Oncology Dose-Finding Workshop Part 3

Transcript: Session III, Considerations for Dose Selection of IO Combination Products

[00:01:30]

Eric Rubin: [00:02:00] [00:02:30] [00:03:00] Hello everyone. Good afternoon. For folks that are still out in the hallway, if you could please make your way in. I know people are still getting back from lunch, but we'd like to try to start soon, so we can stay on time. My name is Eric Rubin. I'm a medical oncologist at Merck and I have the pleasure of moderating the third session of today, which is going to move from the beautiful biology we've heard in the first two sessions into I think more practical aspects of dose finding in the combination setting. I'll note that one of the motivators for workshops like this is trying to get the dose right before it ends up in the label and some of the earlier workshops it was pointed out that there were a number of post-marketing commitments that related to really not getting the dose right in the earlier studies. I think when we move into combinations, of course, it adds yet another level of complexity and this session will focus on approaches to trying to get the dose right in a combination setting.

[00:03:30] There will be five talks. The first talk will be from Drs. Fernandes and Liu from the FDA. There will be a talk from Dr. Bruno from Genentech, a talk from Dr. Roy from Bristol-Myers Squibb. I have a talk and then Dr. Lowy from Regeneron will finish the series of talks and that'll be followed by a panel discussion. So with that, I'd like to invite Drs. Fernandes and Liu up to the podium. Thank you.

Laura Fernandes: [00:04:00] [00:04:30] Good afternoon, I'm Laura Fernandes and I'm a stats reviewer at the FDA, supporting the office of oncology and hematology products. I guess I've been tasked with the big job of keeping everybody awake until the end of the session, given that we just had our lunch break. Dr. Chao Liu will be joining me in giving the pharmacology perspective. We don't have any disclosures for this talk. This is the FDA perspective on combination dose finding trials with immunotherapy in oncology. After a brief introduction on combination dose finding trials in immunooncology, I will present some of the methods used in such clinical trials with case examples. Dr. Liu will continue with the clinical pharmacology overview on dose finding and conclude with a summary.

[00:05:00] [00:05:30] So some of the challenges that are unique to immunooncology trials revolve around efficacy and safety endpoints. We need an efficacy endpoint that is available in a reasonable timeframe that would also capture the delayed response. The safety endpoint needs to capture both short-term and delayed toxicities which are common with immunooncology agents. As widely published, unlike other chemotherapy agents, the more is better paradigm does not apply to immunooncology agents. The efficacy and/or the toxicity profile tends to plateau after a point instead of a monotonically increasing function of dose. We also tend to see seamless designs in immunooncology agents where both the efficacy and toxicity are evaluated early on in the trial, eliminating the clear-cut

[00:06:00] Phase I to Phase II to Phase III approach. Given these features of the immunooncology agents, we need to consider what actually entails in a combination therapy. So, the immunooncology agents could be studied in combination with a targeted therapy or a chemotherapeutic agent or another immunooncology agent. The toxicity profile of this combination could be additive
[00:06:30] or overlapping, while the efficacy profile could be additive, synergistic or in some instances, antagonistic or detrimental.

For example, with objective response rate as the commonly used efficacy endpoint in such trials, additivity implies that the combination of the two agents provides an objective response rate that is in the ballpark of the sum of the objective response rates seen in the monotherapy agents. Synergy, which is a
[00:07:00] desirable outcome, would imply that the combination results in an objective response rate that is much greater than what is expected as a sum of the individual agents, while detrimental implies that the combination results in an objective response rate that is significantly lower than expected from the sum of the objective response rates in the individual agents.

[00:07:30] So, how do we study combinations? The first approach would be to investigate two agents that are approved with monotherapy indications. This would involve having different dose levels that are anchored around the indicated dosage for the two agents to be studied in the combination setting. The second approach would involve combining an approved agent with the first inhuman agent. Examples of this were covered by Dr. Riggs in the previous session today. We
[00:08:00] could fix one agent at the approved dose level and consider different dose levels of the new agent. Or we could consider additional dose levels of the approved agent with different dose levels of the new agent. A third approach involves combination of two agents with no prior indications. In this case, we would have to study both the agents at different dose levels. Many different combinations
[00:08:30] are possible based on the individual number of dose levels for each of the agents. There could be a fourth approach where triplets or even quadruplets are investigated. The possibilities are numerous, but as we discussed in one of the previous sessions, the patient resource is limited and hence we need to find clear ways to optimize and identify combinations that are both safe and provide increased levels of efficacy.

[00:09:00] In terms of methodology, there are two broad classes, the algorithmic or the rule-based approach which mimics the three plus three design by ordering the dose level combinations based on a perceived degree of toxicity and then assigns cohorts of patients to arrive at the entity based on observed toxicities in that current cohort of patients. The model-based approach on the other hand
[00:09:30] assumes an underlying model for toxicity and efficacy relationships with increasing dose levels and estimates model parameters after observing patient outcomes of both toxicity and efficacy to guide the assignment of the next patient.

[00:10:00] This slide summarizes some of the proposed methods in studying combinations with both efficacy and toxicity endpoints. My apologies if your favorite method-

Laura Fernandes: My apologies if your favorite method is not listed on the slide because I is not an There are other methods that consider efficacy and toxicity in a single agent that My first one considers the study design for MEL60, which is a melanoma vaccine studying long peptides and tall like receptors (TLR) evaluating both the efficacy

[00:11:30] and safety using a model based approach to identify the optimal regimen defined as having an acceptable toxicity profile, which is measured by DLTs and a high immunologic response rate, which is the efficacy endpoint.

This study design uses partial ordering approach, which was one of the methods that I listed in the previous slide and it groups the two combinations into seven

[00:12:00] regimens as shown in this table. So only six different orderings assume different probability of dose limiting toxicity that increases with the addition of the adjuvant. The concept of partial ordering allows for making assumptions about toxicity within the same zone as listed in the table.

[00:12:30] Within the same zone the toxicity ordering is unknown and all the possible orderings are specified. The accumulated data is used to guide the best representative ordering based on an updated model. This is an ongoing trial and the methodology in this vaccine setting could be extended to include the immuno-oncology drug setting. Dr Wages who is the primary author on this

[00:13:00] paper will be joining us on the panel and could expand further on the scope of this method.

My second example is an example that uses algorithmic based design in the Nivolumab and Ipilimumab combination trial with two immuno-oncology agents. Both of which had prior mono-therapy indications. Both Nivolumab and

[00:13:30] Ipilimumab were indicated at 3 mg/kg. The trial studied the combination therapies in sequential and concurrent setting. In the sequential setting, two doses of Nivolumab were explored and administered after Ipilimumab. In the concurrent setting, six cohorts were planned at four doses of Nivolumab and three doses of Ipilimumab as the dose levels are shown in this table. Eventually,

[00:14:00] two of these cohorts, cohort four and cohort five did not enroll any patients. Although the trial was planned as a dose escalation, dose finding trial, it ended up being like a four arm trial. Cohort three was chosen as the optimal combination. Dr Amit [inaudible 00:14:21] Roy will be one of those speakers in the session and he'll be expanding further on this trial design.

[00:14:30] The results of this trial is that eventually a total of 33 patients were treated sequentially and 53 patients were treated on the concurrent regimen and patients on the concurrent regimen had better responses. In this example, a rule based design was used and we find that patient assignment was guided only based on observed toxicities without incorporating the efficacy during the dose

[00:15:00] assignment phase. Some of the dose combinations were not explored and the trial recruited only metastatic melanoma patients. The optimal dose combination

was different for patients with non-small cell lung cancer that was explored in a different trial and it's important to note that the homogeneity of the patient population seems to be a key factor in such trial designs.

[00:15:30] To summarize, the second example was implemented using algorithmic design and although it was easy to understand and implement such methods do not explore all possible combinations. In addition, they do not incorporate all the information from all the patients in the trial to inform decisions on the current
[00:16:00] cohort of patients. They also do not use efficacy outcomes to guide the patient assignment. On the other hand, model-based designs an example of which was presented as the first case example incorporate both efficacy and toxicity information from all the patients. They have provisions to include various degrees of prior knowledge in the model. On the flip side, these models could become complex and require additional logistics to implement in terms of an
[00:16:30] expert clinician or a statistician on the team in setting up the model, prior information, ordering of the dose levels, priors etc. And yet these models are more efficient in selecting the optimal combination. This would be the preferred approach to dose combination finding studies.

Dr. Qui will now continue with the clinical pharmacology perspective on dose finding in the combination setting.

[00:17:00]

Qi Liu: Thank you, Dr. Fernandez. Good afternoon. My name is Qi Liu and I'm a pharmaco [inaudible 00:17:11] at FDA. At this presentation I will talk about the dose finding issue from a clinical pharmacology perspective. A well selected dose combination puts exposure of each drug to [inaudible 00:17:23] inside a window in the general patient population so as to maximize the efficacy and to minimize
[00:17:30] the toxicity. Here, exposure refers to various measures of drug concentrations in plasma and the biological fluid. Drug exposure is [inaudible 00:17:41] by not fully intrinsic and extrinsic factors such as body weight, organ function, immunogenicity and concomitant medications. Change of these factors in a combination setting might alter exposure profile, which could potentially impact
[00:18:00] clinical outcome depending on the relationship between exposure and the response for efficacy and safety.

For human oncology combination therapies, a well established exposure-response relationship provides information on a risk-benefit profile at different exposure levels of each drug and also it forms whether a dose combination is appropriate by assessing if the exposure distribution matches therapeutic window where the risk-benefit profile is favorable.

[00:18:30] To estimate ER relationship, exposure-response analysis is conducted. Traditionally, ER analysis takes exposure as the cause to drive the response. However, we found out for multiple immune checkpoint inhibitors the drug exposure is also influenced by the treatment outcome. And we'll talk about these

findings in the next couple slides and discuss its implication for ER analysis and dose evaluation for IO biologics.

[00:19:00] The impact of treatment outcome upon IO biologics exposures were firstly identified during an FDA review of Nivolumab. We found that the clearance of Nivolumab was changing over time and it is associated with the disease response. Here, clearance can be taken as the body's capacity of removing drug. Higher clearance may lead to lower exposure and vice versa. This part showed a
[00:19:30] longer T node change of Nivolumab clearance over time as estimated by the population PK analysis. Patients with different best overall response are shown separately from complete response on the left to the progressive disease on the right. The X axis is time after treatment and the Y axis is the ratio of the clearance to the baseline at different time points as shown in percentage. Each dotted line represented one individual. A solid blue line is a typical change of
[00:20:00] clearance at each response category. During the treatment the clearance showed a decreasing trend ...

During the treatment, the clearance showed a decreasing trend, and the responders had a greater magnitude of clearance reduction, which would lead to an elevated exposure over time.

