Also, adequate dose ranging ... Use
[04:38:30] more than one dose level or dose schedule in the clinical trial to assess drug activity, or efficacy and safety. Collect a PK data in all clinical trials ... Use of those response, and exposure response analysis to help dose selection.

As you can see from the case study, exposure and dose response relationship really

[04:39:00] can help you in dose selection. Also, we need dose individualization for the specific population. For example, hepatic-renal impairment patient, geriatric patient, and pediatric patient, et cetera.

Early engagement with regulatory [inaudible 04:39:13] dose selection is highly recommended. Last but not least, the one is the address those question pre-
[04:39:30] marketing instead of post-marketing as we know it's very challenge to conduct those optimization in a post-marketing setting. We already have that bad experience.

[04:39:43] In the end, I want to acknowledge Dr. Raymond , Dr. Jung , and Dr. Zenith for their input on my presentation slides. I want to acknowledge clinical pharmacology
[04:39:57] review teams, and pharmacometrics team for their review of the cases what I
[04:40:00] presented here. I want to thank you all for your attention.

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Section 29 of 46 [04:40:00 - 04:50:04] *(NOTE: speaker names may be different in each section)*

Hong Zhao: ...present it here. I want to thank you all for your attention. Thank you.

Geoffrey Kim: I'll follow you back to the podium. If we could have all the speakers back to the podium and analysts?

[04:40:30] As an update, Dr. Khleif is not able to join us today so we will not have a speak about vaccines. If you're interested solely in vaccines, you may take leave now.

We are honored to have Dr. Goff from the National Cancer Institute. Dr. Goff, if you could just introduce yourself and then provide your take on-, these were all very focused on large molecules and antibodies. What about the biologic therapies and
[04:41:00] active-, like [inaudible 04:41:00] cells and how does these principles apply to you?

Stephanie Goff: My name's Stephanie Goff. I'm a clinician in the surgery branch at the National Cancer Institute and our work is generally in cell therapy. I have to give the same disclosure, that these are my personal opinions and not the official statement of the NCI.

What I would say is that a lot of the issues that we have to focus on were
[04:41:30] beautifully addressed by Dr. MacLachlan in this morning's session in that cell therapy is highly individualized therapy. What we have to think about is the patient population in which we're using it for. For us, we're not talking about a neoadjuvant strategy or an adjuvant strategy. We're talking about patients with highly advanced metastatic cancer, often in the last 6 months of their life. We're not talking about giving a dose where we know that a micro-dose is not going to cause them any harm. We're giving it in the context of lympho-depleting
[04:42:00] chemotherapy that has its own set of relevant toxicities. We need to push in cell therapy I believe to start at cell doses that we think have a chance at working.

While we find those off tumor on target toxicities and sometimes those modified toxicities, there's not a perfect model yet and we have to get to the human experiment to find them.

Geoffrey Kim: [04:42:30] [04:43:00] Maybe perhaps I could have you kind of respond to what was presented by Dr. MacLachlan in the last-, where he said that there's, often time because of the bioreactor of the human being, unpredictable exposure. In the development process and kind of understanding how each individual reacts, how does one go about looking and addressing this over the development, understanding that for this patient population it may be acceptable to start at a fixed dose? How does one titrate and how does one get to the answers that you need? What type of designs and biomarkers are you looking at in order to get at the answers you're trying to achieve?

Stephanie Goff: [04:43:30] [04:44:00] Certainly. You know, over the course of the last few years as we've explored both CAR and TCR we've used different dose-finding strategies. We have had a traditional 3+3, which has led to very poor accrual with a very low start. Our patients come to us very savvy and so they refuse to go into a very low dose cohort. We've gotten a little bit more aggressive and moved away from that conservative dosing strategy to single patient cohorts where we have a build in 2 to 3 week window before patients so that we can identify any potential immuno-reactivity that comes up. IN particular, you can't always use the human as a bioreactor to predict. Her2 monoclonal antibodies have been given, at this point, hundreds of thousands of women but when we used it in a CAR setting, it had a completely unexpected toxicity. We took a monoclonal antibody that we thought had been given safely to a huge population of women. When you use that variable region and attach it to T cell signaling, you got a different toxicity. It really just requires careful assessment. These patients stay with us inpatient for 3 to 4 weeks, so we have the ability to follow them for autoimmunity on a 24 hour basis.

Geoffrey Kim: [04:44:30] [04:45:00] Since everybody here at least begins with a clinical title, and I know clinical pharmacology is just a clinical, I would like to kind of get an understanding about-, I think in everybody's talk here, they talked about some aspect of a non-clinical model that informed developmental decisions. I think ranging from Dr. Ratain's example of a lack of proof of concept all the way to the ex-vivo aisle 12 experiments. Is there, in the development process, a need to kind of go back and assess? You made the decision on these, now you have this product that is either marketed or in development still. Is there-, what goes back to kind of develop these potential biomarkers or ex-vivo markers of activity or assessment of these markers in humans in the clinical trial to see if they could help optimize dose? If you could-, if the panels could comment on the kind of need to cycle back and look at these markers to inform better dosing strategies.

Eric, I'll pick on you first.

[04:45:30]
Eric Rubin: Thanks Geoff. As you were saying that, I think I just-, and I noticed in Mark's talk as

well, I think you do have to have a good assay. I think in many cases we don't have a good assay and I think as you maybe allude to later, even after post-marketing going back and seeing if we can get a better assay that reflects something meaningful in terms of efficacy or toxicity I think is extremely worthwhile. I know for newer agents, there's always that struggle with, again, speed and trying to
[04:46:00] come up with an assay that one can use for pharmacologic assessment.

Male: I would agree with what Eric said. I think one of the challenges is not always does pharmacodynamics relate to the anti-tumor effects. Not always does
[04:46:30] pharmacodynamics relate to toxicity and safety, so it really can be challenging. I think what Mark had talked about earlier, about doing randomized dose escalations to find the ranges is really the key. Our experience has been it's really narrowing down to that, but then getting to the point where you can test a number of these combinations and schedules is really what's the critical [inaudible 04:46:51] factor. I think the challenge we still have is in order to get there you still have to do some form of escalation and the risk with the old-fashioned design is of
[04:47:00] false positives is what we're trying to eliminate.

Male 2: I think if you're starting with a drug that you know well and then you want to add a new drug to it, potentially even one that's never been given to humans before, I think there's some basic things you can do even if you don't have a biomarker. Pharmacokinetics. Plasma concentration's a pretty good biomarker and I have seen
[04:47:30] so many talks where people have said, "Well, we do a biopsy at the time of resistance to this orally administered agent so we can understand why they're resistant." I say, "Have you checked the plasma concentration?" They go, "Why would I do that?" I think that the drug not circulating, it's not going to work. A lot of these drugs have funny pharmacokinetics and a lot of this we don't really understand, so I think certainly pharmacokinetics can be very useful in that context,
[04:48:00] particularly if one is adding in an oral agent for example.

Geoffrey Kim: I would like to welcome the audience if they have a question to come to the microphone.

Male 3: Hi. Dinesh [Dial] with MUK. Some very interesting presentations. I actually got 2 questions. The first is to actually, to David Feltquate. Very, very nice of how you got
[04:48:30] to eventually the optimal combination with EP and Naval, but what was-, maybe I missed it, was how you got to every 6 or every 12 weeks? It didn't seem obvious, certainly based on the pK. I was just curious as to was there some sort of prior biology or some petty experiment that informed you in that direction?

David Feltquate: Thank you for the question. For lack of time, I really didn't go through what is
[04:49:00] probably the most important aspect of what you're asking. We did a fair amount of pharmacokinetic modeling to start to define what I would consider to be the range of what we wanted to achieve. Thinking of what those limits are, one of the limits was how much EP did we want to have on board. We wanted to come up with this scenario where EP was being cleared, so the trough, the C min, was basically getting down to negligible amounts. Although I can't speak to the immuno-

[04:49:30] pharmacologic effects that could still persist, at least that-, so that was where the q12 week came in. In terms of defining the lower bound of exposure, this is where that 1 in 1 cohort came in on the q6 week schedule. We had, from the previous data I showed you, a good sense of we thought EP was driving the toxicity. We had an idea of what is that, that dose both the Cmax, Cmin, and AUC we wanted to achieve to do that. That's really what flanked what we were wanting to do. What
[04:50:00] was left in the middle was the q6, which we knew would achieve some low level-

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David Feltquate: Middle weight was the Q6, which we knew it achieved some low level of continuous Cmin. But we did not know whether that would be sufficient or not.

Speaker 2: Okay, thank you. The next question is actually to Dr. Zhao. You showed several examples of trying to understand exposure response with the end point being survival. And I think in many of the examples, if I'm not mistaken, was using just
[04:50:30] one dose. Can you, and one of them was actually Trastuzumab if I didn't miss that.

So the question is this, and when you're looking at an end point, it's just survival, you're looking at PK, there's lots of confounding that can come into it in terms of drop out. Where the drop out, one assumes those quartile, the drop out in those quartiles is in a random manner, which is not really the case. So in those circumstances, you get potential confounding that can happen due to performance
[04:51:00] status, due to various factors that can happen, which can give the appearance of an exposure response relationship when it isn't. When you're looking at such a long term end point. Can you comment on that?

Hong Zhao: Yeah, what you said is true. There are lot of confining factors. We can take into consideration what we understand the confining factor, but there are some other confining factors we may not identified or taken into consideration. So, this is just
[04:51:30] based on what we have. But the exposure we used is the first cycle of concentration, so that would avoid the later on, the drop out and the dose interruption. But for biologic therapies, usually that dropout rate relatively low.
[04:52:00] Like a small modicum drugs. But that is the factor. And later on, the exposure response model, we took into consideration of the drop out to use an average exposure and some another way to analyze the data for a small modicum drugs.

Speaker 2: Okay.

Hong Zhao: I acknowledge that in those analysis, there are other factors we didn't realize, or haven't taken into consideration.

[04:52:30]

Speaker 2: So in the case of antibodies, catabolism could be a marker for cachexia for example. So right from the start you could actually get an intrinsic rate of higher or lower clearance which may be more marker of the stage of the patient rather than the drug. So you could actually be fooled into thinking there's an OS exposure

relationship when you're looking at something else.

[04:53:00]
Hong Zhao: Yeah, what you're saying is there is a in the beginning with slow dose. But that was
[04:53:08] one cycle treatment. It is also the is it just, for example, Cetuximab, you have to
[04:53:24] saturate the marker right. But we also identify the with what the dose range is . So
[04:53:26] we take that into consideration.

[04:53:30]
Speaker 2: Okay.

Speaker 3: This question's for Mark. Mark, I'm just curious, if you have a data for immune antibody A and immune antibody B as single agents, and you know their toxicity profiles, is there any rule instead of randomizing for sequential dose escalation, just randomizing to three different dose levels. Because of the problem with just even figuring out. So randomize to a high/middle versus low dose with the other drug. So
[04:54:00] you get to the answer more quick.

Mark Ratain: Well, I mean, that's basically what we did with the Cilengitide and Zanidip, where we just didn't bother with any dose escalation, although we found that the label dose of Zanidip was difficult to administer for four weeks. We didn't have any problem with the combination. So I think that's perfectly reasonable. Obviously if one would be conservative, one could throw in one lower dose level just to be safe,
[04:54:30] you know. But I would agree. I would not do a full dose escalation starting from a low dose when you have in that scenario.

[04:54:40]
Speaker 4: Thanks, and again. The incredibly thoughtful discussion about how to approach a very, very complicated area. My comment was really around just how complicated this area we're getting into is.

[04:55:00] A lot of, I think, what was presented here, started with an assumption that response was going to be a good marker for immunity and generally it is a very good, especially when combined with duration of response. But when we start thinking biologically about what we're trying to achieve with anti-cancer immunity, not only are we trying to unleash potentially pre-existing immunity, or generate immunity, we're also trying to generate sustained immunity. And in not all cases
[04:55:30] are these going to be directly correlated. In fact, there are some biologics scenarios where it could be anti-correlated, meaning you stimulate very potent initial immunity, but lose prolonged immunity. And that can lead to complexity around even shape of the survival curve. So it seems likely that your proposal, that getting to a range of active doses for combinations is a really important goal for us.

[04:56:00] What's less clear is once you're within an active range of combinations, are we really going to be able to optimize dose and schedule. Even in randomized studies, when you look at multiple doses for single agents, we answer the question statistically, meaning we can say that two doses are either different or not

statistically. But it's less clear when we look at that wealth of data whether we've answered truth, meaning, dose X is really not different than dose Y. And so I guess
[04:56:30] my question to you as a panel is, for cancer immunotherapy, as we look at the complexity of combinations, once we're in an effective dose range of the combination partners, do we really believe that we can get to a point where we can say, yes, this is an optimal dose and another dose that's active is not an optimal dose.

Speaker 5: I think those are two different questions. So, optimal is something, I think, different
[04:57:00] than the initial assessment of maybe a range or an effective combination. I share your concern, I think this is going to get complex, we haven't even started talking about triplets and really targeting even more pathways where there may be a biological rational to do so.

I think at a later session, tomorrow we're going to talk about different end points. And I think that's going to be another dimension to this in terms of how we are going to truly understand when there are meaningful signals or not. I'm going to
[04:57:30] pose a question back to the group. There are going to be scenarios where combinations are going to be better than monotherapy. But maybe we won't recognize it. So this is the situation of necessary but not sufficient. So let's just take the premise that there may be a scenario where you want to target three pathways and you're evaluating a combination. By all measures, that combination may not look more active than the monotherapy and you may throw it out. But it may in
[04:58:00] turn, actually, be that now you've actually done something meaningful. You just need to add the third element to that and how are we going to, what systems are we going to employ to help us decipher that to understand that?

I think that fits a little bit along with what you're saying. You're talking more about that schedule. But I think it's another dimension of the same aspect. Would you agree Dan?

Dan: You know, let me rephrase your question. I think we can optimize on any end point we want to optimize on. I think the bigger challenge is defining what that end point
[04:58:30] is. There are some very unusual manifestations of benefit as you pointed out with immunotherapy. I have a patient that you know, one of the first BMS trials with a metastatic ampullary cancer, who's never had a radiographic response, who went
[04:58:53] off therapy years ago because required him to, who has never progressed and even
[04:59:00] had an admission for small bowel obstruction, where he got lapped and the nodules were biopsied and the pathologist read it out as consistent with treated ampullary cancer. Which I've never seen before. And so I mean, what's your readout? Is it survival? Obviously we're going to look at long-term survival as the readout for optimization. We're not going to be able to do that in phase two. I think that's the bigger challenge.

[04:59:30]
Speaker 6: And just to add to the discussion. I think one of the concepts is that there is an underlying reason why you'd want to combine these inhibitors and why there's a

need to go from two to three. I think that understanding needs to be distinctly hypothesized and laid out and the understanding of what each component will do to contribute to a better end point, whatever that end point may be is of critical
[05:00:00] importance. And I think what we're seeing a lot is a wide variety of justifications for these combinations.

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Geoffrey Kim: Variety of justifications for these combinations. We have 496, but we know the number is a lot more than that. There is so much variability in the rationale or what is brought to the table to justify why these combinations should be put together. A follow-up to that point is how can we do a better job before this enters into humans and to, I think someone called it the human experiment, I think before we do that, what can we do as better job to understand and recognize that these
[05:00:30] combinations are the [ones to go 05:00:32] and prioritize versus the ones that may not? Because, as we know, the most valuable resource that we have is our patients, and we want to be faithful and true to them to say that we are doing something for a reason in addition. I think that's one of the critical points for the dose optimization discussion that we've been having over the years. Any thoughts?