The different changing profile of clearance by disease response water distribution clearance from baseline to later period of the treatment. The plot on the right shows the distribution of an [inaudible 00:20:24] clearance at each response category. The red box plus [inaudible 00:20:29] of clearance at beginning of treatment. The green ones showed clearance at a later period of the treatment. Each dot represented one subject. At baseline, the clearance in the responders was only mildly smaller than our responders. However, at a later period, there was a clear trend that responders has smaller clearance as compared with our responders.

Speaker 1: This feature is not limited to Nivolumab alone, but it is also seen in the other
It has been well-known that, in ecology, higher clearance of therapeutic
[00:21:00] The interaction between drug exposure and disease response complicated assimilation of the relationship between drug exposure and the response. Typically, exposure is assumed for the cost, and the response is the outcome. In this case, patients showing better treatment effects had a greater clearance reduction. As a result, drug exposure at a later time period, would be affected by the treatment outcome. In other words, a higher drug concentration at study stage could be the result, instead of cost, of a better treatment outcome.

[00:21:30] Analysis using study to state exposure as an independent variable might lead to biased estimate of linear relationship even if baseline [inaudible 00:23:12] factors were adjusted. Well, it would still be possible to minimize the bias in estimating the linear relationship if the analysis was conducted appropriately. This type of PK disease interaction should be considered when linear analysis is performed for those evaluation of I-O combination.

[00:22:00]

[00:22:30] Besides linear analysis, in the case of an additive or even synergetic effect in a combination therapy, as described earlier by Dr. Fernandez, the clearance reduction might be more evident with greater treatment benefit than what was observed in the monotherapy.

[00:23:00]

Finally, I would like to brief talk about other clinical pharmacology considerations in the I-O combination dose lectures. [inaudible 00:23:58] has the potential for immunogenicity and the formation of antidrug antibodies could be distinct between single agent treatment and the combination therapy. In terms of both incidents and [inaudible 00:24:13] And this should be evaluated in the clinical

[00:23:30] development program. Drug interactions in the I-O combinations should also be studied to the potential for [inaudible 00:24:24] mediated alterations in drug metabolism.

In the wish list, [inaudible 00:24:30] conducting dose funding trials that incorporate the model-based designs to identify optimal dose combinations and he incorporated both early in the delayed toxicities. Trials characterize the PK variability and account for patient heterogeneity. The sequencing of the drugs should also be investigated. [inaudible 00:24:51] conducting adequately dose exploration before commencing trials to support a registration. [inaudible 00:24:57] dose levels and dosing regimens should be investigated with a reasonably wide-dosed range. Collecting PK from clinical studies is highly encouraged. Exploring [inaudible 00:25:09] response analysis [inaudible 00:25:11] and safety is recommended and the potential drug-disease interaction should be considered when performing this analysis.

Finally, I would like to thank our [inaudible 00:25:23] colleagues for their support

[00:24:00] and help with this presentation. I would also like to thank the sponsors like BMS and Merck for their collaborations for our analyses. Thank you.

[00:24:30] Good afternoon. I am Rene Bruno from Genentech and I am a Genentech employee. I thank the organizer for inviting me and giving me the opportunity to present [inaudible 00:25:59] and try to use this model to inform [inaudible 00:26:10] decisions.

[00:25:00]

After a few bygone considerations on the drug [inaudible 00:26:17] ecology and also the drug disease modeling [inaudible 00:26:20] I show you an example

[00:25:30] based on some [inaudible 00:26:24] data and how we can use that approach to inform Phase 1B combination studies.

Rene Bruno: So, [inaudible 00:26:35] no need to go into the details here, but given the number of new drugs that we have and the need to expedite programs, very

[00:26:00] often new treatments are approved based on very early studies, even phase 1 studies. So there is limited possibility to learn from early clinical trials to inform late studies.

The traditional [inaudible 00:27:05] based on MTD or biomarker responses are not working very well. There are no formal dose-ranging studies in ecology. The [00:26:30] [inaudible 00:27:20] are very informative and given the complexity of the field that we have heard about this morning, I think we need to be creative in term of design and end-points.

Here, I am going to propose a model-based tumor growth inhibition and points that could be an alternative to traditional [inaudible 00:27:43] and may be more sensitive to [inaudible 00:27:47] treatment effect and look at [inaudible [00:27:00] 00:27:49] dose response. So, the concept here is that drug-dosing- dose intensity is generating drug exposure and drug is inhibiting [inaudible 00:28:05] growth inhibition. And then there is a link between tumor growth inhibition and [inaudible 00:28:05].

The beauty of this [inaudible 00:28:05] is that the first part here is a link between dose-intensity and tumor-growth inhibition is really a drug and treatment specific, when we believe and [inaudible 00:28:05] that the link between tumor- [00:27:30] growth inhibition [inaudible 00:28:05] survival is [inaudible 00:28:05] specific, but treatment independent. So, that we can learn about this link here between tumor growth inhibition and [inaudible 00:28:43] survival using this clinical data. And then we can inform new drug- new treatments based on emerging tumor-growth inhibition data. So, basically the tumor growth inhibition [inaudible 00:29:00] that we can estimate are used as kind of a biomarker to get your treatment effect [inaudible 00:29:06] was benefit.

We have been working on this [inaudible 00:29:11] for more than ten years. [inaudible 00:29:13] for immunotherapies. The TGI [inaudible 00:29:22] model are believed to be drug independent and this is specific. So, we have [inaudible [00:28:00] 00:29:28] model to estimate our time distribution as a function of policy factors and the tumor growth inhibition estimate. I use as predictor of outcome. As I said, [inaudible 00:29:46] tumor growth inhibition [inaudible 00:29:47] I used as biomarker to capture drug effect. We can [inaudible 00:29:52] model based on [inaudible 00:29:53] and we have already [inaudible 00:29:56] the [inaudible 00:29:57] fiber model [inaudible 00:30:00] tumors with treatment

with treatment, with a variety of mechanism factors. It is implemented by many companies if I can draw your attention to [inaudible 00:30:16] model very early on [inaudible 00:30:17] we getting longer and recently such an approach was presented last year in at the [inaudible 00:30:28] workshop.

To assess the model it's very important to show that they are able to predict studies outcome that haven't been used to build the model. We call that External Validation. That is very important and I will show you one today.

Speaker 1: We have to address a very complex problem as we have heard this morning and I am going to present a simple solution that may be actionable/accessible to help in addressing some of the questions.

[00:30:30] When we look at the T model of our time some of longer diameters, let's say per The growth rate also is of some interest we show were able to assess pre-
When you can see there is some drug effect. Oppositely, here where you've got an indolent tumor, you may want to see a stable disease where there is no effect of the drug. Moving forward, it would be very important to look at pre-treatment
[00:31:30] growth and compare with post treatment effect. Again, we don't have the data because currently there is only one baseline scan that is taken.

Let's see what we have done. anotmosis based on the atomizer poplar facial studies that you have heard about this morning. Those are the study's results. The studies showed an improved cell divide following the single agent to
[00:32:00] compared to those who accel in the cancer line patients. We have taken hemodialator from the study and we have applied this bi exponential model. We found that the model was able to describe the data well. What we see here is the hemo size over time in a typical patient with mid parameters as a model. This patient doesn't exist indeed, but it's kind to illustrate the other features of the hemodynamics. For this typical patient, there is initially more shrinkage with this type of accel, but a faster growth. That is really maddening for the other age patient there is not that much shrinkage, but slower growth. In fact, the difference in growth rate is a bit more than three months increasing them in time to modern time with ... This is about the overall survivor benefit, by the way.

[00:32:30] Now this is for all patients. If we look at the patients on the left, it is the same blood. On the right, we have the patients who didn't progress at a the first visit at week six. The progression is defined using a model based approach. We could use the records too, but here we are using the model. Those patients are the patients whose model predicted some longer diameters at week six, less or equal to baseline. Those patients didn't progress per the model. This is about 50 to 60 percent of the patients. You can see that we here again we have shrinkage and then a fast progression. As use the easy mab the shrinkage is delayed in the end there is shrinkage as we do in excel in the gains across weight much longer. Mature throughout three.

[00:33:00] With those models we are using population models. Whereas patient rate had no effect on the shrinkage rate and the growth rate. Each patient can have a different shrinkage. We found the growth and we can estimate indeed the parameters.

[00:33:30]

[00:34:00]
[00:34:30] Now we are going to see how those parameters are predicting for all survivors. When we take long, normal distribution for all survival. We build the multivariate model, we find that independent predictors of survival are some baseline positive factor like the number of mid atcites. This is a surrogate of the model.
[00:35:00] And the verified which is known as a policy factor. The growth rate that I'm going to label kg here growth rate constant is very significant in the model. When we do the multivariate analyzes actual treatment effect is no longer significant as a model. Meaning that the difference in growth rate across patients is capturing
[00:35:30] the affect of the treatment.

When we have a model like that, we try to assess whether this model is able to predict the study outcome. If this model is able to predict the outcome of independent studies. To do that we perform simulations. What you see on the left, the shaded color areal of the predictive distribution according to the model across a thousand replicate of the study. The line of the observed cap here in bloods you can see that on top to accel, observe the distributions are within 95 percent interpretive data. When we see that we are happy with the model. We are more interested to see the model capture treatment effect because here you can see that there is some overlap in the predictive distributions. For each of the thousand replicated studies, we can estimate that ratio. What you see on the right is a predictive distribution we show, in blue. Together we observe the one here which is something below .7. The dotted lines are the 95 percent prediction intervals. And you can see there's a 95 percent prediction interval that is meaning we are a successful study. That we know already, but it's not by chance.

[00:36:00] This is the overall population in the study that we used to observe the model. Here is additional validation. This shows our ratios again as the dots above are the simulated 95 percent blank. The square are the observed and what you see is a first line, here in all patients. You can see that the model is able to predict the outcome easier carmels. The model is unable to predict the outcome in patients
[00:36:30] with PDA1 expression, either in the chemo cell or immune cell, what level of chemo expression better than the patient with no PDA1 expression. 0 and during chemo cells and individual cells. Those patients possibly didn't benefit, when those benefited. This diagram is not in the model meaning that it is a different in growth rate that is a predictable outcome of two populations. We also looked at the the T factor gene expression that we heard about a little bit this morning too. And again patient with a

... We heard about a little bit this morning too, and again patient with a high level of T-effector expression, benefited a lot more than a patient with a low level of T-effector expression by the median, and you can see the model is able to predict that also. Actually when we look at it, there is a strong correlation

between the T-effector expression and the growth rate estimate. This is 'Poplar' that we have used to develop the model, now we used that model to predict the phase-3 study, 'Oak', that you heard about this morning too. Conditional on the base-line patient characteristics in 'Oak'; number of metastatic sites and albumin level, and the tumor size data observed in 'Oak'. And you can see that the model is able to predict the outcome in 'Oak', the model is able to predict the outcome in 'Oak' in patients with any level of PD-L1 expression, in patients with no PD-L1 expression, and here you know that in 'Oak', for some reason, the patient with no PD-L1 expression benefited also a bit less, contrary as what we have seen in 'Poplar', and the model is able to predict that. Same thing for the T-effector expression.

So we are happy with the model, we can see that growth rate seems to be capturing really well treatment effect in patients populations, so now the question is what can we do with those growth rate estimates, and can we use them to help support decisions in combination studies. And as Dr. Chen commented this morning, the problem is complex, we need to have a good type of disease, we need to have a good platform, and we need to have a good read-out. So can those estimates be a read-out to help decide upon the most promising combinations, and if so, maybe the dose response?

Speaker 1: In those studies, small, phase-1 B-studies, generally decision relies on objective response rate, and, of note, in the two studies I have shown you, 'Poplar' and 'Oak', there was no difference in response rate, and no difference in BFS between the two ones. So now, maybe in confirmation studies, there may be differences in response rate, or in BFS, but we are relying on small course of

[00:40:30] patients, right? So what about if we have 15-20 patients with a 20% response rate, how to decide if we have a good combination? Even in the platform studies, there is a control arm that may be common to multiple combinations, but if you combine Atezolizumab with whatever other drug, then the control arm, in 'Lung',

[00:41:00] for example, will be [inaudible 00:43:19] in 'Lung'. So here we have these two models, inhibition model for Atezolizumab Single Agent, and we can asses [Coviat'a 00:43:30] effect on the growth-rate, and then we can compare growth-rate, Coviat-adjusted growth-rate for Atezolizumab Single Agent.

[00:41:30] Through those profiles we are observing in the combinations studies, so that we can adjust for patient characteristics and compare the growth rate, and maybe identify the signals or absence of signals of increased efficacy in those small course of patients, based on another read-out than just response rate. This is

[00:42:00] really on-going work, so we don't have the end of the story, but we hope that this may help select the best combination, and asses, possibly, those response, or exposure response.

Now, when we have those growth-rate estimates in the combination study, we To illustrate that, I'm just going to show you ... This is a framework, actually. Here I think there is something wrong ... Oh, thanks.

[00:44:30]

[00:45:00] What you see here is hazard ratio, as a function of the effect size on growth rate, it is a large number of simulations indeed, so when the growth rate is unchanged, we have one indeed because it is the same as a Single Agent, but then we the is a 20% decrease, 30% decrease, 40% decrease in growth rate, there is an improvement in the hazard ration that is going from 0.9 to 0.7, for
[00:45:30] example. So that you can, based on early clinical data, you can figure out what may be the overall survival benefit of the treatment.

So this, as I said, it'a ongoing, but the [DSTGI 00:46:37] overall survival modeling methodology which is pretty well established, as I said, for many years. Of course, many tumor types and a wide range of therapeutic agent, this approach is working for immunotherapies, I have shown you [inaudible 00:46:55] cancer, it'a also working in bladder cancer, we could develop a model based on phase-2, that was predictive of phase-3. So external validation of the model is critical to convince our colleagues and the teams, and facilitate the implementation, so we're trying to do more.

And this estimate of [untreatment 00:47:17] growth-rate as a potential, as an alternative end point, to evaluate efficacy in early studies to support design,
[00:46:00] possibly, because if you want a treatment that is going to support a 0.7 hazard ratio you know that you have to decrease the growth rate by, let'a say, 30%, and then you can design a trial to show that, to help prioritize and select the most promising combination therapies and possibly to help select the best dose and schedule to achieve the desired product profile.

[00:46:30] Thank you very much.

[00:47:00]

Good afternoon, my name is Amit Roy, and I'm the head of Pharmacometrics for Oncology as BMS, I don't have a disclosure slide, but clearly apart from being an
[00:47:30] employee of BMS, I also own stock in company, and I'm going to be talking today about our experience with combination dose selection specifically for Nivolumab and Ipilimumab.

So this morning we heard several speakers talk about the rational for, you know, how do you go about picking which drugs to combine, and the clear message was there ought to be a scientific and pharmacological rational for selecting the drugs to be combines. And indeed, we were fortunate to have two immune checkpoint inhibitors, that had complementing mechanisms, that had a very good rational to be combined in the clinic. So in addition to pre-clinical data, we had an understanding that Ipilimumab enhances activation of T-cells and proliferation of activated T-cells, and Nivolumab primarily reverses exhausted T-cells. So both of these working in concert, with Nivolumab reversing exhausted T-cells in

activated T-cells and Ipilimumab expanding the repertoire of these activated T-cells, I think is a very sound rational for the combination.

[00:48:00] Amit Roy: So to start of with, before I go into the various studies, I want to lay out the background for where we were, at the time that the combination studies were being initiated, Ipilimumab was a-

[00:48:30]

... The studies were being initiated. Ipilimumab was approved at a dose 3mg/kg, given once every three weeks for four doses. And the reason why it was four doses primarily was because it does have toxicity that we will talk about in the next slide after this. Nivolumab monotherapy, at that time, was not approved, but we had a very reasonable understanding of the dose and exposure response based upon the 0-0-3 study. And we looked at randomized cohorts with, in melanoma, renal cancer, as well as squamous and non-squamous lung cancer at doses of 0.31, 3 and, I'm sorry, so at 1, 3, and 10mg/kg given once every two weeks. In melanoma, we had gone to slightly lower doses as well.

So, the ipi and nivo doses that I'll be talking about, combinations, were selected on the basis of three Phase 1-B studies, and we'll kind of go into the rationale for these studies. The first study that I'll be talking about is a Phase 1-B study, a 0-0-4 study, in melanoma. And this was sort of anchored at the dose for which ipilimumab was actually approved, which is 3mg/kg once every three weeks. So, it's kind of, this essentially kind of follows the approach number two that Dr. Fernandes talked about earlier in the session. And nivo doses were added to this ipi dose.

Speaker 1: So, I also wanted to, at this point, just take a step back and talk a little bit about the overarching philosophy in these combination Phase 1-B studies, and in arriving at the doses to take forward into the pivotal studies. We heard this morning that combination therapy is complicated. And I'll say, you know, just a [00:50:30] bit tongue in cheek, that there is a solution to the complication, and that solution is randomization. And that's something I think we haven't really heard about very much as yet. And that was part of the strategy that we have taken across all these three tumor types. I say it in tongue and cheek because it's not really [00:51:00] possible to randomize in every single combination, clearly. So, the other part of the strategy was hone in on reasonable doses that are tolerable, that are expected to have efficacy based upon our knowledge of nivolumab and ipilimumab, monotherapy exposure response, and dose response, and then randomizing those doses. So, that's the theme that's going to run through all of the three studies that I'll discuss.

So, first let's take a look at what we knew about the ipilimumab exposure response. This was something that would be published in Clinical Cancer Research back in 2015, and this is based upon analysis of data from five Phase 2 studies in advanced melanoma. On the left hand side is shown the probability of [00:51:30] objective tumor response by RECIST criteria versus exposure at three dose levels, the distributions of which are given at the bottom, 0.33 and 10mg/kg. On the

right hand side, so that's the, sort of the efficacy exposure response, if you like. On the right hand side is shown the safety exposure response, with safety being described, the endpoint being immune-related adverse events. And again, with the distributions of exposure shown at the bottom of the plot. So clearly, what you can see here is that both the efficacy and the toxicity of the drug increase with increasing doses and increasing exposure. And so then, with ipilimumab, it becomes a question of, okay, what's the optimal balance for efficacy and safety? And we arrived at a dose of 3mg/kg, which is the intermediate dose to take forward.

For nivolumab, so this is showing the analysis of nivolumab exposure response

[00:53:00] This shows the design of the Phase 1-B study of nivo and ipi in advanced

[00:54:30] And the results, high level results, are as follows for Cohorts 2 and 2-A. So, the adverse events were slightly higher in Cohort 2, which had ipilimumab 3mg/ kg. Although, not much difference over there, and the ORR results of objective response rate is also quite similar. However, in a markedly higher than the nivolumab monotherapy objective response rate, which is about 30% or so. So,

[00:55:00] markedly higher objective response. Based upon just looking at this data, it's difficult to, both of these cohorts look very similar. Based upon our understanding of the ipilimumab exposure response, both for safety and efficacy, we decided to go with nivo 1, ipi 3 because, and nivolumab exposure response which is flat, so a lowered nivolumab exposure wouldn't be expected to impact efficacy too much, lower ipi exposure may impact the efficacy. So, we decided to go with the higher ipi dose and the lower nivolumab dose.

[00:55:30] And this is the result of the Phase 3 study in terms of progression-free survival. Shown above is the lower green line, dash line, is the ipilimumab progression-free survival. The blue line in the middle is the nivolumab monotherapy progression-free survival, and the yellow line, which showed a better

[00:56:00] progression-free survival for the combination, sort of validated the choice of the dose, at least being better than nivolumab or ipilimumab monotherapy.

[00:56:30]

[00:57:00]

Next, going on to the renal cancer, second-line renal cancer, this is a result of a

[00:57:30] Phase 3 [inaudible 00:59:13], and a randomized Phase 2 study. This was done as a cue once every three week study of nivolumab given 0.32 or 10mg/kg. The 0.3 is the one in the blue, which is slightly lower overall survival, but you can see that the two higher doses had very similar overall survival. So, again, demonstrating that similar to the objective response seen in the 0-3 study in terms of overall survival, again, a very flat exposure response, at least as far as efficacy. So, on

[00:58:00] the basis of this, the initial Phase 1-B study of nivo and ipi, and [inaudible 01:00:01] was the 0-1-6 study, there were actually several-

RP and RCC was the 016 study. There were actually several [arm 01:00:04], I'm only gonna focus on two of them. There were a couple of arms with TKIs that I won't discuss. There was also an arm of NIVO one, NIVO three and AP three, which again was not very well tolerated, so it was stopped after six patients. So in this case, the arm of NIVO three, AP one, NIVO one AP three again, the two designs, the two course of both the studies in the randomized portion of the melanoma study were taken forward, with a robust sample size. The efficacy results are shown here, they were reported in JCU in 2017 by Hammers et al. Essentially, the response rates were very similar. The median duration response was also very similar for the two arms, and the overall survival also looked quite similar.

In terms of safety, however, it looked like the adverse events leading to discontinuation were higher in the arm that had AP three compared to the arm that had AP one. So going forward, on the basis of this given the similar efficacy, and better efficacy, better safety in the NIVO one AP three arm, the NIVO one AP three was taken forward into the [piflou 01:01:33] study. So this was again happened to be a different regimen from the combination regimen taken for melanoma.

Speaker 1: Coming down now for lung cancer. This is showing results, just to put in context what we know about the [expoyer 01:01:53] response for [nevolamap 01:01:55]. This again is based upon data from phase three studies, so we didn't have as complete a picture of expoyer response at the time of the phase 1B study in combination with design. But what we learned from our analysis was that again,
[01:00:30] expoyer response for efficacy is very flat, the safety is also very flat, and non-screeners lung cancer. There seemed to be a slightly lower response rate in the phase one study with screeners lung cancer, but overall, if you take into account all the factors, it looks like expoyer response is very flat, and this was
[01:01:00] represented at ASCPT in 2016 and has been accepted for publication in clinical cancer research.