Speaker 2: Geoff, one thing I would say is that is I think it is going to be hard to stop the
[05:01:00] empiricism because everyone can come up with a rationale even based upon pathway charts as opposed to some type of non-clinical data. One of things is I think that trying to make these efficient again was what Mark was alluding to and maybe again not small [cohorts 05:01:17] and really looking for effect sizes rather than incremental change I think might be one way to do that. I've been struck with by how we're always trying to see some of these where we're getting [again
[05:01:30] 05:01:27] response rates well above the 50% mark where you would not expect that in either mono-therapy drug. I think the likelihood of that, even though there probably is some [confidence 05:01:38] of overlap, the likelihood of that occurring by chance is probably relatively small. You can see that those type of effect sizes in relatively small numbers of patients.

Speaker 3: Dr. [inaudible 05:01:52] is that it [went 05:01:53] phase 3 and went all the way
[05:02:00] back to phase 1, but it did not go back to phase 0. The question is actually not for Mark, but for the entire panel. Do you think that there is still a role for phase 0 into the reality? What I'm thinking of is this morning panel for instance the potential of selecting the appropriate epitope among the different type of antibodies. I don't have a necessarily combination in mind, but the choice of an epitope. You think there is a role for phase 0 in this [setting 05:02:29]?

[05:02:30]

Geoffrey Kim: Anybody? I actually wanted to actually get Dr. [Goff 05:02:37] opinion about this because this might be one of those things where a micro dose or initial dosing of something to see if there's a pharmacodynamics or biologic effect may be worth looking into. For example, we saw the very provocative, non-clinical data about the
[05:03:00] CSF and the expansion of the cell population there which may or may not be

contributing to the neurologic effects of the CAR T cells. Would that be something where that would be feasible to do to perhaps give a smaller dose and then to assess CSF to see if this is safe to expand or, what's your opinion on these things?

Speaker 4: [05:03:30] I think that for those who've not done cell therapy it's, as you might imagine, a complex process. You expose patients to a lot of risk just getting them ready for the cells. To put someone through chemotherapy and give them a period of neutropenia and then not give them something that you feel might be effective, I would have trouble consenting a patient to a phase 0 trial of a cellular product. Those sorts of things can be tested in a vaccine scenario if you're looking just for [immuno-biomarkers 05:03:59].

[05:04:00] I can tell you that finding CAR cells in the CSF is not a unique finding. In our clinical trial, we have seen those cells there as well. However, because of the clinical risks involved with a spinal tap we only do those taps on patients who are having neurological difficulties. It may be that CAR cells are present in every patient whether or not they're having neurological difficulty. It's difficult to say whether that presence of CAR in the CSF is contributing to the neurologic toxicities.

[05:04:30] Obviously that's something that the community as a whole is trying to figure out, but it's becoming one of those neurotoxicity prices that you pay for wonderful efficacy results.

[05:05:00] I'm getting a little off topic, but it's not in particular that CD19, which has moved so far as a cellular therapy toward getting approval, it's not that it's overcome the problem of targeting normal tissue. It just happens to be a normal tissue we can live without. Patients can get IgG infusions and B cell aplasia is not a problem. That limitation still exists for CARs against everything else. To get back to your question in very long and roundabout way, I don't think that we could ethically put someone through a cell therapy with a phase 0 type dose.

Speaker 5: [05:05:30] My question would be to what end? Mark gave the example of working backwards to have a clear line of sight in where you're trying to go. It's just not clear to me in scenarios where the phase 3 would contribute to the totality of what you're trying to build. Maybe there's a particular scenario where it fits well, but I can't think of it.

Speaker 6: [05:06:00] I could imagine it but not before phase 1. After phase 1, I could imagine there would be a question that you're trying to understand something about dose and immune response. You might take patients, saying you understand the toxicity at this point of course, since you understand that there are a range of doses you could safely administer hypothetically before a patient is going off to the operating room and where you really want to look at immune response in the tumor and look at the relationship between dose and response. I think that's a scenario, but I think a longitudinal sense, I can't think of how I would do that before phase 1.

Speaker 4: [05:06:30] Also, as an aside, just to point out the concept of epitope finding, is that that very dramatic picture Dr. [MacLachlan 05:06:29] showed of the woman whose skin developed a very severe rash and then improved. That was targeting an epitope

that we had targeted previously with a lower avidity receptor where we didn't see that, so same epitope just a slightly more avid receptor and we developed different toxicities. Even though you find an epitope that might work, you change the parameters just a touch and you get different side effect profiles.

Speaker 7: [05:07:00] I'd like to get back to the issue of flat dosing versus body-weight dosing. I wonder if the field is ready to adopt flat dosing for new trials of immunomodulatory antibodies because it seemed to me from the presentations that the confidence in selecting a flat dose came from looking back at the data that was done on a body-weight dosing basis. Specifically, to David and Eric, do you feel that we're ready to move to flat dosing for all of the new antibodies that are coming along in clinical [05:07:30] trials?

Eric Rubin: I can say we're trying to do that. We have examples now of newer ones where we're starting with flat doses rather than weight-based doses.

David Feltquate: Yeah, I would agree with Eric. For mono-therapies, I think the preponderance of data for monoclonals is that probably flat dosing would be sufficient. I think the real challenge is going to be in combinations. I'll point to the data that I showed from study 4 with the [epinevon 05:07:56] melanoma. To remind everyone, anti-[05:08:00] pd-1s as a mono-therapy have a very flat-dosed response and dose toxicity curve. When we had a fixed dose of [epi weight-based 05:08:09] dose and we started doing escalating doses of anti-pd-1, we found we ran into toxicity. That would suggest that there is, in fact, a dosed-response curve. How when you put these combinations together and how you're able to manage a flat dosing in that doesn't [05:08:30] mean it can't be done, but I think we need to be careful that the assumptions we built in around mono-therapy are truly going to apply with those combinations.

Speaker 8: I would like to come in on that flat dosing. Actually it happened to have a case as flat dose is better than the [moderate 05:08:45] body weight based dose. That not say every [monoclonal 05:08:48] antibody or [biology 05:08:50] is a flat dose. We [05:09:00] have to depend on the [inaudible 05:08:55] characteristics and also the relationship for [neurolomath 05:09:06], there is a flat dose response for advocacy and safety. That's why it's a good candidate go to the flat dose. Even the flat dose may give a little more [interceptive variability 05:09:20], you still can go to flat dose, but for other [inaudible 05:09:25] protein may not be the case. We had a research paper [05:09:30] published looking back to approve the [monoclonal 05:09:34] antibodies. It, kind of, half/half of the product. It was one dose approach better than the other. The reason why I proposed this because in Oncologist Society, usually, we think [partly 05:09:50] surface area based dose and body weight based dose always better than the flat dose. That is not the case. With both those approach, we need to pay [05:10:00] attention the minorities.

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Speaker 1: We need to pay attention to the minorities. The lower body weight and higher body weight, what impact then with the certain body that those approach to see

whether they are at any risk for [inaudible 05:10:16] or overdose.

[05:10:30] Neither approach other than the oncology area is use tired dosing, especially for patient with lower body weight we can go with like ten kilogram as a tier to have a certain dose level that way. We have to look case by case, not one size fits all. Thank you.

Speaker 2: I'll just throw my two cents in. It only makes sense if there's a narrow therapeutic index drug. I guess what we don't need right now are narrow therapeutic index drugs.

[05:11:00]
Speaker 1: Yes. That's a very critical point. If it's not [inaudible 05:11:02] no matter which dose approach may not matter. But, flat dose may be more convenient, more compliance and easier too ...

Speaker 3: Kelly U. from Cipro FDA. I want to hear some comments about cell therapy dose findings. In reference to Mark's comments about looking at phase three, actually
[05:11:30] FDA had a draft [inaudible 05:11:28] been there for more than almost ten years called the target product profile. Some of you know that. Actually you're looking at the labeling, meaning the package insert, to see what you want to put in there. Then you go back.

One of the things of course is dose. For cell therapy, a lot of good points have already been discussed. I want to point out that the cell therapy is not just T-cell
[05:12:00] therapy. Adopted T therapy has it's unique characteristics but generally speaking, [inaudible 05:12:02] tumor vaccine cell lines, all those actually follow a dose response, so whatever the response [inaudible 05:12:11] find that kind of a relationship.

For the Adoptive T-cell therapy the tiers that Dr. Graff may know better that we
[05:12:30] don't see so much toxicity in a sense that would lead to the cell dose. Difference from cars. The car keys that one pointed out is the vility of the single chain. Also the other domains of the construct might be different so me talking about this is dose but actual functional characteristic of that particular car may be totally different from others.

[05:13:00] It's very challenging for us to determine what would be a, for example, studying dose and what would be optimal dose for further involvement. Also the challenge is that the most, almost all car T's we've seen are autologous T-cells. You may not have every patient able to produce that T-cell. It affects that [inaudible 05:13:26] as
[05:13:30] well. It's very hard to generalize a general schema for the dose finding studies.

What we usually do in the evaluation of these files is that we like to ask sponsor, of course you are the expert, to give us some justifications for why you're studying those. If your dose is low, we actually tell you that. It's too low, it may not be working at all. It's a little too high, then we about to take it back a little bit because

[05:14:00] toxicities are really ... We talk about that in the next session. They're really very concerning sometimes.

At this point, then you talk about dose acclimation and really weighing these priorities stage and a lot of the investigators and our reviewers really had a very close relationship in one on one sessions. They just cause hours and multiple sessions about how to find the correct dose.

[05:14:30]
Speaker 4: I would just say the regulation of cellular therapies is as individual as the cell therapies themselves and I agree that it totally does not fit a one size fits all. Even the words dose limiting toxicity don't mean much when you're only giving a single dose of cells in a patient's life time.

Speaker 5: I just want to comment on the phase zero so what I've heard from the sponsor. One has been once they submit the IND for the phase zero they have to close that
[05:15:00] IND and submit a new IND for the therapeutic phase so that has been a hurdle, a burden for them.

We don't see that many phase zero's. Very little, if any. The one case that I actually recall was because of ethical issues that you mention was when the drug was given to the tumor for a bio marker evaluation and then a few hours later the patient went under surgery. The treatment was surgery and in this case there was no delay
[05:15:30] in the surgery. It's hard because of the ethical issues. I just wanted to ...

Speaker 2: I'd like to thank everybody but before, I have three rapid fire questions. Eric, one of the big things that we're trying to do is broaden the discussion on eligibility criteria. Elderly, pediatric, lymphatic impairment. For these types of therapies one of the exquisite exclusion criteria is auto immune diseases. History of. Is there any safety
[05:16:00] experience of patients with previous existing auto immune diseases being successful treated without adverse events or that are able to tolerate ... We saw the dramatic experience in David's slide but just your comment quick.

Speaker 7: I think it's probably ascertainment biosphere. I think we hear about the ones ... There's others we've heard about where people inadvertently get the drug and I think they have adverse outcomes. I'm sure there are people that we don't hear
[05:16:30] about that have escaped this but I can't give you numbers. I just don't think we have it.

Speaker 2: I think that's something we could think about moving forward.

Speaker 8: There's been quite a number of people that have come on trials with low grade psoriasis. That would be on the far end of the light scale of this. Then the patient I talked about with ulcerative colitus. There's probably a scale here. It needs to be prospectively evaluated to understand that but I wouldn't outright say any history
[05:17:00] of any auto immune disease should be excluded.

Speaker 2: I think maybe as a field we need to work on our eligibility criteria protocols to address that sometimes the blanket exclusion ...

Speaker 7: Something that I think also just how you define an autoimmune disease.

Speaker 2: Exactly.

Speaker 7: It's not completely clear.

Speaker 2: Exactly. Clarification. David, for you any plan to take the Q 12 dosing in to melanoma and recess whether a dosing regime of ipi in the ipi-neva combo may
[05:17:30] initiate some of the adverse events?

Speaker 9: I can tell you what's happening right now in melanoma. There's an ongoing study looking at 3113. Where I showed you the sequential small cohorts and we made a decision. I think it's been enrolling now for about six months, so it's a large trial to try to really understand both from a safety and efficacy stand point. Are there meaningful differences?

In terms of that schedule though. As we were exploring a range of other tumors
[05:18:00] and activity, we're adopting that more and more. A part of the premise has been really going back and looking at the data and trying to understand what is the potential value of long term anti CTLA 4 blockade? There actually is a bit of literature on this generated by Alan Korman and others suggesting that on an intermittent basis but over time having that blockade may be beneficial.

Again, we need prospective studies to fully evaluate that but there's a good rational
[05:18:30] for why you'd want to do that. The Q 3 week schedule with the four doses usually runs into some issues around toxicity and that prohibits the ability to meaningfully do that. This is another reason why to make these adjustments might fulfill the goal of evaluating them.

Speaker 2: Last question. Mark, you've been giving us good advice and good ideas for years. What can we do? What's the one thing that we can do to start implementing these changes that you see us needing?

[05:19:00]
Speaker 10: Well, I think you're doing a great job. You're having workshops like this ...

Speaker 2: I mean as a field.

Speaker 10: I think, look. As I said, I think we have to stop training our foes to develop oncology drugs the way we trained them thirty years ago. I think that's a place to start. I think that it's really ... I mean, look. What we're talking about here is clinical
[05:19:30] pharmacology and it's fair to say that most people that are in principle investigators and studies have little understanding of clinical pharmacology. Maybe the FDA should require at least some training in clinical pharmacology. Full disclosure, I run

a clinical pharmacology training program in Chicago. At least some training in clinical pharmacology so they really better understand what they're doing.

Speaker 2: Yes. And Hong will teach the course.

[05:20:00] Thank you everybody and thank you for all the [inaudible 05:20:01] fabulous discussion today. Thank you.

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[05:20:30]
Mark: To all the panelists for your fabulous discussion today. Thank you. [crosstalk
[05:21:30] 05:20:55] Be here. I'm going to invite Dr. Jedd Wolchok up to the podium here, and
[05:22:00] he's going to moderate the session regarding evaluation of immune mediated adverse events and other unique toxicities of these IO products.

[05:22:30]
Jedd Wolchok: Thank you very much, Mark, and thanks to all the presenters who started off the day. It's been a really exciting day. I'm very happy to have everyone here and very grateful for everyone tuning in online as well. We have well over 1,000 folks who have linked in to this conference so we're reaching quite a wide audience. At the end of the day I'm going to give a couple thoughts about what I heard this morning.
[05:23:00] Apologies to the folks who spoke really early. I had to fly down from new York this morning, and actually flying out of La Guardia, anyone who's done that in the morning knows you get used to hearing, oh, we're number 20 waiting in line and it's already early in the morning. The only thing that's sort of remedied that was an interesting political observation which I promise you this is the only politics I'll talk about, is that we pulled up right next to an aircraft parked at the end of the runway
[05:23:30] and it said "Clinton Kaine" on the aircraft and it was obviously Hillary's plane. The irony, of course, is it's parked in the spot where Donald Trump's plane usually lives at La Guardia, so you can draw your own conclusions about the predictive nature of airport parking.

I just wanted to add a couple of thoughts. I didn't want to delay anybody about having coffee before the break. One of the questions that Jeff asked, which I
[05:24:00] thought was really excellent was, what about eligibility criteria and patients who have prior history of autoimmune disease? Obviously this is a very important topic and we know that there are some that we gloss over, vitiligo, history of thyroiditis, and we do a pretty good job with checkpoint blocking drugs of causing plenty of thyroiditis anyway, and we can replace that. But now the real world of approved
[05:24:30] CTLA4 and PD1 pathway blocking drugs, there is a literature that's beginning to emerge about this. I'll use this as a bit of an opportunity to tout the work of my colleague, Mike Postow, who has published several works on some of the real-world experience on mainly CTLA4 blockade, and some abstracts about PD1 pathway blockade and how, yes, we certainly can see clinical scenarios such as
[05:25:00] what was described earlier where patients who have a bonafied prior autoimmune disease will in fact get worse if you block an immune checkpoint.

That is not universal. There are, in fact, some patients who do not have worsening of quite significant autoimmune disease such as multiple sclerosis, where we've treated quite a few people of histories of MS with ethilium for melanoma. I think it is a ... It certainly is a concern but it doesn't seem to be a uniform nor predictable
[05:25:30] situation. I think my own opinion is that for initial clinical trial evaluations of new agents and new combinations, it is probably best to limit the patients who have true, life-threatening autoimmune disease in their background, and perhaps have cohorts available for those patients once the safety of the agent is better known.
[05:26:00] But we are trying to study this in the real world.

With that addressed I'm going to introduce now our section, which is the evaluation of immune mediated adverse events, which is topical. We have a wonderful group of speakers who are going to talk to us about various aspects of
[05:26:30] this then we will wrap that up with a more global picture of immuno-oncology adverse events. Similar to what Mark Ratain was mentioning about how we need to educate our trainees and our colleagues about the innovative aspects of clinical trial design and efficacy endpoints that are used for these new biologic agents. This is very similar to what we're experiencing with toxicities as well. The toxicities that
[05:27:00] we're seeing are unlike what we have seen with cytotoxic medicines before. Some of them are truly life-threatening. Others are asymptomatic laboratory aberrations and later on I'll use some of the time at the end of the day to discuss how we might reform that, but I think for now we really need to recognize that it's incumbent upon us, the folks who are interested in this field, to make sure that we educate our colleagues.

[05:27:30] That is not just meaning clinical colleagues and academic centers, but this includes the regulatory colleagues as well as industry colleagues to understand that the rules that we usually develop drugs by, they need to be different, modified, in response to the biologic observations that we are seeing with this unique class of drugs. It's really incumbent upon all of us. We're the interested parties who came
[05:28:00] out here to talk about this and I think we have that responsibility.

With that said I'm going to call upon David Berman from MedImmune to talk about the pathophysiology of immune mediated adverse events.

David Berman: Hi. Thank you very much. I'm David Berman. I'm the head of oncology at MedImmune, which is the biologic subsidiary of AstraZeneca. I'm going to be
[05:28:30] talking about what we know about the pathophysiology of immune mediated adverse events, or IMAE for short. At it's very basic, IMAEs are defined as drug-related, inflammatory in nature and for which alternative causes are excluded. There have been a number of IO mechanisms that have been approved over the past 10 years and the IMAEs that occur from these mechanisms can broadly be categorized in three major themes.

First there are IOs that target antigens that are co-expressed on tumors and normal
[05:29:00] cells, and therefore these IO mechanisms have to effectively bypass central

tolerance. They are characterized typically by untargets of tumor toxicities and they may also have cytokine related toxicities, and the classic example is blinatumomab, but we're also going to hear later in this session about CAR T cells and the toxicities associated there.

The second major class are checkpoint inhibitors and there are two approved, anti-CTLA4 which bypasses a central circuit breaker on T cells within the lymph node,
[05:29:30] and anti-PD1 or PDL1 which reverses T cell exhaustion within the tissue. These two checkpoints are associated with IMAEs in multiple organs although clearly anti-PD1 and PDL1 tend to be less severe and less frequent than CTLA4 blockade.

Finally, cancer vaccines and oncolytic viruses do not bypass any form of tolerance and the IMAEs associated with these tend to be more low-grade and not severe.
[05:30:00] I'm going to focus on anti-CTLA4 and ethilium...

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Section 34 of 46 [05:30:00 - 05:40:04] *(NOTE: speaker names may be different in each section)*

Speaker 1: We're going to focus on anti-CTLA-4 and ipilimumab, to be specific, because this is the drug and mechanism that we have had the most experience with over the past sixteen years. Deletion of CTLA-4 in mice leads to massive lymphoproliferation in mice that die by week three. As was mentioned earlier by Alan Korman and some others, blockade of CTLA-4 in non-human primates and in mice does not really
[05:30:30] cause any pathology. There are no really good validated models to model the pathology in mice, although we did hear about the BLT mouse this morning, which could be interesting. Blockade of CTLA-4 in patients does lead to IMEs, as I mentioned. The most common sites include the GI tract, skin, liver and endocrine gland. I'm going to focus on what is known about the pathophysiology in each of these organs and they may range from mild to fatal.

[05:31:00] About ten years ago there was a randomized Phase II study conducted in patients who received ipilimumab, about 115, who were randomized to either oral budesonide or placebo with the hypothesis that the oral budesonide would prevent enteric colitis. Oral budesonide prophylactically administered did not prevent colitis but fortunately there was a series of biomarkers used in the study which have begun to elucidate the pathophysiology of enterocolitis. All patients had biopsies
[05:31:30] within the first two weeks of starting therapy. The reason to do it that early was to catch the incipient changes within the colon before they became flagrant and non-specific.

Up to one out of every four patients had inflammation. It was predominately in the left colon, it was mixed acute inflammation and chronic inflammation. Interestingly, there was no association with subsequent Grade II or higher enterocolitis. Endoscopy, even if it were practical, is not recommended, obviously,
[05:32:00] for screening patients. The histology overlap that was clearly distinct from classic inflammatory bowel diseases such as Crohn's disease and ulcerative colitis, and it was also distinct from transplant-related graft versus host disease. This enterocolitis is distinct from autoimmune diseases that we're familiar with.

There are a series of biomarkers used in the IBD field to try to differentiate Crohn's disease from ulcerative colitis. Crohn's disease is characterized by antibodies to
[05:32:30] microbial antigens such as I2, ASCA, [CEBR 05:32:34] and OMC. In contrast, ulcerative colitis is characterized by antibodies to P-ANKA. In that study of 115 patients who received ipilimumab, we looked to see whether the pattern of changes in humeral immunity would be more characteristic of UC or Crohn's disease. Interestingly, we did see that 10 to 20 percent of patients developed an
[05:33:00] increase in these humeral responses but it was not specific for UC or Crohn's disease. Furthermore, it was not specific for enterocolitis because, in fact, many of the patients who had increases in these humeral responses never had any subsequent enterocolitis. These markers, at least, also cannot be used to identify or to differentiate enterocolitis. Once again, it also reaffirms that this is distinct from classic autoimmunity.

[05:33:30] In that study we also looked at fecal calprotectin. Calprotectin is derived from neutrophils and it is used in the IBD field as a marker for the degree of disease inflammation. We studied this to see whether calprotectin could be used to predict early onset enterocolitis. Although ipilimumab did induce increases in fecal calprotectin, it was not specific and could not be used. For example, the patient on
[05:34:00] the left had an increase in calprotectin after receiving ipilimumab but had no subsequent enterocolitis. The patient on the right had enterocolitis that actually preceded the increase in fecal calprotectin whereas the patient in the middle had an increase in fecal calprotectin that did precede the enterocolitis. Calprotectin is not recommended as either a screening tool or to monitor the degree of inflammation.

[05:34:30] We're becoming aware that the enteric microbiota does play a role in systemic immunity. There was a very nice study from Jed's group actually, last year where they looked at baseline and assessed the microbiome in a series of patients with melanoma who received ipilimumab and they looked at baseline because they knew that after receiving ipilimumab or corticosteroids to treat the enterocolitis
[05:35:00] the microbiome may change. They made two very interesting observations: The first on the left is that patients who were colitis-free, you can see the figure at the bottom colitis-free, patients who were colitis-free tended to have an increase in bacteria detes phylum, I'm showing it in dark blue there, whereas patients who progressed to colitis tended not to have this phylum present.

In a separate analysis they looked at the expression of different microbial
[05:35:30] metabolic pathways and they found that select pathways were less prevalent in patients who progressed to colitis. You can see here in red patients who progressed to colitis tended to have a paucity or less of these metabolic pathways active compared to patients who were colitis-free. There is scientific rationale for why these pathways might be lower expressed in patients more susceptible. They then went on to show that there may be potential predictive value for this to predict
[05:36:00] who might develop enterocolitis but this clearly needs additional follow up and is quite interesting.

Hepatitis as an immune-mediated AE has been more difficult to understand the pathophysiology simply because invasive procedures to obtain biopsies has been relatively difficult. In a case series of five patients who developed severe hepatitis following ipilimumab, we looked clinically and histologically and also at
[05:36:30] autoimmune serology that is usually characteristic of autoimmune hepatitis. What we found is that the histology of hepatitis as an IM AE in these five patients overlaps with acute viral hepatitis and with autoimmune hepatitis. There was some portal inflammation, necrosis, plasma cells, EOS but very non-specific. Interestingly, in that series there was no association with autoimmune serology that is typically
[05:37:00] characteristic of autoimmune hepatitis. The conclusion was that the diagnosis of hepatitis as an IM AE requires clinicopathologic correlation.

Skin is also one of the most common sites of inflammation. In an NCI case series of 63 patients with melanoma or renal cell cancer who received ipilimumab, we looked at eight patients who developed dermatitis. Clinically, it resembled a
[05:37:30] standard maculopapular drug reaction, once again, requiring clinicopathologic confirmation, it's a common theme. By microscopy there were predominantly T-cells, which were very heavy CD-8 positive and occasional eosinophils, but it was also not characteristic distinct from graft versus host disease and from typical autoimmune skin diseases.

[05:38:00] We can understand or hypothesize why patients who receive ipi or CTLA-4 blockade would have developed enterocolitis and dermatitis because these are organs that are exposed to the environment and have tonic inflammation present. We also probably could have predicted hepatitis. The liver is an organ that clears toxins, GVHD in the liver is reported and autoimmune hepatitis, but it's always been perplexing as to why patients who received ipilimumab developed
[05:38:30] hypophysitis, inflammation of the pituitary. Once again, Jed's group a couple of years ago made a quite startling observation that CTLA-4 appears to be a ectopically expressed in the pituitary. They showed this both in mouse pituitary, on the left, and in human pituitary, on the right. They hypothesized since ipilimumab is effector enabled and can bind both complement and FC receptor, they hypothesize that ipilimumab binding to CTLA-4 on these pituicytes can fix complements leading
[05:39:00] to inflammation. This is quite an interesting observation that should be followed up on.

In summary, CTLA-4 was introduced into the clinic 16 years ago, ipilimumab and then subsequently tremelimumab. The management algorithm that was developed mostly with the help of the melanoma immuno-therapists who are on the panel today, including Jed, has remained the basis for all subsequent immunotherapies. It
[05:39:30] falls into four major themes: 1) Close monitoring. 2) Rule-out alternative etiology. 3) Drug interruption or discontinuation. 4) Corticosteroids, typically with a one-month taper. Then there are algorithms for patients who are refractory to corticosteroids. From a pathophysiologic standpoint, of course we know they are inflammatory in nature but we now know that they overlapped but are distinct from classic autoimmunity in graft versus host disease and unlike autoimmune

[05:40:00] disease is usually reversible. In the early days these were called auto ...

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David Berman: Is usually reversible. In the early days these were called autoimmune adverse events, but we moved away from that terminology to avoid confusing non-experts and people in the ER who would have mistaken this as an autoimmune disease and would have treated it differently than these toxicities deserve to be treated. Future work is still needed to predict who is likely to develop immune mediated adverse

[05:40:30] events. Can we differentiate toxicity from efficacy. This is an ongoing discussion. Every time we give a patient a checkpoint blockade. A single target or even combinations or a consummatory agonist. We are perturbing single pathways in what is otherwise a potentially a normal immune system. We occasionally result in immune mediated adverse events. I think this is right for an intersection of people who are interested in studying how the natural human immune system works

[05:41:00] because it's the only situation where we can targeting single pathways and we're getting significant inflammation and toxicity.

Finally, the path of physiology for [inaudible 05:41:08] has been fairly well investigated although still not completely understood. We clearly still need to understand what is the path of physiology of other [IR 05:41:17] mechanisms. PD-1 and PD-L1. The [consummatory 05:41:20] agonists. More work is needed on that front. With that I'll end. Thank you.

[05:41:30]

Speaker 2: Next speaker is my colleague Dr. [Mario Sznol 05:41:42] from Yale University. I had a great privilege of actually conducting that first trial of CTLA-4 and PD-1 blockade with Mario. I'm really looking forward to his thoughts on this.

[05:42:00]

Mario Sznol: We spent many Friday afternoons together. I don't have any data in my talk and I didn't know exactly how to address it. I want to go through a few issues related to the way we think about safety and toxicity of these agents. This is a long list of things we have to think about. In terms when we talk about [IOA 05:42:19] toxicity certainly the AE's are different depending on the type of [IOA 05:42:23] agent we need to talk a little bit about ideology and mechanism which David addressed

[05:42:30] earlier.

The management of these toxicities and how the management may effect efficacy outcomes because I think we're all concerned about that. More practical issues, like how do we educate our nurses and ancillary medical personnel to manage these effects. How do we educate the patients, because they play an important role in the safety of these agents. Without their cooperation we would probably get into a great deal more trouble. We've talked a little bit about patient selection issues and

[05:43:00] prior conditions which are important in maximizing the safety of these agents.

From an academic perspective we also care about how we do phase one trials,

what the DLT period might be. What the D definitions are and how we define the [NTD 05:43:10] and you heard some of that from Mark [inaudible 05:43:14]. We care about duration of exposure on risk because the longer you give these agents, even though the risk is low, you increase a risk of toxicity. From a point of view of simply either doing clinical trials or taking care of patients, we care about
[05:43:30] rechallenging. Can we rechallenge with the same agent whose had the toxicity. Can we challenge with a new [IOA 05:43:36] agent if they've had a new toxicity to a prior agent. These are important for both clinical trials and for clinical care of patients. Then there's the issue which we face often which is a patient is on an [IOA 05:43:47] agent and they go onto another agent. It may not even be an [IOA 05:43:51] agent. What's the safety of those interactions because the antibodies are onboard for a very long time.

[05:44:00] We care about safety of combinations with non-IOA agents form example combining targeted agents with immune oncology agents and that of course not only on clinical trials but occasionally in clinical practice. We don't really understand how these agents interact so we get patients who get colds, and flu's, and pneumonia's, and how do they respond to that. Interested in biomarkers and trying to figure out who's going to develop these. Of course, from an academic perspective, how can we approach prevention and treatment of these adverse
[05:44:30] effects. A couple of things that I won't talk about today but which are really important is the cost of adverse events. When you have a high series of adverse events, many of these involve hospitalizations, prolonged period of steroids, or administration of secondary immunosuppressives and that adds a substantial amount of the cost of these agents. Finally, the risk benefit in that, that we won't discuss today, right now.

I want to make a point very clear, and it was made earlier that the adverse events
[05:45:00] depend on the kind of immune therapy. First of all, they're hyper-sensitivity reactions, for example I've interacted with companies that were developing new cytokines who wanted to call the cytokine related adverse effects, immune related effects and they're not the same. When you give interleukin 2, it's a very different spectrum of adverse effects then when you get with an immune checkpoint inhibitor. For [IL-2 05:45:22] for the most part you don't need to give steroids to reverse the adverse effects, they'll reverse on their own. Where for an immune
[05:45:30] checkpoint inhibitor, if you don't give a steroid, if you get a severe adverse event, they may die from that toxicity. Really have to remember what type of agent you're giving, or you're giving non-specific activation of T cells in cytokine induction, or whether you're giving an immune checkpoint inhibitor which often doesn't induce cytokines at least not acutely.

Then there are idiosyncratic reactions to these agents. Tissue cross reactive or
[05:46:00] immune complex related problems which you may get, which have different mechanisms of actions which may need to be managed very differently. Liver toxicity from [401bd 05:46:09], may well be [epitope 05:46:10] dependent and that changes the way you manage those adverse effects. This has been said before, but we mostly focus now on immune checkpoint inhibitors or [inaudible 05:46:24]

because this is the agents that are in the clinic now. As I said, these don't induce
[05:46:30] [inaudible 05:46:30] effects but they can induce either autoimmunity or auto-inflammatory type of events. It can affect any organ system. It's mostly skin, GI, liver, and endocrine, but almost any organ can be effected. It's clear that different agents induce different incidence. With [anti-CTLA-4 05:46:46] you get more adverse events than you get with PD-1, PD-L1 antagonists and you saw the basis of that earlier today. For the costimulatory agents not excluding [anti-CD28 05:46:56] the pattern of toxicities are very different. The [401bd 05:47:01] and [inaudible
[05:47:00] 05:47:01] have been very well tolerated in the clinic with a very low rate of adverse events. With the exception of, like I said, a few idiosyncratic events.