So I wanted to point out a couple of things over here, actually, and tying it back to something that Doctor Liu described in terms of the association of clearance and response. So, because we had more than one dose, we were actually able to
[01:01:30] factor in the association of clearance and efficacy. This is something we noticed very early on in the clinical development of nevolamap. We were factoring this into our expoyer response, and what we had not realized was that there was a time varying component to this clearance. Once we became aware of that, we revised our PK models to incorporate the time varying clearance. In this case, what we used, and [anassis 01:03:31] what we have been using is baseline clearance.

And actually, to show you over here what this plot actually represents is the

So, it seems like the hypothesis, and we actually have the same hypothesis The other thing I want to point out with this is that even though we have randomized studies, even though we may have randomized arms in phase 1B, let's say, they're still relatively small, and so what this allows you to do with a model-based analysis is to account for all the different factors that are
[01:04:00] prognostic for survival, that may not be balanced in across these, because they're relatively small.

[01:04:30]

So, going onto now the results of the phase 1B study for lung cancer. We start off very similarly to the other studies with NIVO one AP three, and NIVO three AP one, but we had separate arms for screeners and non-screeners. In this case,
[01:05:00] however, there was high levels of toxicity that were observed, and the objective response rate was not better than seen with more therapy, so clearly these doses, the doses that were reasonable in melanoma or in RCC were not feasible doses to take forward for lung cancer.

[01:05:30]

We went back and looked at possible other doses that we might explore and made the hypothesis that if we extended the AP dosing interval, that would give
[01:06:00] a time for the system to recover, perhaps. And so what is shown over here are PK simulations of NIVO one, AP one, the reason why it goes up after a while is because we revert to NIVO three [micpokik 01:07:37] after the fourth dose of the combination therapy. This is NIVO one AP three, start with lower ... AP concentrations are quite high together with the NIVO concentration, this is NIVO three AP one, so with NIVO stays high all the way through. And this one was the one that we explored with NIVO three once every two weeks, with AP now given once every six weeks instead of once every three weeks. In addition to this, we also looked at AP given once every twelve weeks.

One of the reasons why we also chose this, I didn't mention earlier on, is that we had evidence that it's important go get both of those drugs simultaneously,
[01:06:30] because when you give the drugs simultaneously it was noted that there were higher levels of activated CD4 and CD8 cells in the system. And when you gave it sequentially, we didn't get as high levels of those two biomarkers. We call this
[01:07:00] the second generation of the AP NIVO combination, the 012 study. The first one, this row is showing NIVO three with AP one given once every twelve weeks. Here is the same thing, except NIVO AP given, AP one given every six weeks, compared with NIVO [ammono 01:09:05] therapy.

The spacing of the AP dose seemed to have addressed the adverse events leading to discontinuation, they're quite comparable in the combination and NIVO ammono therapy arms. Moreover, in the combination arms, now you saw
[01:07:30] much greater levels of activity in terms of a response rate compared to the

ammono therapy arm. So on this basis, it was decided to take the NIVO three AP one every six weeks into a pivotal study, again on the basis that the safety was no worse and it's possible to get better efficacy if you gave AP more frequently. Wanted to show also the safety data in terms of a [caponmap 01:10:03] plot,

[01:08:00] because I want to

Empty data in terms of [inaudible 01:10:02]life because I want to make the point here that we usually look at the safety data in terms of tables, but if you look at it in terms of tables, we miss out the information regarding the extent of follow up. That would be different in different treatment now, especially in studies like this that have several amendments and have patients enrolled sequentially in some cases.

What this is showing very clearly, these are the two arms in which Etti was given once every three weeks, and then clearly, you know, very sharp increase in toxicity. The blue line over here is showing the poverty of adverse event being discontinuation for the needle amount in more therapy arm. And the arm that we chose to take into the field study is the [inaudible 01:10:53] showing the green with the circle is right over here is very similar to the needle amount [inaudible 01:11:02] therapy. Indicating that the safety is very similar to [Inaudible 01:11:03] therapy.

Speaker 1: So with that, I'd like to summarize saying that it's certainly feasible to reach a combination of higher agents, that the evaluation of different dosing schedules benefit from larger sample sizes in the Phase 1 we study from [Inaudbile 01:11:28] normal we started out with sample sizes from XVI to XX, we expanded to more XL to L subjects in ICC and lung cancer and from randomization. I think that's a very important part. What we don't know very much of the system and this is way back when before we knew anything about [inaudible 01:11:47] burden, before we knew about [inaudible 01:11:48], before we knew about DNA mismatch repair, so way back then when there's a lot of uncertainty, randomization is one solution that one might consider.

[01:10:30] And thirdly, we actually ended up with different schedules, and combinations for each of these three different tumor types. I would argue that this was based upon very robust evaluation in Phase 1D that these different schedules were mandated.

[01:11:00]

And finally, model based analyses can inform those misscheduled because it will

[01:12:00] Just one more slide, sorry.

[01:12:30] I want to acknowledge David Felquit who I borrowed half the presentation from his presentation at the [inaudible 01:12:57] development workshop last year. Investigative, of course. And [inaudible 01:13:02] teams that came up with these designs. I was uninvolved in these designs. And the [inaudible 01:13:07] who basically, almost everyone in the group had [inaudible 01:13:10] in some way. Thank you.

Eric Rubin, from MERCK.

I'm going to talk about clinical trial approaches to dose finding for combinations with immunolocology agents. And I'll start with this graph, this has been alluded
[01:13:00] to. This is a graph of the number of combination studies over time, and actually just concludes the major four PD1, PDO1 antibodies. And I think it's very interesting to look at this curve, and goes back in 2014, there weren't too many. This is current as of two weeks ago. So you can see some exponential rise, that interestingly is really showing no signs of plateauing. I presume at some point it will have to plateau, and I guess we can speculate on when that might happen.

Speaker 2: I'll say that in the Merck number here is about 300, so 300 of these studies are with [inaudible 01:14:17]. Many of these involve collaboration with other companies, where Merck is not the sponsor. While we get to review the protocol, we actually don't write the protocol. I chair our protocol review committee, and I get to see all of these, and it is quite interesting to look at the diversity in the approach to dose finding. I'm going to give you three case studies of different approaches to dose finding.

Eric Rubin: Of course it's been discussed there are multiple variables in dose selection for
[01:13:30] combinations. If you look at just dose and schedule, and I'll note that even schedule can have a twist of inconvenient schedules such as one drug being every two weeks or every three. This can create real problems for patients and additional issues.

[01:14:00]

So if we look at just two doses and two schedules for two drugs, you get XVI possible cohorts to investigate. And if you use a typical design where you got three to six patients per cohort, that gets you to at least XLVIII patients depending upon the currents of DLT's. If you're really an efficient study and you
[01:14:30] have a one month DLT assessment time and you have no delays and accruing all your patients once a new cohort opens, that translates to XVI months to find a preliminary recommended case two dose, again depending on the recurrence of DLT's. That's sort of a fairly long time. This is simple.

I think it's points you can do before that hopefully we can find simpler approaches. One of course is just to fix the dosing schedule for one of the drugs. That reduces the complexity. We've done that for our combination approaches
[01:15:00] for Pembrolizumab, we fixed the dosing schedule at 200mg every three weeks. Now again among those CCC studies we actually have several where we have data. I can tell you that at a high level many of the combinations are tolerable with the recommended dose of the combination agent, but not all.

One good successful example here is the combination with chemotherapy, it's already been discussed. In a study known as [inaudible 01:16:24] 21, started several years ago, this was an umbrella type trial in lung cancer. There were several combinations that were explored. One of those was a combination of

[01:15:30] Premetrexed and a carboplatin, and in a dose finding cohort, it was established that the standard doses of Premetrexed and a carbo were well tolerated in combination with Pembro 200, and based upon preliminary promising efficacy data, the study was pre-specified to move into a randomization approach which is known as 21G. Those data are ultimately lead to accelerate approval for the combination based on response data and progression for survival data which is shown on the left. Despite a high rate of crossover, about 75% updated survival data which [inaudible 01:17:19] show a trend towards OS benefit as well.

[01:16:00] Now if we look at the variations in the approach to determination of combination doses, this is example one. Company A, small [inaudible 01:17:34] there was no MTD identified yet, for drug A, the sponsor proposed a three plus three up and down approach to find an MTD using what we call standard DLT criteria. I'm going to come back to this towards the end of my talk. Because again there's some diversity around how one would find DLT criteria in a combination setting.

[01:16:30] The starting dose of drug A was based upon clinical safety and pharmacodynamic data, and the recommended dose has not yet been identified. There was a pre specified max of administered dose in case no maximum tolerated dose was identified. Although, I surprisingly find this common in protocols there is no rationale actually for how the maximum administered dose is selected.

[01:17:00]

[01:17:30] This is a quote from the protocol: "The [inaudible 01:18:21] dose will be based on all available data, including DLT data and an assessment of inducible genes and safety and tolerability data". And there was also a comment the sponsor could choose to investigate lower doses and enroll three or more additional patients prior to the Phase 2 component.

[01:18:00] The comment here is that if the monotherapy dose selected is based on a MTD, you can get into real issues with small numbers and a three plus three up and down approach in the combination setting which can lead to actually selecting a dose that's incorrect based on chance. I'm going to take you through this example because I think it's an important one.

[01:18:30] If again, we take drug A, which has a recommended dose based on an MTD, so it has an underlying DLT rate, that I just picked 25% as a sort of average rate. Typically, the DLT rates for MTD are somewhere around 25 to 30%. If you use this, and you use the three plus three approach in combination, the question is what is the chance of selecting a dose lower than the monotherapy recommended [inaudible 01:19:30] dose in combination with drug D, simply due to DLT's arising from drug A. I have three choices here. Who says 20%? You'd pick that one? 50%? 80%? Okay, not a lot of hands there, so a lot of people aren't too sure.

Here's the three plus three algorithm. You can see that you have three patients depending on the number of DLT's, you enroll another three patients, and there are ten possible out-.

[01:19:00]

The number of DLTs, you enroll another three patients, and there are ten possible outcomes. Seven of those outcomes result in selecting a lower dose, and I've highlighted those with the red arrows. And if you work through the math, with the underlying DLT rate of 25% for Drug A, it turns out the probability of selecting a lower dose for that drug in combination simply based on it's own toxicity rate is 53% so Dr. McKee, glad to see you got that one right. So yeah, so it turns out that by chance half the time, you're gonna select a lower dose in combination than you would in monotherapy that has nothing to do actually with the combination setting. So, we're trying in our protocol view committee to really make sure that sponsors are aware of this and they're avoiding this approach because of this concern.