The dose response, there's a clear dose response relationship for [anti-CTLA-4 05:47:15] 10 is worse than three, which is worse than one and you don't see that across the [inaudible 05:47:18] for PD-1, PD-L1 so again their different types of agents. The rechallenge issues are important. If you rechallenge with the same agent, for example if you go back to [CTLA-4 05:47:28] after you've seen a grade
[05:47:30] three toxicity you're almost always see it again, but not always. It's important to consider, because rechallenging with [anti-CTLA-4 05:47:37] in some cases is indicated cause you can get a second response to that agent. It's clear that if you get a high grade AE to one agent, for example to [anti-CTLA-4 00:07:48], it does not preclude the safe administration of another class of agent like anti-PD-1. This is work done by Jeff Weber, and clearly you can have grade three colitis from [anti-
[05:48:00] CTLA-4 05:47:59]. You can go back later after those toxicities resolve and give anti-PD-1 and you won't see colitis again.

They're not the same in terms of, and that's an important consideration when thinking about clinical trials. Many clinical trials exclude prior grade three of four adverse events from a prior immune checkpoint inhibitor. That excludes a huge number of patients, particularly now where we're giving [anti-CTLA-4 05:48:23] and anti-PD-1 together, many of those patients will develop grade three toxicities. They
[05:48:30] are then excluded from a trial of another checkpoint inhibitor down the road. It's important to remember that a vast majority of these events, with the exception of endocrine events, are completely reversible over time. You can discontinue the steroids at some point and they will have complete resolution of those adverse events, but not in everybody and there's a rare patient that has continued. For example, neurologic toxicity that we've seen for a very prolonged period of time.

[05:49:00] Finally, the treatment of AE's with immune suppressant agents, doesn't markedly effect outcome as far as we can tell and you've heard that before today, but we don't know because we've never tested the question whether you don't give a steroid to someone who has an autoimmune adverse event. We can't do that. We don't really know whether steroids really dampen activity from these agents.
[05:49:30] Although they can still have very good activity despite getting primary or secondary immune suppression. With greater experience and giving these agents more and more, we're seeing more rare, we're getting to see the rare adverse events which can be life-threatening or fatal. When I first started doing this. We didn't really see, we saw about toxicity and the usual toxicities, but mostly reversible. Now we're

seeing patients that can have very serious toxicity and even die of their toxicities.
[05:50:00] It's very rare, but these can include cardiomyopathies.

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Mario Sznol: These can include: cardiomyopathies, pneumonitis, Steven Johnson syndrome, which we've seen, which lead eventually to death. Not necessarily from Steven Johnson syndrome, but from prolonged meylosuppresion and then other rare adverse events, which can be a little harder to manage, like systemic inflammatory syndromes, induction of diabetes malness, it's insulin-dependent, sometimes prolonged debilitating arthralgias do eventually resolve. CNS toxicities, for example,
[05:50:30] are sending a multi-focal motor neuropathies, which then cause a significant morbidity. David talked a little bit about the mechanisms of immune checkpoint blockage, their toxicity or the toxicity of tho co-suminatory agents. The fact is, they're mostly unknown. We really don't know the ideology, but we really still don't even understand how tumors regress in response to these agents.

[05:51:00] The toxicities for 41BB Lee Pin Cheng has looked at this and it may be epitope dependent on the mouse model is depending on the epitope you target you do or don't see liver inflammation. Could result from cross-reactivity with antibody, if you're giving it with normal tissue, as you heard with CTI4, could result from activation of sub-clinical prior auto-immunity, this could be recognition of self-antigen or some other approach. They may be a prior genetic disposition, and there are now large G-West studies ongoing to see if that's really the case.

[05:51:30] Cytokines may play a role in the pathologies in some cases, and there may be a role of inducing antibody dependent toxicity, so sterologic responses against normal tissue. And you saw some data from Jud's group, again, that the microbiome may play some role in the induction of auto-immune toxicity for these agents. But in fact we really don't understand these mechanisms.

In terms of general principles for management, this is really important from the point of view of somebody who treats these patients all the time. The established
[05:52:00] algorithms are very useful, we never get prophylactic steroids, let me just say, because they might reduce clinical benefit. Generally once patients develop toxicity we focus on supportive care for the symptoms, but some patients may need very high dose steroids. In some cases we've given as much as a gram of Solu-Medrol a day to reverse toxicity. In our hands, we have the very low threshold for admitting these patients to the hospital for diagnoses or management. Although we try and
[05:52:30] rule out symptoms from other causes, it's almost always related to the drugs. It's really important to be on alert for the common severe events, like GI toxicities, or function test abnormalities, or ipothicitus, or hypothyriodism, which we see quite often actually, all of those, with the combination of ibi in ebo.

You also have to be on high alert for very unusual and potential severe morbid events which I just listed before, somebody who comes in with symptoms of
[05:53:00] myocarditis, those patients you want to get into the hospital, or pneumonitis, get in

the hospital and treat very aggressively. It is really important from the point of view of management to encourage patients and their significant others to report the symptoms by phone immediately. You have to train your nursing staff to manage these calls, because you can't possibly take all these phone calls yourself. What we usually do is not only have the patients call but we have our nursing staff call them.

[05:53:30] Prophetically or preventatively, to make sure we're calling them on a daily basis because there are patients who are reluctant to come in. Then there are the issues of giving prophylactic antibiotics for patients who are on immune suppression for prolonged periods of times. Some of those patients can then go on to develop opportunistic infections.

For example, patients who have colitis, who have been treated for steroids for a while, who develop recurrent diarrhea, could have CMV colitis and therefore that

[05:54:00] needs to be in the differential. We tend to reassure patients that their ease will likely resolve over time. In order to get them through these therapies, you have to sort of set the stage that they may be feeling poorly for a while. When we manage this in the academic setting or even in clinical trial settings, there's some major questions we don't have answers to in all patients and these are, when do we start the steroids, what dose of steroids do we use, is this going to be done inpatient or

[05:54:30] outpatient? IV or PO? How long to give the high dose steroids before we start to taper? When do we start the secondary immune suppression? Can we use steroid baring approaches for example, give the secondary immuno-suppression quickly so we can stop the steroids because there's no question that some patients can have a very severe long term adverse effects from the steroids?

Now even when to do the diagnostic test, like a bronchoscopy or a colonoscopy, comes into play? All of these are really important in terms of managing the

[05:55:00] patients. Of course, if they've had a response, when and if in their toxicity exhaust can we re-challenge them with the agents? What's the effect on efficacy? I don't think we completely understand that. Within the practice of the hospital, it's not just your nurses and your staff, you have to educate the fellows, the consulting attendees, the in-patient attendings to are going to manage your patients, who're they going to admit to the hospital, the sub-specialty consultants, the people in the

[05:55:30] E.R. need to know about these agents. They can either get steroids inappropriately or not get steroids when they really need them. You have to educate their primary care physicians, they could go to their primary care physician for a cold and get put on steroids which might affect efficacy in some cases.

What we've started to think about is to really develop dedicated, multi-disciplinary management teams within our centers, to manage the different toxicities, and also

[05:56:00] to create alerts within the hospital, so that when patients are on these drugs the other medical staff and personnel can see it right away and know what to do. I've talked a little bit about patient selection in prior conditions. I think this is both important for treatment on a standard of care basis, and also for trials. We really don't know what effect these drugs have when somebody has major organ dysfunction, because these patients are usually excluded from trials. Issues such as

[05:56:30] a prior brain MET can be important even if it's been treated because you can

induce inflammation and create morbidity with that.

We've talked a little bit about prior immunity. We've actually treated patients with standard of care who have prior immunity and have gotten away with it in some and not in others. Just a simple issue like compliance and distance from the center is important in terms of giving these agents. If they don't have a support network and they live far away it may not be possible to give these agents safely. Then there are other issues such as prior viral hepatitis, prior allo transplants, patients who
[05:57:00] wouldn't go on trial, but you might consider for treatment for these agents anyway. There's no known predictive biomarkers so you can't select who's going to be able to do this. For certain things, like RT cells, there are people who are developing bio markers that will tell you who's going to get very sick and so you can be prepared for management of that soon.

I've almost run out of time and I probably have a few more slides than I need to
[05:57:30] but, in terms of drug development in the DLT period, I think this mostly impacts combination development. Most AEs, despite severity, can be managed with immune suppressive agents. We're not so scared, we're scared of the really serious adverse events, but we're not so scared of these adverse events because we know in most cases we can manage these very well. When we start seeing a high instance of severe grade 34 events, it's costly and it's problematic, but most people have
[05:58:00] reversible aes. The duration is an important consideration for defining a DLT. It's possible to accept a very high rate of grade 34 aes if you're seeing a high rate of efficacy. Standard DLT and MTD definitions may not apply here. It's also important when you start thinking about DLTs and you start writing these protocols, to define unacceptable events.

You may accept a 50% rate of grade 34 toxicities, but you may not want a single
[05:58:30] episode of myocarditis. Putting that into your definition and what's acceptable and what's not acceptable, is really important. The DLT period I think is critical, these can occur very late, if you're trying to do a dose escalation and you're trying to get through the trial quickly, but your DLT period is 16 weeks you'll never get done with the trial, so you have to be able to take those late adverse events and include them in consideration of what your maximum tolerated dose or at least your acceptable dose is.

[05:59:00] The dose schedule relationships for these agents are really poorly defined. It's not clear to me that if you go up on the dose of an agent you are doing to increase the incidents or the severity of adverse effects. That really complicates the development of these agents in phase 1 trials. I think Mark pointed this out, that a 3+3 design when you're starting with agents that have high rates of toxicity doesn't make any sense. You really have to evaluate much larger cohort sizes in order to understand what you're doing. It's very difficult to detect these late and rare
[05:59:30] events, so you have to be flexible in being able to go back and decide what is an acceptable dose level. I'll just skip over this, re-challenge as I talked about, it can be problematic but it doesn't always lead to same toxicities but often it does. You have to think about carefully the risk benefit ratio of doing that, the interactions with

other therapies because of the long half-life it's important. Severe toxicity from one agents does not mean that you will have severe toxicity from another agent in the
[06:00:00] same class/

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Mario Sznol: A severe toxicity from another agent, in the same class. I think we need to think about the future, and what we need to do here. We need biomarkers for the use of these agents. We need genetic markers possibly, for predisposition. People are starting to look at that. Maybe there will be serologic ... other evidence of clinical or subclinical prior autoimmunity, that may help us decide who's at risk. Maybe
[06:00:30] there are ways to serially measure something in the serum or plasma, that might tell you who's going to get into trouble. David talked a little bit about that. That's been not very useful, up to this point. Of course, when there is cross reactivity between tumor and host antigen, whether we can identify that, prospectively. I think that'll be very hard.

Finally, in terms of experimental approaches to prevention and treatment. Obviously, if we can deliver some of these agent specifically to the tumor marker
[06:01:00] environment where the action really is for most of these drugs, we may avoid some of the immune adverse events. Alteration of dose and schedule, you've heard about it as a way to possibly, preserve efficacy and reduce toxicity. There's some interesting agents that go beyond budesonide that are non-resorbable, that are going to be studied for treatment or prevention of colitis. Then the whole issue of what role cytokines have in the development of autoimmune disease at least
[06:01:30] locally, and whether anti-cytokines could prevent toxicity.

With that, I'll conclude. I'll just say that there's again, different pattern of toxicity and implications for treatment depending on the agent that you give. At this point, despite our best efforts, there's not a lot of science that guides the prediction of toxicity, and the methods of management. If you're going to manage these agents or give these agents either on a trial or standard of care, you need substantial interaction between patients and the medical staff in order to do this safely. You
[06:02:00] have to train and communicate with ancillary physicians. That happens all the time. They have to know at least, that they're on these agents in order to maximize safety and reduce the possibility that you might do something that would reduce efficacy.

The clinical trial designs, I think need to be reconsidered. We've talked about that a little bit here. Certainly, given that we're dealing with agents that have irreversible toxicities and high rates of toxicities. The standard 3 plus 3 designs, really, I don't think work. There's these very murky dose response relationships, which make it
[06:02:30] very difficult to establish dose going forward for phase II. Finally, when considering the cost of these agents, it's really important to add and assess the substantial cost of managing toxicity, in terms of future resource allocation. I'll stop there. Thank you for your attention.

[06:03:00]

Speaker 2: Thanks, Mario. I'd like to next, introduce [Diko Kazandjian 06:03:06] from CDER; from the FDA, to give a regulatory perspective on the unique aspects of immune-mediated adverse events.

Diko Kazandjian: [06:03:30] I'm the medical officer at the FDA at CDER [II 06:03:26]. For the past few years, I've been fairly involved with the PD-1 inhibitors. The goal of my talk was to give you some flavor of the things that we undergo, and some of the things that we think about. A lot of the items that I'm going to be discussing were previously mentioned, by two previous colleagues. I will be giving our kind of flavor of things.

[06:04:00] In normal conditions, activation of signaling pathways balance activation and inhibition of the immune system. Cancer cells contain operations compared to normal cells, which can signal T cell-mediated anti-cancer immunity; which is one of the primary defense mechanisms of the body against neoplasia. Important pathways have been identified as we've been speaking about. The CTLA-4, then PD-1, and quite a few have been discovered since those two.

[06:04:30] Identification of these pathways have led drug development to focus on overcoming cancer cell's ability to evade the immune systems. Most of the drugs focus obvious, on inhibitory pathways or activating a stimulatory pathways. Activation of the immune system with drugs requires a balance between the anti-tumor effect and unwanted consequence of autoimmunity, as we've been discussing. Immunotherapies presented a distinct repertoire of toxicity due to this autoimmunity.

[06:05:00] Immune-related adverse events can virtually involve any organ. Frequency, duration, and onset vary between the different classes of immuno-oncologics. CTLA-4 and PD-1 pathways are involved in different subsets of the immune cells. As you can see in this graphic, CTLA-4 is found on CD 4 T-cell, and PD-1 on CD 8 T-cells; along with PDL-1 on the tumor and the antigen-presenting cells. This leads to characteristics in both efficacy and immune-related adverse events. For example, a safety-wise, PD-1 inhibition leads to activation of more restricted repertoire of T-cells; likely leading to less frequency of immune-related adverse events. In terms of [06:05:30] efficacy, time to response in general, observed with PD-1 inhibitors seems to occur more quickly. It's also been discovered that you cannot reactivation of tumor-infiltrating lymphocytes in metastases.

[06:06:00] Here's a list of a lot of the commonly immune-related adverse events we see. A lot of them are similar between the PD-1 inhibitors or PDL-1 inhibitors, and the CTLA-4 inhibitors. Here, this is a list to give you a flavor of what we see. Common immune-related adverse events as I mentioned, are similar across drugs. It's the frequency and severity that may differ. These differences are probably due to the disease indication, which cancer. However, differences are more likely a factor of patient characteristics than tumor type.

For example, in pneumonitis. Is all pneumonitis immune-related? Lung cancer

[06:06:30] seems to have more ... in some series, appears to have more pneumonitis, but that may be just due to the patient's smoking history or previous treatments that they received, including radiation or potentially, even targeted therapies. In the case of Hodgkin's disease, potentially, previous bleomycin. Here's again, a few isolated adverse events in this pictorial graph, over here. As you can see, that for the most
[06:07:00] part in many of these, the combination of ipi and nivolumab gives you the most toxicity. In some cases overall, the PD-1 inhibitors seem to have less frequent immune-related adverse event. Interestingly, at least in the case of thyroid disease, potential PD-1 inhibitors have been noted in a number of literature to occur less.