So, here's a second example of a case report with Company B and there was no NTD identified with monotherapy. They selected a six up and down approach against standard DLT criteria and the starting dose in the combination setting was based upon the recommended Phase 2 dose of the monotherapy drug. There was one dose level minus one specified in case the recommended monotherapy dose was not tolerated in combination with [inaudible 01:21:20]. So this one I think is better because you've got bigger numbers and again the recommended Phase 2 dose is not based on an NTD so there's not that same concern of selecting a lower dose by chance just because you're at sort of the upper end of the toxicity profile for Drug B in this case. They're still, however, relatively small numbers.

Speaker 1:

So the last example I'm gonna give you is the one we like to use and this is how generally we do our dose-funded combination studies. So this is Company C. This is a monoclonal antibody, Drug C, again no NTD identified as is often typical for monoclonal antibodies. So they used what's called a toxicity probability interval design, which I'll expand upon in a minute, with a targeted dose-limited toxicity

[01:20:30]

rate of 30%. And that was how they were gonna identify an NTD for the combinations against standard DLT criteria, starting doses based on pre-clinical data and pre-seeding monotherapy cohort data, and there was a maximum administered dose that was specified in case there was no NTD in the combination. Although, once again, no rationale for the selection of that maximum administered dose. And again, there's some hedging language, which is true for most protocols, I think, that indicate the totality of the data will be considered before deciding on the doses to carry forward to an expansion cohort and, interestingly, in this case the escalation schedule could also be adjusted based on pharmaco dynamics, PK, and safety data.

[01:21:00] So I wanna take a minute to show you an example of what typically ends up in a protocol when one selects this toxicity probability interval design and it comes from publications from Dr. G and colleagues and they actually have what's called a modified toxicity probability integral method, which was published in clinical trails in 2010. That's the one we typically use. So the nice thing about this is as opposed to some of the other modeling approaches where it becomes a black box for the clinician. You know where basically you ask the statistician "Okay,
[01:21:30] what dose do I pick next?" And there's really no dose table in the protocol. Here there actually is a dose table and this table, which actually shows you what to do depending upon the number of patients enrolled at a given dose, as well as a given number of DLTs. And you can see this goes out to fourteen patients. Number of toxicity is on the left, and it starts with three, and there's an E, an S, a D, and a DU in each box. E says to escalate, S is stay, D is decrease, and DU means it's an unacceptably toxic dose and you would not revisit that dose at a later time. So, again we like this approach because we think it doesn't have some of the pitfalls of 3+3 and it's relatively easy to explain and to follow for clinicians.

So some of the advantages of this over 3+3 are that you can adjust the DLT Okay, the next topic I wanted to discuss was the standard DLT criteria. One of the So, again this is an argument to avoid small numbers in the 3+3 approach. And if you use something like the toxicity probability interval approach with a reasonable number of patients, you can also avoid that type of pitfall while
[01:24:30] maintaining I think what would be considered not trying to second guess DLT criteria.

[01:25:00]

The last slide I wanna talk about, this was alluded to by the prior speakers has to do with again trial design approach. So the approach in the middle is actually the one that therapeutic areas outside of oncology typically will use. And this involves once you have a preliminary dose that's an MTD or MAD, there'd be a separate dose finding study, randomized dose fining study, with two doses. And
[01:25:30] then once that's completed you'd pick a dose and then go to registration. You know what oncology, we typically don't do that, we're typically up in this space. I think in part because of the unmet need as well as the speed interest in industry where we're picking, we go from a cohort expansion with typically relatively small numbers of patients right into a registration study. Again, I think this is probably why we're seeing post-marketing commitments for several drugs. So
[01:26:00] we've been using sort of a hybrid approach, which is depicted in this bottom category where there's initial dose finding and determination of recommended dose or two. And if the drug looks promising, we'll amend the study to add cohort expansions with two doses in a randomized way, typically in just one indication to make sure that we think we've got more information about a correct dose before we actually proceed to registration studies.

[01:26:30] So with that, I'll just acknowledge colleagues from Merc who have helped me put together these thoughts for this presentation and I thank you for your attention.

Hello everybody, I'm Isreal Lowy. I'm at Regeneron, I work for Regeneron. And a
[01:27:00] lot of actually what I'm going to talk about which is a subject that I wasn't sure would be of interest but actually from this morning there clearly is a lot of interest. Which is, how long do we need to treat with anti-PD1- or anti-PD-L1 as well. When is enough, enough? I guess I moved this slide. So, what I'd like to do, I didn't think there would be that much prior discussion about it but what I was hoping to do was start a discussion but I guess I'll continue it is how do we think
[01:27:30] about it and what is the context that we need to think about it in terms of how we got to where we are today? I saw a lot of really nice modeling studies in the last couple of talks. I'm not a modeler. I'm kind of a practical guy and there are some things that I think I'm gonna let you in on some inside baseball into how some of the doses were actually initially chosen. They weren't quite as scientifically sophisticated as they look but they sort of worked for a shoot from
[01:28:00] the hip ...

-luck. But, they sort of worked for a shoot from the hip biotech company, which is what Met-Rx was in the early day of CTLA-4 and PD-1. And what decisions were made and where are we now and how can we move forward. And, what I'd like to do, for discussion at the end is get agreement that people think we do need to work on optimization and figure out what does that mean. And maybe we can even define some biological criteria that will help us be comfortable with it beyond just looking and seeing how patients are doing.

So, let's move on. So, I also come to this from a slightly different perspective. I'm actually clinically trained as an infectious disease doctor. And once an infection is cleared or under control, I typically wouldn't continue antibiotics in an open ended fashion. In fact, that's frowned upon. So, the question is, what is the construct? And I think before the tremendous success of immuno oncology actually establishing actually establishing that it's a viable approach, the approach has always been give toxic drugs for as long as the patient with tolerate, or until the patient progresses. And that was the paradigm. And what that reflects, actually, is that you're relying on the drugs to really do the entire job of controlling the pathogenic process, in this case the tumor. And if you are actually, though, looking at an approach where you are enabling the immune system, wherever the defect is, we can talk about checkpoints, we can talk about other areas in the immune system that need to be enabled if they're the reason that the tumor is having the upper hand. If that's the case, and you've really reset the balance, then maybe you can actually, comfortably lay off of it.

Israel Lowy: And the model, again, the analogy to infectious diseases, is that the truth is, antibiotics don't usually eradicate infections. You rely upon the host to really do the job at the end. The antibiotics are an assist. So, you see that in normally
[01:30:30] healthy patients. If they were exposed to TB, they just need one TB drug for

several months. Or if you have strep throat, you take penicillin for a few days. But, if you're amino compromised, then you need very high doses, frequent doses, and then, even when you have the process controlled, you're taking something for profilaksis or suppression. That's certainly the way I looked at immunotherapy of cancer when I got involved in it at Met-Rx.

And so, therefore, I think looking at the fine courses is appropriate, and I actually
[01:31:00] think it's probably in the best interest of patients. I think we are all very optimistic these days in that we're going to find more terrific drugs, but we had two great drugs before PD-1, PDL-1 that had this really impressive, durable tail, IL-2 and Ipilimumab . Both of which, that durable tail is actually achieved with very few doses. And part of the reason for that, is that the dosing regimen was constrained, in part, by toxicity. So, nobody would have imagined open ended
[01:31:30] dosing with IL-2 or open ended dosing with Ipilimumab.

[01:32:00]

But, in the setting now, where we're looking at PD-1, we hope we will see
So, this was what we had before, where it's very clear you can get very durable
[01:34:00] So, the first thing, is the does of three milligrams per kilogram for anti-CTLA-4, was not chosen by a careful dose response assessment, but pre-clinical models, the serum levels were, those that corresponded to an EC-50, that blocked binding to CDAD and CDAD-6. So, in fact, the phase one study just tried one does at one dose level. The original schedule dosing every three weeks, for four doses,
[01:34:30] did not come from a careful analysis of what an optimal dosing schedule would be, it came from little Met-Rx coming to the wizard of the NCI, Dr. Steven Rosenberg, who said yes, I will try your MDX- 010, and together, with my GP-100, which I happen to give every three weeks, for four doses. And then it worked a lot better than people thought, and then Met-Rx ran right into a phase three trial.

So, that's the origin of the three milligrams per kilogram dose, and the four doses every three weeks. Now, you heard about some very careful analysis subsequently that were done over dose ranging, and it was very clear that when
[01:35:00] you went higher, you got higher response rates with the attendant higher toxicity. And actually, that long study followup that I showed you on the right there from the Shadendorf Paper, actually includes patients that got either three or 10, and actually the long term outcome for them, was no different. So, it turned out that three was probably okay.

But, we still always had this nagging question. Should a long longer dosing regimen, and yes there was toxicity, but once you learned how to manage it, you could do it, maybe we should have dosed longer. So, one approach, that you
[01:35:30] didn't really see discussed, cause it was sort of a fashionable thing that fell out of

fashion, was every three months, after six months, they would give a booster shot of EB. But that is no longer being done.

[01:36:00]

So, PD-1, PDL-1, when we came to start the first trial, and we did it working closely with the group at Hopkins, and we realized that we weren't going to do a
[01:36:30] single dose. We're going to allow patients to get repeated doses, but we were cautious about it, cause we didn't know if it would be worse or more well tolerated than Ipilimumab. And then it looked really well tolerated, it was also pretty clear that it was having some significant activity. And so, then we had to think about, how do we want to set up the, what was referred to as the 03, but also the 04, which was the studies that looked at multiple dosing of PD-1 and PDL-1, which had come along at that point.

[01:37:00] And I will take responsibility for being the one that said well, let's dose up to two years, no one will ever tell me that I didn't dose long enough. And, the plan though, was not to stay there. The plan, in fact, was to roll that back to a shorter duration based on the emerging data. But, the drug was so successful, and obviously [inaudible 01:38:50] realized they had Pembrolizumab and then ... So,
[01:37:30] the stampede was on, and people said the heck with it, it's well tolerated, let's just go with it. And I think that, to be candid, is the origin of why we have these ... Some people dose 'til two years, some people dose until progression, and that's why it's there.

But, that was not the intent. In fact, when we were then planning the first combination study of anti-CTLA-4 and anti-PD-1, and again, let me make a minor correction, at the time that this study was submitted to the FDA, neither drug was approved. So, it wasn't one of those, it was ... Both drugs were unapproved.
[01:38:00] We actually had a vigorous debate at the time. There was some of us that wanted to go up on the PD-1 and down on the CTLA-4, but CTLA-4 was ahead in development. This is actually from the protocol from the [we'll chuck it out 00:09:54] paper from 2013, but the study started in 2009. And, as you can see on the left, the initial plan wa-

As you can see on the left, the initial plan was to stick with the IPI regimen and then modify anti-PD-1 to fit that every three weeks, go a little longer to six months, and then the plan was actually to stop, except that they already had this every 12-week booster dose of IPI, so we were influenced and said, "Okay, throw in a PD-1 booster, too." That was the design. You had the 1:1, the 3:1, the 1:3. The truth is, the results of that study didn't really show much difference between the 1:3 and the 3:1 in terms of efficacy and I do think if you look back at the data, that even back then it was pretty clear that the Nevo-3/IPI-1 was better tolerated even in the melanoma.

Then, the other thing that changed was when the dosing was set upon to do the pivotal study, Checkmate 67, they dropped the stopping at six months and went back to dosing Nevo for every two weeks up to two years. That's how these doses have emerged. The question is, what do we do now? There are some

people that would say, since this is relatively well tolerated, if it ain't broke, don't fix it. Why would you tell a patient, after a year, when they're doing well, "You know, you don't need to take this anymore.' They say, "But I'm doing well. Why do you want to take it away from me?" There are plenty of physicians that don't like the idea of that either.

Speaker 1: We still are in the process now, because we sort of went at this a little backwards, of figuring out what, in fact, is the durability of responses in general, after you discontinue treatment? It hasn't really been established in a
[01:40:30] randomized prospective way. If you want to do randomized discontinuations, etc.

[01:41:00]

What are the arguments for stopping? We heard some of them this morning. It is actually burdensome. It's not just burdensome to the patient. It's burdensome to the healthcare system. If it's really not necessary, then maybe we shouldn't be
[01:41:30] doing it. Although typically PD-1 is very well tolerated and when you do get, or PDL-1, and when you do get toxicities they typically emerge within the first sixth months, generally. There are case reports of very serious toxicities that emerge afterwards, in the second year. I'm starting to collect these as a little series when I see them. The more important thing is there's really no data to suggest that if you have a response, that continuing to treat after it is going to make that duration of that response when you stop, longer.

[01:42:00] What I do know is that if somebody relapses or progresses while they're on this On top of which, although the late occurring toxicities are relatively rare, if we Also, it just doesn't fit the biologic paradigm. It just scientifically doesn't make
[01:43:30] sense. WE don't do this and we shouldn't do this just because we can. What are the data that would make you think about that it really makes sense to do this. I think, if you look across a variety of trials, different indications, different agents, it generally emerges that most people have their response by six months, and certainly by 12 months, they've stabilized whatever response they've had. It's
[01:44:00] very unusual to see somebody, who, at a year-and-a-half, suddenly has a major change and further shrinkage in their tumor. On top of which, even if you stopped at 12 months or 48 weeks, whatever you do, the drug doesn't go away the next day. It has a 2-week half-life or three-week half-life depending on the antibody. You have adequate levels in the blood for probably another two months. On top of which, we know that receptor occupancy, at least for PD-1 on lymphocytes, has an even longer half-life than the detectable serum PK. You're actually not really stopping at a year, you're probably stopping at a year and four months, when you actually stop administering the dosing.

You see when you do, we've talked about evaluating combination therapies. It's very clear that you see faster, deeper responses that should make you more
[01:44:30] confident when you do combinations that you certainly don't need to keep the

parent PD-1 going on. We're going to have to really, I think, ask what the emerging data are. I know at [ASCO 01:47:29], there was one presentation on patients who had completed their two-year course of Pembro and were showing
[01:45:00] good durability after that. There are increasing numbers of reports, patients who have to stop early because of toxicities, but they had a response at the time that they stopped and their responses continued to be durable. We are at [Regeneron 01:47:55] are actually developing a data cohort sets of patients that, from the outset we decided to treat less.

[01:45:30]

This is the study 03 of the PD-1. What I've done here with this arrow, is I've pointed week 24, six-months, and in general, when you look at these, what you can see is all the little yellow spots, time to first response and most of them are
[01:46:00] within six months, and certainly very rare to see one afterwards. You have a lot of people that had to stop treatment before they got to the two-year point because of some toxicity and further follow-up shows that they do have a reasonable durability.

[01:46:30]

[01:47:00]

This is the phase one data presented by [Merck 01:48:45] on [Pembromisilab 01:48:45], same phenomenon. Here's 24-weeks. Here's where you see here all your responses. I think they measured it only every 12-weeks initially so there's only one line. Point is, it's very rare to find them. Here's one out to week 50,
[01:47:30] okay? That's the exception that proves the rule.

[01:48:00]

Now, what happens when you combine agents? This is another depiction from that multi dosing study from the [Topalian 01:49:16] et al paper. You see the spider plots at one meg or three megs per kg. Again, six months after that, the spider plots are pretty flat. You don't have people, here's an exception again,
[01:48:30] somebody who dropped, but very rare. It's not the typical one. On the other hand, when you combine Nevo and IPI, you get a much faster, deeper, and at six months, man, they're done. That's why we thought, initially, we don't need to even treat after six-months at all.

Patients that had progressed on Ipi, he basically tried to dose them with Nevo, using the six month course. And what you can ... It's a small study, I think there were a total of 31 patients, so it's not much to make out of it. But again, by six

months, you have people getting their responses, and again, they were durable. And he stopped at six, or I think he may have done the Q12 week booster with that one.

What about other indications? So, we heard before about the dose ranging study in renal cell cancer, going from .3 to 10. So, yes, three ... Two to ten had a better, slightly better overall survival, but duration of response, not really any different. But most importantly here, six months look where all the dots are. They're all in here. They're very few dots out here. And the last one I have to show is a study from the Phase 1 portion of CheckMate012, that just looked at monotherapy. Again, small numbers here, but the same idea. The spider plots drop, and the responses are there.

Amit Roy: So, at Regeneron, in our phase ... So, we're developing our own, obviously Anti-PD-1, because we want to use it in combinations, but we don't want to over use it. And we actually set in our Phase 1 program that 48 weeks should be the duration. With the allowance that we continue to follow-up patients for at least 6 months after that if they get to that. And if they do recur, well we allow them to be retreated. And this is still developing data, but for like 16 patients that entered post-treatment follow-up, we've had so far only one and ... Who've had now follow-up for multiple months not just like two weeks. We've only had one patient who recurred at about five months, and she was retreated with ... I'll show you the scan. She was retreated with our Regeneron 2810, and responded at the next scan with complete response.

[01:50:30] We've also seen in general in our own experience that we too see ... And I'll you some data we presented at ASCO. Nonetheless, I will say that some of our Phase 3 studies, that we have started, have been planned to dose out to two years, and this is the "Just in case" from the people that don't want me to screw up with this expensive development plan. And part of it also, was actually a discussion
[01:51:00] we had that I think actually led to my invitation here, when we were talking about one of our programs I said, "You know, after a year, patients may just go elsewhere to get PD-1, and it will screw your analysis." So, we just have to make sure that we're comfortable with what we recommend and that patients actually will stick with it.

So, this is an example of a woman with cervical cancer, who had a near complete What's an acceptable operational definition for optimal treatment? And could it Maybe the criteria should be different for patients who have what looks like a total complete response versus patients that have a 60% reduction, but they have a significant amount of tumor left. And maybe you want to keep going. I
[01:53:30] think ... I was gonna ask the question 'cause I wasn't sure what people thought, but obviously I think people do think optimization of treatment matters. I think given that this is currently our best agent out there as the anchor of almost everything else we do, that it's really important that we further understand how to use it optimally. And I think we need to figure out how to find studies that we can do, that would help us be comfortable with this. Maybe, it's just getting

more and more data. Maybe there are other biologic indicators apart from Pk that we can use to say, "You've hit your mark, and you can stop." But I think this is an important issue, which will actually make a huge impact, not only on patient care burden healthcare cost, but also even how we ... When we start new combinations, how they actually work out in terms of being tolerable and effective. So, that's all I had to say. Thank you.

PANEL DISCUSSION SESSION III

Can I have the speakers come up please? As well, as come colleagues from the FDA will also be panelists. Dr. Qi Liu, Dr. Lei Nei, Dr. Marc Theoret and Dr. Wages also, as a panelist. And I think we have about 40 minutes. Yeah, about 40 minutes for the panel discussion. While folks are making their way up to the chairs, I do want to follow-up on a comment from Dr. Fernandes, with regard to Dr. Wages approach to dose finding. So, Dr. Wages would you like to spend a minute telling us about your approach that I think Dr. Fernandes included on one of her slides.

Speaker 2: Sure.

[01:57:00]
Eric Rubin: Did you just want me to tell you more about it?

[01:57:30]
Nolan Wages: Yeah, tell us how it works.

Okay. So, that study was ... The objective was to try to find the optimal regimen of those vaccine regimens, and that was defined as the one that indicated that is has the highest immune response rate, the highest biological activity. Conditional on it being safe. They didn't expect many DLTs in that study. Not many were observed. But still we accounted for the safety, and worked our way thought the regimens as if it was a dose excalation study. And then once we've escalated through those regimens, the allocation is driven much more by the immune response rate at regimens that are indicated to be safe. So, how we modeled the DLT probabilities, is we used a model-based design, that's what she was indicating in her talk.

Eric Rubin: For the ... How we model the DLT probabilities was based on a continual reassessment method that is geared for combinations. And what's characteristic of combinations or even in the second example that she showed, where there was several dose levels of each agent creating that grid, we have some combinations in which we're unsure what their toxicity relationship is. So, we might ... We don't know if it's escalation or de-escalation, so basically that method takes in ... Basically accounts for either one of those being the case.

[01:58:00]
Nolan Wages: So, there's like a CRM, continual reassessment method like model for potentially X being the dose toxicity relationship. And then there's one for Y being the dose toxicity relationship. So, the curve could take different shapes and it takes into account multiple-

[01:58:30]
The curve could take different shapes and it takes into account multiple models that reflect those potentially different shapes. So then its like a CRM with one extra step of let's see what the data tells us is the most likely to be the correct model.

Great. Thanks

Speaker 1: Does that help you?

Speaker 2: Yeah, thanks. So, and did you have any ... were there issues with investigators or IRBs? Sort of understanding this or having questions about versus the simpler-

Speaker 1:
Speaker 2: Thanks.
[02:00:30] Yeah.
Speaker 1:

[02:01:00]
Speaker 2: So people ask us who are the new FDA panelists who come if you have any comments that you'd like to make either in terms of presentations that you've heard or just your own work.

Speaker 1: Hi. My name is Chao Liu. I'm from FDA Office of Clinical Pharmacology. I think this meeting has been fascinating and one phrase is we've heard repeatedly is, "This is complicated." We hear people saying, "We cannot do everything, answer all the questions in every program." And we've heard from Dr. Rubin's presentation there's over 800 combinations going on. So, I started wondering, "How many of those questions belongs to the pre-competitive space?" For example, the duration of the treatment for the immunotherapies and also the sequencing of, for example, immunotherapy and chemo, et cetera, should those ... may not be drug specific questions, those may be class specific questions. So, how can we collaborate on those issues?

Speaker 2: And also, another important thing I hear people mention a lot is biomarkers. And this also involves ... the development of the assay for the biomarkers. So for those also not drug specific, so how can we collaborate?