Characterization of toxicity in early registrational studies with anti-CTLA-4 and PD-1
[06:07:30] was challenging for FDA review. It was unclear how patients were classified as having immune-related adverse events. There was inconsistent documentation, and evidence across centers, and investigators. FDA early on, requested a sponsors to develop case definitions for immune-related adverse events, for correct characterization and description prospectively, to avoid issues with quality of data collected. When more recent PD-1 and PDL-1 therapies developed, sponsors have
[06:08:00] also more proactively, at the onset, develop case definitions at an educated study sites.

For example, case definitions for immune-related adverse events have evolved to number one, exclude adverse events with clear alternative non-immune etiology. That makes sense, obviously. Expand the list of adverse event and terms, potentially qualifying as immune-related adverse events. Then capturing immune-related adverse events up to 100 days after last dose. Modification of the template
[06:08:30] as CRFs, that capture laboratory and pathology data, timing of events, and co-morbidities. Then requirement for administration of the immune-modulating therapy, except in the case of endocrinopathies.

Here's an example of a CRF, over here. You can see, this is where you would list the adverse event. The immune-modulating medication would be stated here. Then clearly, the dates that they were given. How many doses? What dose? Route of
[06:09:00] administration, etc. DCRFs have been created which has been very helpful for regulatory review, along with the whole field. With introduction of ipilimumab and new toxicities immune-mediated in nature, there's a creation of REMS, initially. This was very successful at educating the community not only for ipi but basically, the basis for management guidelines for anti-PD-1s.

Currently, many centers are comfortable at managing immune-related adverse
[06:09:30] events, which is for the most part, done empirically. This was already discussed previously. For example, most immune-related adverse events that are grade 1 and 2, can be managed with minor adjustments. Whereas, grade 3 to 4 tend to be in general, more significant.

Various immune-related adverse events have been histologically studied to describe the pathophysiology. However, at a patient level, most immune-related adverse events are presumed. For practical reasons, are really biopsy-proven. This

[06:10:00] raises questions as true frequencies observed on clinical trials. For-

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Diko Kazandjian: Raises questions of true frequencies observed on clinical trials. So for example, in trials zall pneumonitis and [inaudible 06:10:06], are adverse termed pneumonia truly a microbial process? Are they an outcome of therapy or consequence of patient history or prior treatment with other agents?

[06:10:30] So as PD1 and L1 inhibitors are approved than more diseases, combinations, and indications, the safety data base grows. Drug labels also expand further and incorporating more clinical trial data. In regard to immuno-related adverse events and incorporation of pulled safety data, the label potentially could overload the prescriber with data for each disease separately.

[06:11:00] For immune-related adverse events, is there truly a reasonably that significant differences exist across diseases? So this was a case example of a Nivolumab as of September 30, 2016. The label was 59 pages long; the warning and precaution section its self was 14 pages long. Together with the sponsor and FDA guidance we were able to condense the section to 7 pages. On the left you can see, this is just an example, the old label for immune-mediated rash, and these are all the subsections with specific diseases, monotherapy or in combination, and this is actually longer, but [inaudible 06:11:21] about a page and a half.

[06:11:30] As of recently, the label came down to actually three quarters of a page which I think in general is more helpful for prescribers. Consistency across drug labels important to eight prescribers as agents are approved for more indications prevent the label from becoming a data dump. Maintaining meaningful brevity and consistency i.e. in the warnings and precautions that I just showed, management guidelines for immuno-related adverse events should be consistent across the drug labels. Adverse event management guidelines should be meaningful to prescribers as further knowledge is gained.

[06:12:00] For example, there is a lack of validated hormone monitoring guidelines, a baseline for endocrinopathies, so in a label 'monitor patients for changes in thyroid functions that started treatment periodically during treatment as indicated based on clinical valuation and for clinical science and symptoms of thyroid disorders' may be somewhat not as helpful.

[06:12:30] Case definitions describe being immuno-related adverse events should also be consistent across the drugs. Perhaps, potentially there is role of academics and sponsors to coordinate together to standardize some of these definitions.

What are potential approaches to actually have more meaningful data represented in the label? This is from a recent manuscript publication for a Atezolizumab, and

here we thought this was pretty graphically helpful for prescribers, and potentially there is a role of this kind of representation down the road.

[06:13:00] So moving forward, the sciences evolving recognition by field of potential synergistic benefit of combination immuno-therapy regimens has come across some novel immuno-therapies observed not to have monotherapy efficacy, but presumed synergy with anti-PD1's. There has been a general push by the community to do trials and not beginning with mono-therapy but in combination from the start.

[06:13:30] Other than the problem of isolating the drug effect, that potentially poses a challenge in being able to isolate and describe the given novel drugs given safety profiles. So challenges include describing adverse events for combinations with other non-IO drug types, which was previously mentioned.

For example, pneumonitis and anti-PD1, and tyrosine kinase inhibitor combinations. Although knowledge of the safety profile of ios quickly is expanding imperative to pharmacal diligence for new safety signals, again this was previously
[06:14:00] mentioned. With more and more patients treated some of these safety signals came up such as encephalitis and Stevens-Johnson syndrome.

The advent of checkpoint inhibitors has marked a paradigm shift in treatment options for many cancer types, directly translating to patients living longer. As excitement grows with further development in the field, it will be crucial to consistently and scientifically collect safety data, and educate the community with validated management guidelines. It is also imperative to ensure that quality safety
[06:14:30] data is collected in prospective manner on clinical trials, and not just as an afterthought.

In addition, shared community data will be important in identifying bio-markers, which can potentially predict immune-mediated toxicity. So collaboration between all sponsors and investigators in scientific findings down the road is going to be very important. I want to thank everyone for giving me this opportunity.

[06:15:00]
Speaker 1: Thank you Diko, as you know the discussion of toxicity is as important not just for checkpoint blockade, but also for cellular therapies and so we are grateful for David Porter from the University of Pennsylvania to come talk to us about complications of CAR-T cell therapy.

[06:15:30]
David Porter: Thank you very much, and I greatly appreciate the invitation to be here today. We are going to switch gears a little bit, and I was asked to talk to you about complications of CAR-T cells. It's been touched on a little bit through the morning and early afternoon. I am at the University of Pennsylvania the one part here that I left out was that another role that I have is as the Director of the Blood and Marrow Transplant program, and in fact I'm not going to talk at all about transplant

[06:16:00] which I take as a sign of success of this therapy. These are my disclosures ...

Just to very quickly summarize and review for everybody what we are doing and what we can expect with this type of therapy, and why this is so important to discuss the complications, I wanted to review very quickly what CAR-T cell therapy is.

[06:16:30] Everybody knows this, but we use gene transfer technology to stably express a CAR molecule, a chimeric antigen receptor, on a T-Cell conferring novel antigen specificity. And the CAR modified T-Cells can now recognize an antigen that they couldn't before. So here you see a lentiviral vector bringing in a new gene, directing expression of this CAR ... That CAR is transported and stably integrated to the cell membrane where it now can recognize CD19 or whatever its target antigen might
[06:17:00] be, engaging and leaving behind a dead tumor cell when it couldn't do that before.

So that's really what we are talking about. At University of Pennsylvania we've now treated, in fact, close to 300 patients with these genetically modified T-cells. Several hundred have been treated at other centers, and so there really is good experience here with CAR-T cells.

[06:17:30] Now, we started out by treating CLL, CLL is thought of as a chronic disease in many cases but in fact once CLL becomes refractory resistant to standard types of chemotherapy the prognosis is dismal. The patients we have been treating are chemotherapy resistant, you can see their anticipated survival; median survival is about a year with almost no patient living beyond five years.

[06:18:00] We went on to treat CLL apropos to this afternoon's discussion. We actually started with a pilot trial; we did not due a classic phase 1 study, and that was followed by a randomized phase 2 trial of two dose levels. But if you combine those two studies we have good mature outcome data on 43 patients. The complete response rate was 26%, these are patients who had no viable options left. Partial response rate
[06:18:30] was 23%, and the overall response rate just under 50%.

So these are the patients we were dealing with; once we had some experience with CLL in adults we started treating another B-cell malignancy ALL both in children and adults. ALL is even more aggressive ... The prognosis for these relapse refractory patients is dismal, the median survival is less than a year ... Less than a quarter of these patients survive beyond 3 years. I do mention transplant, I couldn't resist, but
[06:19:00] transplant is largely ineffective for these patients. These are truly people who have no other options.

This shows you the outcome of adults once they relapse, no matter now you split it you cannot find a category of patient where there is a reasonable outcome. We began treating these patients and the results were truly unprecedented. In this group of patients, and our first 30 at Penn which included 25 children and 5 adults,
[06:19:30] the complete remission rate was 90%. There is just no precedent for that in treating acute lymphoblastic leukemia.

It's important to note that this isn't just specific to Philadelphia or the University of Pennsylvania, other centers doing similar types of therapy with slightly different products and slightly different manufacturing still get similar results. Just as Asko
[06:20:00] this past year there were presentations that dealt with over 200 patients with relapsed refractory ALL, and if ...

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David Porter: ... over 200 patients with relapsed refractory [ALL 06:20:02]; and if you look at the outcomes, they vary anywhere between about 70% to 94% complete remission rates. This really is a function of the technology, and not just something specific to what we do at my center.

Getting the reason we were talking today; there is significant toxicity in this therapy. The infusion is fairly straight forward; we do that as an our patient. There's
[06:20:30] no particular infusion toxicity. There has been some organ toxicity; [hepatil 06:20:35] and and renal toxicity. This is generally in the setting of other issues, particularly hypotension from other causes. This is not direct toxicity form the T cells.

We've had a number of patients develop a Tumor Lysis Syndrome. This is something that happens when you kill large amounts of cancer cells all at the same time, and they release their cellular contents into the circulation. This is potentially
[06:21:00] life threatening, and organ damaging. Once we recognized it, it has been completely either preventable, or manageable and referable in all cases. Certainly this is a toxicity, but on another level this is truly a testament of the potency of these T cells.

We're targeting CD19, which is not just on cancer cells, but it's also on normal B
[06:21:30] cells. We heard [Dr. Goff 06:21:30] earlier, tell us how patients can survive without B cells. I've heard the expression that this is disposable tissue; sounds somewhat true. We know that patients can live with B cell aplasia, that is an anticipated side effect. Again, whether we call this toxicity or efficacy, I will leave to your judgement; but it can be supported with intravenous immunoglobulin infusions. Certainly, as of yet, we have not seen any excessive or unexpected frequent
[06:22:00] infections related to Hypogammaglobinemia.

There is a unique syndrome neurologic toxicity, which I will touch on briefly; then the thing that I think most of you are familiar with, the cytokine release syndrome. This is just showing you B cell aplasia. These [Car T cells 06:22:20] are alive; this is a living drug. If this functions properly, they can persist for long periods of time.

[06:22:30] This is showing you one of the first patients we treated back in 2010. I apologize, the formatting is a little bit messed up. In this top panel, you can see staining for [car T cells 06:22:45]. By one year, they still represent 13% of all the CD3 positive T cells. At 18 months, they still represent just over 3%; 0.3% at 3 years; and at 5

[06:23:00] years, 5 1/2 years these gene modified cells are still present, they represent 1% of all the CD3 positive T cells.

If you look at the lower panel, there are no detectable B cells. They were not there a year, 18 months, 3 years; and they're still not there 5 1/2 years later. This tells us that, not only are the [car T cells 06:23:24] detectable; they're still functional. This B
[06:23:30] cell aplasia is a bio-marker; if you want to call it that. It is a measure of functional persistence. As long as these [car T cells 06:23:34] are present, patients cannot recover normal B cells. This is a marker for us; that the B cells do remain active, that are persistent.

The most unique, and certainly most dangerous toxicity, is the cytokine release syndrome. Almost all responding patients who get these [car T cells 06:23:56],
[06:24:00] develop CRS. The onset, in some cases, can be very quick; within the first 24 hours. More typically, it's 6 to 9 days later; but can be out as late as 14 days. We have not seen it; except in one very extraordinary case, after 21 days. The duration is variable, it can be between 1 and 10 ore more days; up to 2 weeks. Some of that depends on whether you intervene, and try and stop the reaction. It is coincident
[06:24:30] with [car T cell 06:24:28] activation and expansion; so when we see the CRS, we see rather massive expansion of these [car T cells 06:24:36]. In fact several hundred fold [In-vivo 06:24:39].

It always begins with a fever. It generally starts with low-grade fevers for 24 or 48 hours, that escalate over several days. These fevers can become quite dramatic, 104, 105, we've even gotten to 106 degrees. It's associated with myalgias and
[06:25:00] arthrialgias, nausea, anorexia, diarrhea; this could be quite severe. By that point, most of these patients are admitted. Rather severe fatigue. As you let this progress, it can develop into a capillary leak syndrome associated with pulmonary edema and hypoxia, and lead to hypotension; the need for pressers in an ICU; and the need for ventilator supprt as well, in the most severe cases.

[06:25:30] There are also similarities during the cytokine release syndrome to macrophage activation syndrome, or HLH. You will find biochemical parameters in almost every patient; that you will see patients that have HLH or macrophagia activation syndrome. Ferritin's can be dramatically high. We've seen ferritin levels as high as 600,000. If you do bone marrow biopsies in the midst of this, you can actually see hemophagocytosis.

[06:26:00] This is just showing you some of the bio-markers we've noticed. Responding patients will have these massive elevations in IL6. We noticed that very early on. In fact in the very first child received this therapy, was critically ill. We found only modest elevations in interfering [GAMA 06:26:18], TMF; and very mild increases in IL2.

The cytokine profile does correlate with response. What I'm showing you here, is a
[06:26:30] patient who achieved a CR, in green, with these very, very high IL6 levels; patients who have a mild CRS, have less intensive elevation; and patients with no CRS, don't

have any of this cytokine elevation.

We knew that IL6 was dramatically elevated, and these patients were getting really critically ill. In fact there are medications that can block IL6 activity. There is a drug [To-so-lys-im-about 06:26:55], that was available back when this first patient was
[06:27:00] treated; that is an IL6 receptor antagonist, that blocks i=IL6 mediated effects. When we give anti-IL6 therapy; when we use [To-so-lys-im-ab 06:27:11], the clinical effects of CRS are rapidly reversed. In fact, within a few hours. Patients who are hypotensive, normalize their blood pressure and hour later. Patients who have 105 degree fevers, normalize their temperature; they start weaning off of ventilator.

[06:27:30] We have now figured out, I think, a good way to intervene for this CRS. We, kind of, know what to do. What we don't know yet, is when to intervene. We don't know if earlier treatment is going to abrogate the anti-tumor response of these T cells; and, in fact, have trials ongoing, trying to administer anti-cytokine therapy very early in CRS to see if that will inhibit the anti-tumor response. You could imagine that's a
[06:28:00] touchy type of trial to do. This has been reviewed. There's a nice blood review in the 'How I Treat' series, about managing CRS, for anyone who's interested; published in late 2014.

This just shows you how this looks. Clinically, this was a patient we were managing with these very, very high spiking fevers: 105, 105.4. Here he's 105.7, and is becoming hemodynamic ally unstable, and needs intervention; receives [To-so-lys-
[06:28:30] im-ab 06:28:29], and you could just see this rapid resolutions; a normalization of this fever, that did not occur. That's how they respond clinically.

Almost every patient will get CRS. Only about 1/4 of these patients develop severe CRS. You just look at some of the different studies published; anywhere from about 25% to about 40% of patients will have what we call severe CRS.

[06:29:00] You might ask me: "What do you call severe CRS? That is actually a major issue. This is a novel toxicity of a novel therapy. It was very important that we start to describe it, for many reasons; so that others could understand it; but also, so that we knew how to treat it. This is a situation where the CTCEA were inadequate and inappropriate for this toxicity. There was no grading scale for this. If you look at the CTC criteria, it talks about interruption of the infusion. This was really designed for
[06:29:30] monoclonal antibodies; and, of course, once you give these cells, they are in, and you can't interrupt them.