Chao Liu: Thanks. Dr. [inaudible 02:02:28]
[02:01:30]

[02:02:00]

Yeah, so far enjoyed all the talks. Also, everyone agrees it complicated. But also I [inaudible 02:02:38] should be science-driven, data-drive. Then how do we generate the data, that's what I'm thinking. In [inaudible 02:02:48] Drugs, we have very successful story. We develop the drug cocktail and make [inaudible 02:02:56] drug. The success story we can learn. As I understand, [inaudible 02:03:02] have a superb biomarker[inaudible 02:03:06] we don't have these. In [inaudible 02:03:10], they have pK drug drug interaction study is very predictive, and here is very difficult. But still we can learn something from that. I would like to see more drug drug interaction study, that's the first point I want to make. And second one, I need to be surprised in drug drug combination, we still use [inaudible 02:03:33]. Obviously, that's not going to work, not going to help a lot. I would like to see more model based approach.

Speaker 1: Again, it's very complicated. The dose regimen and how long we do it, but if we can not get right in the early phase, we can do in later phase, or even post approval. It's a life cycle approach, that's the third point I want to make. Thank you very much.

[02:02:30] Then maybe Dr. Theoret, then we'll go to questions from the audience.
Speaker 4:

[02:03:00]

[02:03:30]

So, why don't we just go to the questions from the audience at this point?

[02:04:00]
Speaker 1: Okay, sure.

Speaker 2: This question is for Marc.

Speaker 1: Perfect.

Speaker 5: Thank you.

Speaker 1: [inaudible 02:04:22]FDA. When I think of the dose question, I think of it in two sort of separate thought exercises. The first is the question of dose selection for later testing in clinical trials. That's not very controversial, whether you are using rules based approaches or model based approaches. I think what's more controversial is the second thing, which is does optimization. You know after the drug development program comes to completion and then we take this sort of totality of evidence approach in regulatory review, it's not uncommon to do dose response or exposure response analysis to try to figure out what is the best regimen or regimens for therapeutic individualization or patient optimization. That's met with much more skepticism for a variety of reasons. And so my question is, to the panel is, what is the utility of this exposure response for the purposes of therapeutic individualization or regimen optimization after completion of development. Should it be routinely done and if not, what are the scenarios where that approach is credible and useful?

Marc Theoret: Yes[inaudible 02:05:39] I'm a statistician. I think dose exposure response, you always face issue to do more. I think a lot of work has been done. After the data corrected, we continue to do it. If there's a signal, we can even after post drug approval we can continue to optimize it using the post marketing approval, PMR studies.

Speaker 5: [02:04:30] I really like [inaudible 02:06:10] questions. And I think for this, I think what Dr. Amit Roy just presented for the [inaudible 02:06:18] combination is a very, very powerful example. So here, if after the initial approval in melanoma, it comes to the [inaudible 02:06:26] and [inaudible 02:06:29]lung cancer. So very often people when they find the dose appropriate in one indication, got approval, when they move to the other one, they would just take the dose and move to the other indication. But here, [inaudible 02:06:40] decide to do randomized [02:05:00] dose finding phase Ib trials, which in the end really paid off. Because it's ... I would like to borrow a phrase I learned today from Dr Liu that's "shockingly successful." Because here, by optimizing the dosing regimen you are able to almost actually, more than double the response rate while not compromise safety at all. I think that's a very powerful example to show how post approval dose optimization can be very useful.

[02:05:30]

Speaker 7: If I can just add to that, thanks Chao. Is this on? I guess it's on. So I think that example one might argue that, that with for melanoma and RCC 1331 we're pretty close and I think the future will tell whether how right we were. But [02:06:00] clearly, for lung cancer, it sort of showed that the ... in selecting the dose I think, in one tumor type and then assuming that it holds for others, is not always the case for all tumors.

Chao Liu: And then, I also want to add to Dr. Sommes question in terms of the role of exposure response in dose optimization subsequent to approval, I think the robustness of exposure response is going to depend on having sufficient data to
[02:06:30] do the exposure response whether that comes as part of the approval process, whether that comes from studies in the dose selection, and clearly what we've seen for antibodies against anticancer antibodies that we need more than one dose because of this confounding, potential confounding, we would clear it. Once we have the more than one dose, there were ideally three, I think you can tease out that confounding and get a better sense of whether exposure response
[02:07:00] flattens off.

Speaker 9:
[02:07:30] My name is Rick[inaudible 02:08:57]. I'm from [inaudible 02:08:57] First I'd like to thank the organizers for this great meeting. And I ... throughout the day ... and I enjoyed it and I think I receive a lot of very valuable informations. One word I heard, "It's very complicated." Actually I have a question for, not just this panel and for the other speakers who are still in the audience, it's a question for everybody. I heard it's complex because if you look at a one end, it's a therapy and although this workshop is called a dose finding, basically it's a dose regimen. And a dose regimen is made up of APIs, how many, it's a combination you can have one two or two three four, whatever, and then you have number, the dose levels for each and then you talk about the schedule, which is the duration you guys talk about and I called a drug-

Duration you guys talk about, and I called the drugs holidays. You can have a holidays for one drug and for another one. So, if you add all those combination together, and then you have ... I don't know quite astronomy Nick, but it's a huge number. And then we look at other end, is a disease we are treating.

The disease to me, in my perspective, cancer there's emitting self cancers, and the cancer is characterized their molecular profile morphologies. So you can group them say this is a cancer or lung cancer, but it's not a lung cancer. There's many, many, many sub groups, and I've been doing modeling the simulation for more than a decade, maybe approximately 15 years.

Speaker 1: So it's all deterministic PK, PD modeling, Bar marker translation from animal to human, that's my space. So recently I'm thinking of ... before I using those PK, PD deterministic modeling simulation and then population in the past four, five years. And then I'm think ... reasons I'm thinking of ... to bring this artificial intelligence into this, because we have more and more studies, more and more datas, we have emitting self cancers there.

They are characterized by the profiles, and you have the clinical data, actually you can bring incorporate pre-clinical data even into the clinical data, because
[02:10:30] these are the input, and they will inform your ... the probability of each therapy, which is a combination of dose enlargement and the drugs.

So I start to think about Artificial Intelligence because human intelligence is very So, I want to know and what is your perspectiveness, and also if you're in favor of So I think that this is a more latest the information because this is afternoon data, so ... but it's still huge amount of data, if FDA start to require the sponsors
[02:12:00] to put this data in the same system, and then they will allow academia and also some other people interested to investors, so what is your perspective and how we can enable this initiatives if you all really like that idea, but that's something I'm recently thinking about it and I'm going to do it, but obviously I will lack data.

Can I respond that? I think Artificial Intelligence is complicated, but ... you know,
[02:12:30] there are a lot of things that I don't think are that complicated, and I think we should be really careful not to over complicate things that aren't complicated.

[02:13:00]

So, for example, I thought the time dependent clearance that we're seen ... for both [Nevo 02:14:14] and [Pembro 02:14:19], I'd not seen that before with other agents, and I think, in addition to thinking about how ... what the mechanism is that it's consume, the fact to me that it actually seems to sort of settle out at the
[02:13:30] same time, that we're looking at stabilization of most people's responses, could be a coincidence, but you know, it's like jee, that could be interesting.

Speaker 2: So, sometimes there are things that don't have to be that complicated that we should just look at, and as I said before, I think we're all extremely hopeful that
[02:14:00] there's a slue of new things that are gonna build on the success of the PDL1 pathway blockade. It may not happen that quickly, and I think we owe it to ourselves to really look very hard at optimizing that, because that is the fundamental agent.

If I could ask a question?

[02:14:30]

Sure.

[02:15:00]

I really was wondering actually, Rene it wasn't clear to me when you were describing the models, first, is there also time dependent clearance of PDL1 in patients that respond? And second, if there is, do your models take that into account?

Speaker 3: Yes, there is some level of degree of time dependent clearance too, I think this is probably far to the, all the Monoclonal antibodies, provided there is an improvement good enough for the patients so that we see there is a change in clearance right? Now, in the model, I am just modeling the tumor size profile plus image metrics, so there is no exposure in this model, so it doesn't count for fulltime dependent clearance.

Speaker 2: [02:15:30] Okay, the other follow up, I thought that was really helpful, and that's something we don't normally have, is what the kinetics of tumor growth are, of patients coming into studies. 'Cause I agree that you look at changes and it could be misleading, if you had something relatively slow growing versus slowing down something that was exploding, and that shouldn't be too complicated. We should be asking to get the scans, or the most recent scans whether they were on study or off study. So, that's something that's not big data.

Rene Bruno: Amit did you have a comment?

[02:16:00]
Speaker 2: [02:16:30] Yeah I just wanted to comment. So we've also seen the ... when we've gone back and looked now, time dependent clearance for [APLM 02:17:05] as well. This is something the FDA have also confirmed, so I think this has kind of been leading to the working hypothesis that this is related to cachexia high levels inflammation and when these things controlled as the status of the patient improves, that's when the clearance of these Monoclonal antibodies decreases along with, you know, decrease in whole body protein turnover.

Speaker 3: How about non-IO agents, people looked at that, you know like Cetuximab or Herceptin or?

[02:17:00]
Amit Roy: I suspect that any kind of antibody ... I think I don't quite recall, but I seem to recall anecdotal reports that's the same for any kind of anti-cancer antibody.

[02:17:30]
Speaker 3: Actually excuse this is Sandhya Girish from Genentech, and I was right waiting here to make a comment on that very exact point to kind of follow up on what Rene also mentioned previously. We have seen this with other Monoclonal antibodies, as well as with antibody drug conjugates like Kadcyla.

Amit Roy: And we've often found the disease severity to be related to the faster clearace so in other words the covariant such as albumin, tumor burden, a number of metastatic sites, all of these covariants have been significantly impacting the faster clearance. So, when made the point about the time varying clearance, and given that we already know this in the context of other Monoclonal Antibodies as well with our immunal oncology Monoclonal Antibodies.

Sandhya Girish: [02:18:00] In my mind, what I was trying tease out is how much of this is because of the disease severity aspect, as well as what is really attributed to the potentially improvement from the treatment. It could also be that with time, you might he

sicker patients fall out of the trial or drop put of the trial, just because they're not responding. So, this clearance could be potentially impacted by both those aspects.

So, it's complicated, but definitely there are some trends here that we are monitoring in the context of Avastin, Herceptin, Kadcyla post marketing
[02:18:30] commitement as well in the context of Dicentric and [inaudible 02:19:37]. So it remains to be seen.

Do you know if the time dependent clearance that's seen with other antiboies,
[02:19:00] does it track with people who have better responses the way it was seen here?