As part of this work, we had to develop a novel grading scale for CRS. My point here is not to go through the grading scale at all; this has been published in an article we had back in 2015; but just to say that we had to come up with something
[06:30:00] that was relevant to these [car T cells 06:29:58]. This works very well for us. However ...

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David Porter: For us, however, what you're probably going to hear, perhaps from Dr. Liu, is going to admonish me next, because all the different centers who do these trials now have their own grading scales, and they're not all the same, and so that makes it very difficult for us to work across institutions, and I'm sure difficult for regulatory agencies like the FDA.

[06:30:30] But it has allowed us to use our grading scale to develop a treatment algorithm, again, I'm not going to go through this. We don't treat grade 1 or 2, we treat everyone with grade 4, and grade 3 there is some clinical judgement, but our first treatment is Anti-IL-6 therapy in all cases.

We can now predict severity in some cases. We know in ALL, the tumor burden is directly related to the severity of CRS. That's not so clear in other B-cell
[06:31:00] malignancies. We do know it's more frequent in ALL than other B-cell malignancies. There may or may not be some contribution of the infused dose. In fact, the infused dose is more relevant when it is related to the tumor burden, so it's not just a dose-toxicity relationship.

We think that it has something to do with some product composition and the health of the T-cells and what type of lympho-depleting chemotherapy we give
[06:31:30] these patients, so it really is quite complicated how we predict severity. We can also predict it based on some clinical characteristics, patients with early elevation of cytokines and CRP seem to have more severe course early onset of symptoms generally predicts a more severe course.

The other thing we found with patients with concurrent infections have a dismal prognosis. The only treatment related mortality we've seen is severe CRS in the setting of active infection. This is just showing you that patients who have a higher
[06:32:00] disease burden are more like to have a severe CRS in ALL. And this is just showing you after treating about 100 patients with ALL, we have treated 3 that developed concurrent infections, influenza and 2 bacterial infections. All 3 patients have refractory CRS and died of therapy. Now this is modifiable. We test everybody for pre-existing influenza and viral infections. We've started using prophylactic
[06:32:30] antibiotics and have had no further treatment related mortality.

And finally, I just want to end with 1 slide, I'm over my time, about neurologic toxicity. This seems to be independent of fevers and is not directly related to severity or to CRS. The incidence is about 20 to 40%, but I want you to note that the presentation is variable. We call this neurologic toxicity, which should hint to you that we really don't know much about this, we don't know what it is, we don't
[06:33:00] know what causes it. Neurologic toxicity is vague and it's variable. There are just generalized encephalopathies, some delirium. Some patients get aphasia. Some will go on to have seizures. It is not an encephalitis. There is not active inflammation. Many cases happen after resolution of the CRS. We do find CAR T-cells in the CSF, but we find them just as frequently in people who don't have neurologic toxicity. It
[06:33:30] does not seem to be the cause. In all cases, it is resolved at baseline. We don't know the mechanism yet. We don't know whether it's directly t-cell mediated or

cytokine mediated. It has happened in all programs with variable frequency as well.

So just to summarize, the CAR t-cell, or we call our CAR CTLL19, the dosing schedule, and I didn't get into anything about schedule, but the dosing schedule do
[06:34:00] correlate with toxicity in response, but it is related in part to disease burden. We use a fractionated dosing scheme, which allows for essentially real time interpatient dose modification. And it allows us to maintain high response rates, and we've been through that both in CLL and ALL to define the best dosing schedule. When they have concurrent sepsis, it's a very, very poor outcome putting
[06:34:30] in these T-cells into an inflammatory environment makes it very hard to stop the t-cell activity, and future studies determining the impact of fractionated dosing, inverse dosing based on the disease burden starting with a lower dose for patients with more disease and how to time anti-cytokine therapy.

And I can skip this and just go back to this slide, and just tell you that it takes an enormous group to do these kind of studies. This is the very short list of all the
[06:35:00] people involved led in large part by Carl June, who really is pioneered this work that this whole group has brought forth. So thank you very much. Sorry I'm a little late.

Male:
[06:35:30] Thank you, David. And the final speaker this session is Ke Liu from CBER at the FDA, who is going to discuss the regulatory perspective of CAR t-cell mediated toxicities.

Dr. Ke Liu:
[06:36:00] I just wanted to thank media organizers to have me talk here, and also thank you for staying the whole day until very late. I want to give a little bit historical reflection. So about 3 years ago, we had a regulatory policy and sign session with AACR in their annual meeting, actually here in D.C. I was fortunate to co-chair that session with Dr. Carl June. Back then, we had only commercial sponsors that
[06:36:30] develop CAR, and we have over 80, eight zero, R&Ds that modify the T-cells, they including the CARS, this is about 20 or so, and you'll see that the field really had record events or explosion within the last 3 years because of the science. I appreciate Suzanne's opening lecture pointed out 3 of these times treatment driven the development of a union oncology.

[06:37:00] The other thing I appreciated that now seems to community also recognizes that Immuno-Oncology, it's not just PD1 and PDL-1, it's including also other form of treatment, so I appreciate that as well.

So I have no disclosures, and I would add that I also pay taxes. So my remark would
[06:37:30] be, actually pretty short. I'll give you overview of R&D PortfolioStat in our sen-ory review, and then talk about toxicity. I think Dr. Porter, he really excellent overview about CAR T, so that's going to be a lot of work on that. Then I'll focus on what we're doing for the CAR Ts.

I mentioned about within the last 3 years, we have a total of 30% increase in total
[06:38:00] R&Ds for genetically modified T-cells . This including t-cell receptor modified and also is the CAR Ts listed here. You can see the distribution of each. So the majority

of that actually the CAR t-cell R&Ds. And also back then, 3 years ago, we only have 1 commercial R&D sponsor, and now we have more than 10 that developing the
[06:38:30] CAR Ts. And this is dissecting the total portfolio we have in terms of the modified T-cells for histological malignancies versus solid tumors. As you can see, about half have, and then you look at the anti-CD19, as Dr. Porter mentioned about, and it's about 1/3 of this CAR Ts really geared toward targeting the B-cell, but against these
[06:39:00] that express the CD19.

So in term of toxicity, Dr. Porter covered a lot already. What we've seen of the infusion reactions acute, and cytokine released syndrome and emission of the
[06:39:30] toxins CAR T, yes, it really pose a big challenge for us when we evaluate a given efficacy events coming from different sponsors that, you know, what grading system that you use called grades 3 or grades 4, some maybe similar events that others may call differently. And that's created not only for the assessment, but also for how you manage the patient overall. And also in the survey I listened to, as Dr.
[06:40:00] Porter pointed out, the importance of monitoring the cytokine levels.

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Ke Liu: ... Self-monitoring the cytokine levels. When you're talking about cytokine release, of course, you've got to monitor that. So there's almost in every protocols that we review, we remind our sponsors that this the important part, corollary the test that they have to collect.

[06:40:29] Neurotoxicity is more and more we recognize that, and the types Dr. Porter already
[06:40:30] talked about it. It's very important that you evaluate those neurotoxicities ... The baseline presentation during the treatment and also end of the treatment.

The others ... We do not realize early development of the [CAR T's 06:40:46], the cardiac ... That, we've seen those also reported as well. That's can manifested as
[06:41:00] mild carditis and cardiomyopathies as well.

Then the optimal management for toxicity is really something that we ask our sponsor come up with. In our discussion with the sponsor we always asking for the algorithm that the deal with and manage the CIS syndrome.

[06:41:30] We talk about a lot of those ... Today is on target and off tumor effects, and some of the ... Not a cause, but the cross-reactivities of the TCR modified T-cells may have the on-target but off-tumor effects, and also the cross-reactivity and off-target effects manifesting in the heart, and also seeing it as in the long term one of the advantage of Dr. Porter mention about the PCR and those patient bases online
[06:42:00] [inaudible 06:42:00] perhaps for their whole life. Then, the persistent of a [CAR T's 06:42:06] ... Does that correlate with long-term efficacy or not, and also does it follow up [inaudible 06:42:14] for all the trial data? What those transactions or modifications with retrovirus or lentivirus has any long-term safety, we don't know.

Then, potential for second malignancy is related to that as well.

[06:42:30]

Optimal management for toxicity, short term versus long term, and still need to be worked out. There's two major things that our center doing ... One is working on the grading criteria, really something I think the field recognize that as well. We,

[06:43:00] meaning the FDA, in discussion with National Institute of Health, Office of Biotechnology Activity, Recombinant DNA Advisory Committee, that last year we had that special session to invite all the investigators that involve in the CAR T to come to Bethesda to talk about the grading criteria. If you talk about management,

[06:43:30] you don't have a criteria to grade, then it is really hard to talk about that. I think that it's true really a lot of work behind scene of the RAC and also all the investigators including Dr. Porter's group ... That something will come up soon. That's really will be a help to the whole field.

[06:44:00] The other thing is about the CAR T safety database ... Seeing the earlier slide, that for the pre-clinical they form a CAR T consortium ... The FDA, we cannot call self-consortium, so we can only call ourselves database. We think we are in the actually good position to do some data minings and also to compile the database from all of the CAR T developers, including commercials and also [inaudible 06:44:27]

[06:44:30] investigators so that we can analyze the trend and figure out some management outreach as well.

To do that, we have tried couple of years ago using very primitive ways of doing

[06:44:47] egg cells into the sponsor, and ask them to figure out. We find that that's really not working, so there's also the objectives I just talked about if you want to perform a

[06:45:00] cross study, cross-IND analysis of a CAR T data, then really, the goal is to develop risk mitigation strategies for this adverse events. Now the database is being developed, so basically is asking our sponsors to submit their data in CDISC and

[06:45:21] SDTM format. Actually, two databases ... One is for clinical, one for CMC, as I

[06:45:30] mentioned in one of the comments that not CAR T's are same. They are constructed different, they may have [CD20 06:45:37], some may have [4MBB 06:45:38] and all different thoughts. Whether that has any relationship with development of the [inaudible 06:45:47] and how we can [inaudible 06:45:48] that, that's very important aspect. Those kind of integrated but remain separate track.

[06:46:00] For clinical database ... Basically, this what we are trying to do is one, to do standardization of data then collection data and management, and eventually do analysis of all of them. Some of the sponsors sitting in the audience help us a lot by providing us with the data from their trial.

[06:46:30] I'll just conclude the CAR T-cell therapy really is an innovative, personalized, and promising because it is a promising therapy. It also has a high rate, and the adverse events, so we have to really take a close look at those for us to have overall risk and benefits assessment. As talked about, unique challenges in the toxicity

[06:47:00] management, including find out what mechanisms of the toxicities, including the neurotoxicity, short-term and long-term and follow-up ... It is an opportunity for all of us working together, and we encourage the developers to engage with us early

and often.

Thank you very much.

[06:47:30] I'm sorry, I forgot the most important slides. This is our contact information and those are the people in the trench who actually do all the work. Some of them sitting in the audience, I appreciate it a lot. We have a T-cell working group in our center that meet monthly to discuss those new development, including adverse
[06:48:00] events then to figure out what we could offer any advice to our sponsors. One more slide ...

This is database. Those are people involved, which is database. Dr. Bindu George spearheaded that project, thanks very much.

Speaker 2: Thank you. I'd like to invite all the speakers from the last session to come up for a panel discussion.

[06:48:30] Look at that, sorry.

Elad Sharon. Thank you very much. Actually was not on the version of the agenda that I have, but we're very happy to have you speak. Come on up.

[06:49:00]
Speaker 3: I hope my slides are here. Okay, great.

My name's Elad Sharon, I'm a medical officer at the Cancer Therapy Evaluation Program, CTEP, as it's more commonly known. I've been there for about five years, and worked on the initial development program for pembrolizumab. I worked with some colleagues on nivolumab, and since then I've brought in atezolizumab,
[06:49:30] durvalumab, and some other agents.

I just wanted to sum up, hopefully ask some provocative questions. I also have no disclosures that are financial in any way, and I should probably mention that I'm not speaking on official capacity. These are my personal opinions, not that NCI's opinions.

Of course, we're all very interested in this area in general because the imagination of the industry has been captured by immuno-oncology given the broad efficacy
[06:50:00] that we've seen. There are other molecules and other alternative strategies ...

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Speaker 1: ... Other molecules and other alternative strategies of utilizing the immune system, that have also received invigorated and renewed interest; as a result of the broad level of efficacy and activity that we've seen with PD1 and PDL1 inhibitors. In looking at the adverse event environment, the challenge here is just how not to miss opportunities for further development of these innovative and efficacious

therapies.

[06:50:30] One thing that I just wanted to bring up. This is a article that came out, around the same time I was [inaudible 06:50:33] last year; even though, it says ACR over here. This is ... [Amino therapy 06:50:39] is really a different mentality of therapy. It's just maybe a special category of targeted therapy; in that it has emerged. It's really much broader than that, and I think that the broader oncology community is going to be an [Amino therapy 06:50:54] community for the most part, in the decades ahead.

[06:51:00] I would say that the revolution is now. We're seeing that, of course, first in metastatic patients, as it is probably appropriate; but, we'll soon see this more often in patients with Atrovent and Neo Atrovent therapy. [Amino therapy 06:51:14] will be more commonly used there, as well. It's really due to this broad potential of PD1 and PDL1 inhibitors, but that has not really yet been seen in this
[06:51:30] era of targeted therapy. The broad testing, that I think we've seen, is probably warranted and I think that it actually does have tremendous positive benefit for patients. If you look at clinicaltrials.gov, you can see the 728 active, or open trials that are being conducted right now, with the 5 leading companies in this area. The NCI actually has [craters 06:51:53] with [Merk 06:51:55], BMS, [Genintac 06:51:56], and [AstraZeneca 06:51:58]. The NCI intramural program, was instrumental in
[06:52:00] working with [MED Surona 06:52:03] in the initial trials, and is continuing.

In general, regardless of PD1 and PDL1, you can see from the [Chad and Melman 06:52:13] article from 2013, [T cells 06:52:17] have really been the final common pathway, for most effective [Amino 06:52:21] therapies that we've had in the clinic
[06:52:30] to date. The specifics might be different, but you really do have to focus on the [T cell 06:52:30], and while that might mean that other strategies, like [NK cell 06:52:36] or other strategies, might come up as time goes on. We haven't really seen any proven benefit to date. The mediation of these adverse events, is also largely been [T cell 06:52:47] mediated, although there are some exceptions. I think that [Dr. Liu 06:52:52] said correctly, these adverse events, essentially are on target off tumor.

[06:53:00] There are some hints that we might be able to have as to how to deal with these adverse events, based on similar settings, or similar mechanism of actions; and we can see that in a couple of examples I wanted to just describe. In the case of [Novolamad 06:53:16], which was recently approved in May 2016 for Hodgkin Lymphoma, there was a potential risk, warning, and precaution that was issued for
[06:53:30] patients that subsequently receive a [Alganax 06:53:28] stem cell transplant. In terms of sever [Graft-versus-Host Disease 06:53:32], that maybe needs to be investigated a little bit further; but, similarly another therapy that works in a slightly different mechanism [Mogamulizumab 06:53:43], which actually is a anti-body targeting CCR4, which is present on T regulatory cells. It's an agent from [Keawikarena 06:53:51] not yet approved in the United States, but it is approved in
[06:54:00] Japan for ATLL, PTCL, and CTCL. That agent also has had some concerns lately for pre-transplant administration of the agent, leading to potentially severe, and

potentially fatal [Graft-versus-Host Disease 06:54:11] in subsequent transplants for some of these patients. It's important to think of these agents more or less as a group, not really just in a specific category.

[06:54:30] Another area, which I think [Dr. Porter 06:54:28] also brought up fairly well, is that ... In here is actually an article for ... That was from the Group It Pen, where you can see the [comaric 06:54:39] engine, [angine 06:54:40] receptor against CD19 was utilized in Myeloma. They mention, and I think he mentioned in much greater detail, that sometimes these therapies can be complicated by a severe side of [acona release syndrome 06:54:54], neurotoxic effects ... There's another agent,
[06:55:00] which you could argue is a totally different category, except that it's not. It essentially has the same target, by specific anti-body that is, a more or less an off the shelf [adopt-a-cell 06:55:10] transfer mentality of therapy. CD19, CD3, by specific anti-body is approved, when the 2 met that was very similarly neurotoxic effects. It has [cytokine release syndrome 06:55:24]. We should be able to
[06:55:30] anticipate some of these adverse events, based on some similar molecules.

Another area, I think that we have to think about, are issues related to dose intensity, and we mentioned already earlier today, about the benefit [ipilimumab 06:55:45] in combination of [nivolumab 06:55:47]. [Ipilimumab 06:55:48] is now FDA approved in 3 different strategies for the treatment of Myeloma. In Metastatic Myeloma, it was initially approved in 2011 at 3 milligrams per kilogram. In Atrovent
[06:56:00] Resected Myeloma, it was approved at 10 milligrams per kilogram; that's important, because atrovent trials take a little bit longer to read out, and this was started a little bit earlier. That came out about October 2015, based in a ERTC trial; which was also recently published in the New England Journal, this past week. In combination with [nivolumab 06:56:23] at 1 milligram per kilogram, along with [ipilimumab 06:56:26] at 3 milligrams per kilogram.

[06:56:30] When we worry, of course, about adverse events they're also some practical things that you have to consider. In the case of potentially patients that are being treated out in the community, you may have some patients that have Myeloma, that are coming off Atrovent therapy with 10 milligrams per kilogram of [ipilimumab 06:56:46], experience some sort of metastatic event and then are later treated with a [peembolismab 06:56:52] or [nivolumab 06:56:54] as a single agent. Given the
[06:57:00] long half-lives, that we have of these agents, essentially we maybe treating a patient with almost 10 milligrams of [ipilimumab 06:57:07] in combination with a PD1 agent, that it may be inappropriate dose of 200 milligrams or at a [inaudible 06:57:17] equivalent.

You may also have some patients that are coming off PD1 therapy, and there aren't very many salvage regiments that are actually available at this point for Myeloma
[06:57:30] patients. [Ipilimumab 06:57:31] is often offered, that means that patient is essentially being treated at 3 milligrams of [nivolumab 06:57:41] with 3 milligrams of [ipilimumab 06:57:42]. Which wasn't necessarily the intention, maybe that's something that is reasonable for a given set of patients. It's important to note that BMS and [Dr. Feltquate 06:57:54] mentioned this earlier, has been focused on a

[06:58:00] dosing strategy in the combination of 3 milligrams of [nivolumab 06:58:00] or the equivalent, along with [ipilimumab 06:58:03] at 1 milligram per kilogram, in various [inaudible 06:58:08]. We end up essentially, potentially ... I don't know if over treating is the right word, but we end up with at least with some patients, that have a higher likelihood or higher risk of adverse events being given. Doses that we didn't necessarily intend.

[06:58:30] I should mention, actually, that we do have the ability and in the near future the NCI, had a trial E1609, which would be reading out in the next year or so; that looks at 3 milligrams per kilogram of [ipilimumab 06:58:42], so at least that might actually be in the Atrovent Myeloma setting; so, that might actually be mitigated to some degree by then, over time. I think Mario mentioned very distinctly, and I think
[06:59:00] it's wise to consider now, you have patients who have had adverse events, now what do you do? We haven't really as closely investigated how patients get retreated, with the same agent, or potentially with different agents, how soon this re-treatment can actually happen. We don't necessarily know, at this point, why [does testillation 06:59:20], or reduction in treatment intensity, or total exposure,
[06:59:30] is not a successful strategy. We, at least with the agents we have that are currently available in that particular setting, there's not been enough work in that department, and that's something that we should probably consider going forward.

While steroids are a great strategy, there are other potential risks mitigation strategies we could consider, with the intent of helping patients obtain access to
[07:00:00] these beneficial therapies. Potentially, Cyclosporine, I think was one, suggestion at one point in a particular setting.

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Section 43 of 46 [07:00:00 - 07:10:04] *(NOTE: speaker names may be different in each section)*

Speaker 1: -sporin I think was one suggestion at one point in a particular setting. There is something that we're certainly considering. I think lastly, at least in terms of major issues, the mention earlier of the human-as-a-knockout animal model by Dave Berman is something that is actually very close to my heart. Immune-related
[07:00:30] adverse events potentially can have relevance for the study of auto-immune disease in particular. That treatment and management can actually teach us something about the auto-immune diseases in particular, even though there may be some distinctions and some differences, and vice versa.

There's also a responsibility, we have learned something from these auto-immune disease from other fields. There's a responsibility that we may have actually to
[07:01:00] teach something to other areas of medicine. We potentially could have some sort of national strategy maybe. Collecting blood and tissue from patients that have had severe or significant adverse events on trial. Sharing that and looking at it in a more intense fashion to see where there may be some commonalities between patients who exhibit these adverse events. Trial patients often have these samples that are available.

[07:01:30] I think, at least personally, that the analysis of that severe adverse event should

potentially take priority over planned analyses of other correlatives, at least when there's significant ... NCI trials can potentially be available for that, but I think that we should also be very interested in talking to industry colleagues who may also be able or willing to share samples from patients who experience those severe adverse events. Finding the right labs to more significantly evaluate that. We can
[07:02:00] potentially even build this into our consents, in the sense that patients may be able to be asked a priori enrollment of trials whether or not they're willing to share samples at the outset.

It was also discussed briefly here, that the CTCAE may be inadequate. This is
[07:02:30] something that the NCI actually publishes and goes through irregular updates. Version 5 is actually essentially public at this point. I think it might actually be available for comment, although most people at this point are using Version 4. There will be a Version 6. In fact, if Dr Porter is interested in updating and allowing for a cell-based therapy approach for a cytokine release syndrome in terms of
[07:03:00] grading, that's something that the NCI would be very open to ... If the FDA is willing to collaborate, or interested in actually collaborating on putting case definitions into a new version of the CTCAE ... If that might actually be helpful for the drug development community, that's also something that we would be very interested in.

We already know, and it's probably already been mentioned, that diarrhea was certainly on the early trials, was probably over-reported, and colitis was probably under-reported. The real question is would having specific AE terms in the CTCAE
[07:03:30] be beneficial for the overall community?

Speaker 2: Okay. This is the last major point. Eligibility criteria I think could also be made a little bit more rational. We have too many patients that I believe are actually excluded from our clinical trials, potentially without evidence. One area that's very close, I think, to our hearts at the NCI are patients who are HIV positive that
[07:04:00] happen to be almost uniformly excluded from industry trials regardless of their overall health, their HIV status ... meaning if they have a high CD4 count, no detectable viral load. On NCI trials, generally we've allowed those patients to enroll. Even when that actually happens to exist on the product label, sponsors and potentially actually more academic investigators have been reluctant to liberalize criteria, which is something that we should really consider as well, allowing for
[07:04:30] patients, at least with moderate renal and hepatic dysfunction to enroll on trial.

The field in general is probably slow to change in this regard. I think that's largely due to templating. That leads to a lack of innovative thinking, or at least more accessible thinking. That would help real-world patients better understand what their risks are, and where they might be able to go ... whether or not they should
[07:05:00] enroll on a trial ... whether or not they should actually take a given therapy.

Summation ... Just everything I really discussed ... We can really anticipate adverse events based on similar mechanisms of action, and we should. We should also consider the real world use of therapies, both in approvals and also instituting

guidelines potentially. We can, and are certainly open to updating the CTCAE in a
[07:05:30] way that would be beneficial for the immuno-therapy community. We may, and this is something that I think we should at least strongly consider, develop these large, publicly accessible mechanisms for the analysis of these severe adverse events, and how we might be able to learn a little bit more from them, along with different risk mitigation strategies and obtaining real-world evidence.

I think I went a little over my time, but I appreciate the meeting organizers inviting me. I look forward to the panel discussion. Thank you.

[07:06:00] [applause]

Speaker 3: You're allowed to go over considering I almost cut you right out of the program. [laughter]

While everyone is kind of settling into an effort to make sure we do finish up
[07:06:30] around five. [Elod 07:06:29] I want to pick up that last point that you made about revising the CTCAE, and adapting to the new observations that we're making. I'll just bring to everyone's attention some experience that we had, along with Mario's group, in developing the combination of [inaudible 07:06:49] and [inaudible 07:06:50], where actually the dose escalation stopped because of the observation
[07:07:00] of a high frequency of elevations in amylase and lipase, with no symptoms either radiographic or clinical of pancreatitis. According to the CTCAE guidelines as written, patients were having an increased frequency of grade 3 amylase and lipase, which was falling into the category of pancreatitis. That actually stopped the dose escalation. In fact, some of these patients even reached grade 4. Yet no one became unwell. Most of these resolved spontaneously without any intervention whatsoever.

[07:07:30] After a quite exhaustive literature search, and also a follow up of many patients treated outside of clinical trials, again my colleague Mike [Postau 07:07:43] led an effort to revise the CTCAE criteria along with colleagues from CTAP. Very grateful for the open-minded approach of the team at the NCI around this. This will now be coming out and actually include a clinical requirement for symptomatic
[07:08:00] pancreatitis, if these asymptomatic laboratory abnormalities are going to lead to in fact a grade 3 or grade 4 significance. I think that we are making some progress. There's actually a publication that will come out in JNCI around this very shortly. I think that what you have predicted, what you have asked for, is happening. We're really grateful, again, like this meeting, for a very collaborative effort between
[07:08:30] colleagues and industry academia, and the regulatory agencies to make this happen.

Okay, so we'll take some questions. Whatever, don't fight. It's okay.

Speaker 4: I hope for once I'm a [inaudible 07:08:45] second.

Speaker 3: All right Mark, you're number one.

Mark Ratain: [07:09:00] Mark Ratain, University of Chicago. The identification of patients at high risk of immune ... particularly serious and life-threatening immune-mediated adverse events is obviously of critical importance, both from the standpoint of minimizing morbidity as well as what Mario pointed out, the costs of these therapies. One plausible and testable hypothesis is that there are genetic differences that predispose individuals to these adverse events. Just wondering, since FDA [07:09:30] published a guidance in January 2013 calling on all sponsors to collect DNA essentially on all patients in clinical trials under IND, both industry and NCI, what the sponsors are doing to collect DNA and analyze for this, and what FDA is doing to encourage sponsors to analyze these data?

Speaker 6: [07:10:00] For the CAR t-cells, we are doing just that. At Penn we are collecting DNA and doing genetic profiling and batch. I don't have much to tell you-

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Dr. Porter: ... I don't have much to tell you. The one thing that did come out of this was very early on in the pediatric setting, I mentioned that cytokine-release syndrome is associated with a syndrome which essentially is HLH or macrophage activation. I was curious in of the very first patients identified a genetic abnormality putting the patient at risk for HLH.

[07:10:30] We haven't done all the analysis and all the samples, but I think that's a really good point. We certainly are looking at that.

Moderator: [07:11:00] I would actually say that the team at Penn led by Kate Nathansen is actually doing a GWAS analysis of samples from our center at Penn and other centers as part of their sporegram to look at genetic associations with the occurrence of ipilimumab induced adverse events.

Speaker 3: Yeah, Eric's right here. I don't know how many thousands of patients you guys have treated in clinical trials. You certainly have the capability of doing these studies. What is Merk doing?

Moderator: So Eric, for the help of those online.

[07:11:30]

Speaker 3: Yeah, so Eric Rubin from Merk, replying to Dr. Ratain's question. It's not 100% ascertainment we ask for, but it varies in terms of whether we get to DNA or not. But we are collecting it, and I think we will certainly be looking at those types of associations.

Moderator: Anyone else on the panel want to reply?

Speaker 4: [07:12:00] Yeah, I'll just comment. For ipilimumab at least those polymorphisms were looked at extensively for both gastroenteritis and hepatitis, and nothing really popped out.

Moderator: Okay.

Female: I'm [inaudible 07:12:07], I'm one of the oncology medical officers at [saber 07:12:10] FDA, also a member of newly established "The Office Oncology Center of Excellence" under Vice President Joe Biden's "Long Shot" initiative. Thank you very
[07:12:30] much, and what an excellent panel. I have one question for Dr. Snow and two questions for Dr. Porter. Am I allowed to have three questions?

Moderator: Sure [laughter].

Female: Thank you, I like number three, but anyway. So for Dr. Sznol I appreciate your presentation of adverse events from your academic perspective. Particularly the 3 plus 3 model for toxicity I understand that it's kind of outdated for this new field.
[07:13:00] So what would you propose other than have you seen some of the [inaudible 07:13:05] for the toxicity assessment what else would you think would be good?

Mario Sznol: Again, for example, if you're doing a combination with the ipilimumab you're starting out with, if you're using 3mg per kg, you're going to start out with at least a
[07:13:30] 15% rate of grade 3-4 AE's [adverse effects]. So doing 3 plus 3 doesn't make any sense. That's the reason I asked [inaudible 07:13:38] the question you could randomize. I actually propose that we randomize patients when we do the combinations to 3 different dose levels. Not necessarily do a standard dose escalation, and then treat, you know [inaudible 07:13:50] and treat enough patients where we might be able to at least get a sense if there is really a difference in toxicity between those 3 different dose levels.

[07:14:00] I'm also very concerned that if you see a 40% rate of toxicity at dose level "x", if you go one dose level higher, it may still be 40%. But if you increase the efficacy or not I don't know.

One thing I'm sure of is that three patients aren't enough to know whether you have a tolerable dose or not.

Female: Thank you.

Mario Sznol: Somebody else can comment.

Moderator: No I agree, I think that especially with the scarcity of some of these adverse events
[07:14:30] that we see where it took literally hundreds to see some of the more rare adverse events it is important to consider the numbers.

Mario Sznol: I just want to make one point. I've given epi needle a lot and I can go six or seven patients in a row without seeing colitis, and then I can see colitis in four out of the next eight. There's a huge amount of variability in knowing you're talking very small numbers to try and determine tolerability, again it doesn't make sense.

[07:15:00]
Female: Okay. Should I go ahead with another?

Moderator: Please.

Female: Thank you. I have two questions for Dr. Porter. And congratulations for your stellar results on [inaudible 07:15:07] 19 cells. My questions is: I'm interested in, you mention about the toxicity associated with the current infection. And you have adopted some kind of prophylactic measures. I would like you to elaborate on what
[07:15:30] you have done specifically or if this should be recommended to all the clinical trials using this approach.

David Porter: Thank you. We did, we went through a rapid, rather devastating period where we had three treatment related deaths after having none. The one thing that was consistent was that all three patients had an infection. One, an unsuspected
[07:16:00] influenza infection, was not symptomatic when she received the T-cells, but several days into it developed fevers and probably current influenza as well as cytokine release syndrome. Two others where neutropenic and develop bacteremia and bacterial sepsis. This is a little bit akin to a bone marrow transplant setting where patients who get infections and have inflammatory cytokines are more prone to Graft versus Host Disease.

[07:16:30] We think it's putting in the T-cells into an inflammatory environment that makes them impossible to turn off. They received very high levels of anti-cytokine therapy, three different anti-cytokine therapy, high dose steroids etc.

And we've talked about other ways to try and kill T-cells when they are not stoppable. But it was very obvious to us that they were the only three patients that
[07:17:00] had concurrent infections in the midst of this and all three of them had refractory cytokine release syndrome. So we started by detecting the occult viral infections is easy, and we do anti-viral testing initially for the flu, though I will admit we have a packaged PCR assay, and so we get five different common respiratory viruses.

We've argued up and down whether that should just be in flu season, and nobody
[07:17:30] could agree on when is flu season exactly, and when does it start, where does it end, and we just decided we would do it in every patient. We've detected a couple occult respiratory viruses, we just put off the infusion. And we have added prophylactic antibiotics to patients who are neutropenic. We do that in other clinical settings, and we again have not had any similar cases certainly in the last
[07:18:00] couple of years now after instituting that.

I think that should that be standard policy? I feel strongly that these T-cells can become auto-control, in the right cytokine environment. But I will say that everybody's T-cell's react a little differently. So the ones made with our lentiviral vector and our costimulatory domain may behave differently than somebody else's
[07:18:28] car T-cells.

[07:18:30] It is hard to suggest that that is mandated. I do think it's easy and I think other centers probably already use prophylactic antibiotics. I don't think everybody does routine viral swabs. So I'm going to just leave it out there as our experience, but acknowledging that different car-products may actually behave different both clinically but also in that setting as well.

[07:19:00]
Female: Thank you. And my last question is also Dr. Porter. You mention of course the visual aplasia is long term side effects or efficacy, evidence, whatever. So you use IVIG can mitigate this issue. But what about the patient if they are anaphylactic reaction, or hypersensitive or renal toxicity IVIG, what you going to do?

[07:19:30]
David Porter: Obviously we wouldn't give it. We have not had that situation yet. We certainly know that patients can live with hypogammaglobinemia, even without aggressive repletion. There are a couple different immunoglobulin products that I believe you can try, but ... If we knew ahead of time that the patient could not receive IVIG I
[07:20:00] would question whether or not they could give this therapy If they got this therapy and had an anaphylactic reaction, couldn't get it any more.

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David Porter: ... Therapy and had an anaphylactic reaction and couldn't get it anymore. We would certainly do all the right clinical things. We'd try and pre-med them. We'd give it slow. We'd see if we couldn't sensitize them but it would be an issue, I think, if we couldn't give it. Our lymphoma patients don't get IVIG, which is for a number
[07:20:30] of different reasons. We just started preemptively giving patients IVIG so this is what we do in patients who develop B cell aplasia or have hypogammaglobinemia. We have not done this without IVIG. We don't know that it's necessary and I suspect that would be a way to find out and I think moving on, as there are more and more patients and we get more experience, that would certainly be something to learn with better experience. Do we need it and how much do we need? And right now it's very empiric.

[07:21:00]
Speaker 2: Thank you.

Speaker 1: That's a good thought.

Speaker 3: Can I ask a question actually? It's about [dih-quard-uh 07:21:06].

Speaker 4: Absolutely.

Speaker 3: This is mostly with the CD nineteen car-t, I'm assuming. Potentially as the feeler goes forward and on target there's going to be less of an issue.

Speaker 1: Right. This is only an issue with D cell targets; CD nineteen, CD twenty. It would not

be in BCMA because none of them are mature B cells. Although, it is on plasma
[07:21:30] cells but our few myeloma patients who've gotten BCMA have not developed DB cell aplasia but any B cell target this would happen but it would not happen with mesothelin target or CD one twenty three myeloid target or any of the other tumor targets.

Speaker 4: Thank you. Yes?

Amanda: Amanda Walker, FTA ... What we've heard quite a bit today about combinations of drug and drug and all the issues that surround this in drug development. My
[07:22:00] question is actually related to the combination of radiation therapy and immunologics. There's a variety of mechanisms in which this may be a promising therapy, including [en-uh-junt 07:22:09] release by some of doctor Wolchok's work and while it's other ways in which radiation therapy can sort of modulate the tumor micro-environment.

My question is, to the panel and doctor Wolchok, in terms of the safety concerns ... Theoretically there's a lot of reasons to be concerned about overlapping toxicity yet we've had enough clinical experience, I think, to have at least formed some type of
[07:22:30] opinion about this whether or not patients are getting treated on trial with the combination or just getting treated with drug and then patients require palliative radiation at some point shortly thereafter administration of drug. My question is where those initial concerns? Are they validated, in your opinion, based on what we've seen so far or do we have a little bit more experience to move forward and pursue the combination with a little bit more comfort?

Speaker 4: That's a great question and I think if I could just answer a little bit and the we'll
[07:23:00] open to the panel of course. The initial observations have been anecdotal, of course, from patients who we tried to palliate after the fact. Where this enter a little bit more wide spread use, we've tried to just use some common sense approaches. For example, when we've given palliative radiation therapy in the middle of ipilimumab based therapy we've tried to not do that when there is
[07:23:30] intestine in the radiation field for fear of a radiation enteritis triggering or adding to the colitis.

It's really been some common sense observations where I personally, and again everyone else speaking of personal opinion, had a little bit more concern now as with concurrent brain radiation and either CTLA four or PD one blockade where
[07:24:00] inflammation in the brain which can occur after radiation and is usually one rational for using corticosteroids around the time of brain radiation. We have seen, and this has been documented by Catherine Beal from our group and others, that when ipilimumab is given around the time of stereotactic brain radiation there can be an increased observation of inter-terminal hemorrhage. Thankfully, none of it fatal and all controllable but an increase frequency of inter-terminal hemorrhage
[07:24:30] has been seen and more recently, again, in the real world observation outside of clinical trials, we've seen more encephalitis-like situations with PD one pathway blockade when patients have received brain radiation which, in some cases, has led

to the need for long term steroid use and sometimes steroid refractory brain edema.

[07:25:00] I think that we're now, thankfully, having some clinical trials, which are prospectively addressing this and I think we'll collect the data in a more careful way. Timing may be very important. I don't think we really have a clear cut answer of whether you give an immune modulating intervention before, during or after radiation therapy especially when it comes to brain and whether the dose symmetry of the brain radiation has an impact on that. I think we still have plenty
[07:25:30] of questions to answer for the interim outside the clinical trial. I'm trying to actually give immunotherapy at least a week before or after radiation. Certainly, if the patient is still requiring any kind prophylactic corticosteroid around the time of brain radiation at the discretion of the radiation oncologist, we stay out of that window.

[07:26:00] Anyone else have experience or observations? Guidance?

Speaker 1: We should soon have more for the NCI sponsored trials but of you look in clinical trials like [uhv 07:26:07] there are over a hundred trials with PD one or PDL one inhibitors in combination with the radiation in various forms. I think that we're going to have some sort of answer and not all of them are really safety trials. A lot of them are actually combining them with, more or less, standard of care. At this
[07:26:30] point I would say that there is some element of safety that we feel, more or less, comfortable with. Probably, there are some distinctions we have to make with various types of radiation therapy like doctor Wolchok just said but I think that we're at the point where we're looking at efficacy.

Amanda: Thank you.

Speaker 4: Maria did you have anything or [ah-kee 07:26:48]. [crosstalk 07:26:50]

Speaker 6: Well we have a lot of experience. We routinely give immune therapy first and then
[07:27:00] give the radiation whether it's for palliative or Gama knife radiation to the CNS after we start the immune therapy and all of Jed's comments are exactly right. I don't think we've seen an increase rate of bleeding but certainly all of those patients are at risk for developing radiation therapy necrosis and that could happen a year or two years after. We're not completely sure that it's related to giving the [ip-pee 07:27:21] or the NTP one before the radiation and some of those patients can get into really bad trouble with the radiation therapy relate necrosis but I'm
[07:27:30] not sure it would be any different if we radiated first and then gave the immune therapy later.

Speaker 7: Some of that bleeding, I'll just add, was incidentally noted on a short interval MRI that the radiation oncologists were doing to asses for just that. It was not the people presented with the symptomatic inter-terminal hemorrhage. I would also say, with the PD one blocking drugs and the PD one pathway blocking drugs ... I would also have concern about long radiation of any kind at the same time, for the

[07:28:00] same reason we would avoid bowel on the field with ipilimumab.

Speaker 8: Terms of radiation in our world that usually tie in the context of the [tof-tee-firs 07:28:08] cell therapy, the intent is to eradicate whatever the indulgent is suppress the t cells together with chemotherapy. I think a lot that the surgery branch found this year I presented a randomized trial that compared proper [prahp-truh-tuh
[07:28:30] 07:28:28] regimen including total evaluation is not insuring that in the metastatic under a normal setting after two therapy that did not basically show the increase in the response rate but it brought more toxicity. In our world the radiation really did not help that ... not to the tumor though.

Speaker 9: Okay thank you [kee 07:28:54] Next question.

Speaker 10: [don-eh-suh-bon-es 07:29:17] from [turn-uh-tech-rosh 07:28:57] ... Doctor Small
[07:29:00] you mentioned that you never give prophylactic steroids because they could damper the efficacy. My question to you and the panel; is there really a regular consensus in the field based on studies that this is the case and also what is the experience that prophylactic steroids could even avoid immunilate adverse events?

Speaker 11: There's really no data. In the brain tumor study there was only ipilimumab, the
[07:29:30] cohort that was on steroids, and guide ipilimumab had a very low response rate but the response rate was pretty low on the other arm also. I don't think there's any data that it can either prevent toxicity or reduce adverse events in humans. In animal models, if you give the steroids first and then give the immune check point inhibitor, you inhibit activity. I just got a phone call last weekend of a glioblastoma patient, who was on dex four TID and then received a couple of doses of
[07:30:00] pembrolizumab and came in with florid transaminitis.

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Speaker 1: Florid transaminitis, and I was shocked that they develop toxicity and it turned out to be drug-related toxicity while they were on very high doses of steroids. So maybe we should throw all those assumptions out the window. But for now, I'm still not giving anybody steroids before they get their checkpoint inhibitors.

Jedd Wolchok: Especially since it doesn't seem to be preventative, at least in that one example, right?

Male 2: Thanks.

[07:30:30]
Jedd Wolchok: Yes.

Paul: Hey, Paul Kluetz with the FDA. In the past we didn't have to ask this question about metastatic melanoma, but for those patients who have had successful therapy and are now years out, we've been talking a lot about acute toxicities and life-threatening toxicities.

[07:31:00] What have you seen as far as chronic, sort of, bothersome, maybe moderate continued immune stimulation-type toxicities, if any, is it that they are bothersome to patients that they feel pretty well far out, say 3, 4, 5 years out?

Jedd Wolchok: That's a great question. I'll take the first stab at it.

[07:31:30] This is Jedd Wolchok, Memorial. I think that from ipilimumab the standard labeled indication is a short course, so we don't really see much downstream toxicity from that. Where we are seeing a little bit of that is in the patients who are sort of persistent, PD-1 pathway blockade ... The toxicities that ... At least our patients ask us about the question of stopping most often is really arthralgias and myalgias, which tend to come up with more long-term use. Incidentally in patients, because they're still on it, those who are benefiting. So it does raise the question of, "When do we stop?" And I think we can have another 2-day meeting on that question. Because again it kind of violates all that we think we know about designing drug
[07:32:00] regimens for cancer patients, "More is better", and if you stop the tumor will come back, right? This is what patients ask us all the time.

[07:32:30] And I think we learned a lot from a presentation given by Caroline Robert at ASCO this year from the Keynote-001 study, where she showed data from patients who stopped pembrolizumab after having a complete response, and 97% of those patients remained in complete response, admittedly not a very long [inaudible 07:32:28] but still 10 months, 97% of those responses were maintained despite stopping drugs.

So we use that as some degree of comfort for patients to say, "You know, this fatigue or this joint pains is really getting me down, and what can we do about it?" Drug holiday is a reasonable thing to offer.

Other suggestions or experiences?

Speaker 1: [07:33:00] Completely agree, and we have a very long follow-up now on patients who've got beneva and most of those patients don't have, other than hypophysitis and vitiligo, I don't think they have any ongoing adverse event. We have seen an occasional patient though who's had a neurotoxicity that was progressive, or at least progressive to a point and didn't stabilize, but didn't reverse.

Jedd Wolchok: Thanks. Yes, next question.

Brett: [07:33:30] Brett Williams, Philadelphia. I don't know if [inaudible 07:33:23] has left the room yet or not, well maybe I shouldn't ask this. But let's say we're using one of those archaic dose escalation designs. Given the carnosity of these toxicities, is it ever the case that you would require the monitoring for more than 28 days to define DLT for the purposes of dose escalation?

Speaker 2: You know, Dr. Walker brought up the issue of radiation, so there is actually some

experience that we have with different strategies to actually monitor toxicities long
[07:34:00] term, late toxicities. Designs like tight CRM, which you might be familiar with.

Brett: Well I guess what I mean is, if you're really concerned about going to the next dose [crosstalk 07:34:07] are you ever so strict as to require, not just to consider picking the dose for phase 2 or phase 3, but for actually allowing the next patient to get a higher dose? You know usually we say 28 days regardless. But I've heard a rumor
[07:34:30] that on occasion there was some real fears of some serious toxicity occurring after 28 days that maybe the FDA has said, "You might need to wait longer than that before you dose escalate", because of these concerns that really serious toxicity is going to occur beyond 28 days.

So I guess the proposal would still routinely be 28 days and you take it all into
[07:35:00] consideration. But is there ever such a high concern that ... FDA for instance is requiring a monitoring period for DLTs for [inaudible 07:35:03] escalation that's beyond 28.

Jedd Wolchok: David?

David: So 28 days I think originates from when we were using our old drugs and chemo therapies and you achieve steady state before these 20 days were over. With these monoclonal antibodies and fusion proteins, it can take several months to really achieve the appropriate steady state. So that's on one hand, yes, it does make
[07:35:30] sense that you do want to monitor patients. And the other hand, you have to be practical. We could be spending [inaudible 07:35:34] doing dose escalation. So what we do, and I think probably what everyone else does, is we do have a defined period. Sometimes it's 42 days by the way, mandated by health authorities. But other times it's 28 days, and we continue to monitor the patients. And if there is late toxicity then we take that into account.

[07:36:00]
Jedd Wolchok: Anyone else, comment? Okay, I actually think that's a really good point to end on because it tells us how much we still don't yet know. That there is really a spectrum of timing of when these toxicities can occur, and I think we have an open mind about how these dose escalation or DLT periods should be handled with new agents and combinations. We got 11 seconds left, so I'm going to summarize what I learned this morning.

[07:36:30] First of all, thank you all for the presenters and the participants, both in person and online, for the attention and the excellent questions. I think that we've heard some really important messages about the need to think further about clinical trial design and dosing regimens that address the unique biology of the types of therapies that we have, in terms of toxicity. Similarly, we have to adapt the guidelines of how we grade toxicity, how we manage expectations in terms of timing of dosing in regard
[07:37:00] to this toxicity. And I think we've heard a strong call out, which I completely agree with, [inaudible 07:37:03] mentioned this, for really harmonizing the management of these toxicities across different programs, across different companies. Actually

some of us were at a meeting last week between representatives of the FDA and the Parker Institute, where a major take-home message was a call-out to really unify the way these toxicities, at least for the checkpoint inhibitors, but the same could be said across different T-cell programs: the way in which these are graded
[07:37:30] and managed should be consistent since the mechanism underlying them is similar.

Obviously I'm not talking about crossing the pathways between CAR T-cells and checkpoint inhibitors, but I think we need to have much more open dialogue and sharing of data so that we're talking about the same events and the same management pathways. Because it does appear that there is a lot of overlap and a
[07:38:00] lot of similarity. And I think that this will strengthen the recommendations that have been given.

I also give credit to Dan Chen for really an excellent question earlier about how we optimize therapy, how we come to the best treatment that will cure the most patients. I think that's what we're all here for. I think this is going to be a remarkably complex task. But we're all up to the challenge Dan.

[07:38:30] It is almost going to be patient-specific in understanding between patients what the immunologic needs are. You can already see from some of the data that Dave [inaudible 07:38:35] presented that there is a different immune set point, the threshold for toxicity, between diseases. What is safe in a melanoma patient is frankly intolerable in a patient with non-small cell lung cancer. So there are just many more moving parts here than we're used to dealing with in more straightforward drug development. I think this has to do with the fact that we're
[07:39:00] treating the patient and not just the tumor.

And so we have a lot of considerations, but I think with a lot of hard work across all these different constituencies we will get there. So thank you very much again.

(applause)

(music)

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