I have a very small data set that I can comment on, and this was in the context of
[02:19:30] Kadcyla and in a hepatically imparement trial, where we found that in patients-

... trial, where we found that in patients that were very sick in cycle one, the clearance was much faster in the moderately impaired patients as compared to patients with normal hepatic function. However, by cycle three or by steady state, we found the difference to be much less. In other words, there was at least some evidence that the patients that responded, their clearance seemed to have reduced over a period of time. So, we have seen some evidence of it, but it's very limited at this time.

Is there a possibility that individual measurements of clearance could have the necessary discrimination to decide that the clearance has decreased and is stabilized? To see if it's a independent marker comparing also no more change in resist measurements?

Speaker 1:

Yeah, I think it would be good to see that in the data set that Amit just referred to earlier. At the individual level, I'll be seeing that track, as well. So it would be great to see that as data, if available.

[02:20:30]
Speaker 2: Thanks.

[02:21:00] Thank you.
Speaker 2: Can we make a quick response to that?
Speaker 1: Yeah, sure. Yep.

Speaker 3:

So, just to respond to question about FDA requirement. So, FDA generally encourage data sharing. FDA does not have the authority to require sponsor to share.

Speaker 4: David Norris with Precision Methodologies.

[02:21:30] Speaker 3: So, I'd like to push back a bit on this idea that dose individualization ought to wait until post-marketing phase. I've written a couple of papers this year, one that directly attacks the notion of "the MTD" or "the recommended phase two dose" or "the dose on the label", and a second one, which follows up with a quite plausible demonstration that failure to individualize dose may cost us something like half of the social value of the innovation embodied in that innovation that's coming off the bench. So, this great innovation comes off the bench and then we hit it with these wrong ideas and these wasteful statistical methodologies.

David Norris: So, I'd like to offer that suggestion and welcome your criticisms of it. I'd like to point out a number of problems that abandoning a fixed-dose notion could possibly solve for us. Just, first of all, nobody would ever think of doing a trial of short acting insulin or Warfarin in with three fixed-dose arms that range over an order of magnitude, clearly right? So, what do we do there? We do therapeutic drug monitoring. And what we're evaluating then is, what's the effect on the rate of stroke when you achieve an INR of 2.5 or 3, and what is the effect on microvascular outcomes when you are targeting this hemoglobin A1c or that hemoglobin A1c, right? We can start actually asking scientific questions when we engage in, what a biostatistician would recognize as, a variance reduction exercise. So you reduce this variation in individual pharmacokinetics and pharmacodynamics, and then you can ask scientific questions about the interesting variation that remains.

So, to begin with, this back-of-the-envelope calculation that Eric Rubin did with this proliferation of arms, it disappears immediately if you approach each
[02:22:00] individual's treatment in phase one as a process of dose titration. Secondly, well I think I've already addressed this variance reduction perspective. But again, Eric Rubin's talk shows that the three-plus-three design and its relatives and descendants are essentially random number generators, or random dose generators, that we attach to these drugs, wasting the experience of these
[02:22:30] generous participants in the trials and the possible outcomes that we could get in them.

Approaching the phase one study from a individual therapeutic optimization perspective also sets you up to solve ethical problems like the one we discussed at the end of the first session here where, you've got a patient expressing some concern about long-term therapy. You can, at a point like that, ultimately do
[02:23:00] some kind of probabilistic model-based counseling that allows this patient to engage his or her values and circumstances in that question. You could offer the same probabilistic forecasts to one patient and another, and each of them applying his or her own values with this principle of individualism we value could make a different decision, right? There's some ethical value to that, and to not imposing a decision by the mere fact of randomization to an arm.

[02:23:30]

And then finally, I would just suggest that, if we change this concept from "the dose" to dose optimization, then when a DLT happens you don't just abandon "the dose", it becomes readily a part of your sort of mentality that, "Well, okay

[02:24:00] we'll reduce the dose." That's what we plan to do with this therapeutic optimization. So finally, I'd just like to posit that I doubt that any progress will be made against this problem of dose selection and combination profits until we've made a serious attack on the single drug problem, and done that via dose optimization at the individual level. So, I welcome your thoughts on that.

[02:24:30] Thanks. Quite provocative. I guess my comment would be, I think I'm not sure we have an endpoint as good as glucose or INR, which makes it difficult. I think there actually have been some approaches to individualized dose optimization with chemo that I'm sort of familiar with. But, anyway, I think it, you know ... Other comments from the panel?

[02:25:00]

[02:25:30] Yes. Okay, go ahead.

[02:26:00]

Speaker 4:
[02:26:30] I think if you're a shrewd seasoned private doctor and you were working with the patients, that's what you do every day. Question is, if you do that in clinical trials, how do you put together the information that you need so that a regulatory agency can make sense of it and say, "Okay, we can agree to this." I think there's nothing wrong in principle with what you said because there's a lot of stuff that, you know, that's why you know physicians are allowed to prescribe as they see fit, 'cause we usually hope that they have good judgment. But that's what you're basically saying. Let good judgment ... You have a protocol. The protocol should just be a general suggestion, not something that you have to follow to the letter or that you write it in such a way that it's really no longer a protocol. It's sort of like, "Here are the ingredients. Cook something."

Speaker 5:

Thank you so much for that feedback. Now, I was at [Bestivas Co. 02:28:05] last week and stood around in a circle with an oncologist who complained that his elderly patients, so much older than the patients who are enrolled in these dose-finding trials, they usually make it through about three courses of their chemotherapy and the fourth one does them in. And I asked him, "Well, are you using the same dose that is found in these trials in the younger patients?" And he says, "Well, of course, yeah." So, you know, the fact is ... He came across as a caring, thoughtful man and so I think that we establish a mentality by doing these trials and it's very hard for the community oncologist to rebel against that.

Speaker 2:
[02:27:00] And now, you did ask a question, "How do you replace the arm as the location into which we learn?" The concept that I develop in this paper, which I call "dose titration algorithm tuning", or DTAT, is that you replace "the dose" with a dose titration algorithm and that it is the tuning parameters of that algorithm that you learn into as you acquire experience with the patients.

[02:27:30]
[02:28:00] Next question. Thanks.
David Norris:

[02:28:30]

[02:29:00] Hi. Bharat [foreign language 02:29:25], FDA. My question to Amit. So Amit, you presented a lot of very interesting data. You guys tested a lot of combination doses and a lot of combination regiments. You showed basically top-line data clinical safety and efficacy. My question is basically, did you look at the pharmacodynamics and biomarkers for the different combination regiments? Can there be any learning in terms of the mechanistic aspects of why sometime combinations work and some don't?

Speaker 4: Yeah, so we do have-

Yeah so we do have an effort to look at biomarkers so look at that as an extensive biomarker effort both for Ipilimumab, and for Nivolumab. I think it's bearing fruit more recently now with some of the prognostic biomarkers like, tumor mutational burden, and msi high coming out. In terms of sort of following dynamic markers there hasn't been anything that's very striking. For Ipilimumab for example you have a very strong increase in absolute lymphocyte count. With those very nice dose response for absolute lymphocyte but not everyone who has a high absolute increase in absolute lymphocyte count responds.

So there's a bit of a disconnect there but we do actually in our ... come back to use your question to come back to the suggestion that Dr. Nie made was we do have an effort similar to the one in Genentech looking at tumor burden as a biomarker and looking at long tumor growing time for positive tumor burden. Tumor growth is one measure but there's many other measures that you could actually look at. You could use the intact time course. So and that could be used to relate your response to survival, that's an effort that's ongoing, it's not very mature as yet but we do have that effort going on. So the kind of provocative question that I might maybe put to everyone is could this tumor burden time profile, however you might want to define it as a sum of lesions or in some other way, be the sort of biomarker similar to the one in HIV viral load. Could some ... could we mine something out of how we are doing it right now and use that really as the equivalent to your viral load in HIV as a way of really guiding treatment. Where you have a treatment and you see this response and that response will then predict your survival independent of what treatment actually got you to that response.

Speaker 1: It's a good question and actually I sent this question to Dr. Bruno by email when I [inaudible 02:32:22]. One question I have, which I think there's a lot of, it's very attractive but I think that in some ways in what's happened with imagining

[02:30:30] where we've gone from two dimensional to one dimensional, is it really any better I guess was my question than just using RECIST as the end point. With all the problems with RECIST, now I understand that by using continuous variable measurement as opposed to categorical you're increasing power but my question was, if you actually just used that end point, RECIST response, is that good enough right?

[02:31:00] So RECIST actually seems to work pretty well. But in principle when you go from one treatment modality, from one method of action to another, you might find the relationship between the research response and survival I think that's not very well established. If you get better research response generally that's better survival but how much better one doesn't know. We've also seen progression through survival differences don't always translate to overall survival differences.

[02:31:30]

[02:32:00]

Eric Rubin: So I think the potential for a more continuous measure of tumor response has

[02:33:00]

Just a comment on RECIST and tumor size. If you are using a [inaudible 02:35:43]

[02:33:30] or response then you are losing a lot of information. Not only because you categorize but you are missing the time component. RECIST can be also time dependent. You have an assessment at each of the visits right, so you can also use RECIST as a time dependent outcome and these advantages on maybe some of these diameters because that includes a new lesions, non-targets plus [inaudible 02:36:12] due to all those things. So RECIST can be used also as a time

[02:34:00] dependent to evaluate those.

[02:34:30]

Speaker 3: Second, regarding some of [inaudible 02:36:22] diameters of target lesions, you are within your range of new lesions as your known targets. This actually comes to the [inaudible 02:36:32] between lesion viability in the time course and as a prediction of [inaudible 02:36:40] survival. We have looked at that a little bit and we didn't find a lot of viability across lesions. Lesions seem to be behaving quite consistently. So that for example in the case I have shown, just looking at the

[02:35:00] target lesions we could predict it also. This means that the metrics is [inaudible 02:37:03]. And the last thing is that to com back to viral load for example. If we are using, if we can use tumor markers like PSA or [inaudible 02:37:14] those things can be modeled the same way and here you have the [inaudible 02:37:20].

[02:35:30]

Man, French: So I just want to make a few comments about this, regarding RECIST and the importance of having them. And so, it was mentioned that HIV has this very excellent endpoint I can use that's actually an established surrogate. We are

[02:36:00] actually somewhat fortunate in oncology we do have an intermedia endpoint, which is objective response and [inaudible 02:37:46]. Looking at tumor

shrinkages and whether you categorize that or use a continuum but looking across all checkpoint inhibitors and the approvals there's been in 29 new or supplemental indications for the 6 approved checkpoint inhibitors I think as of the end of May. Of those, about 17 or 18 were accelerated approvals. All but one of those were based upon objective response rates based on RECIST or other conventional type of criteria. I think it's just very important and I think you were bringing these points up is the categorization doesn't look at durability but of those approvals, duration of response in a durability response was at a critical component of the evaluation for efficacy in those standards.

Where it is unclear and I think there is much efforts looking at alternative type of endpoints or alternative type of endpoints in tumor measurement criteria is,
[02:36:30] what happens when you start to look at time to event endpoints using these alternative type criteria such as a modified pfs. That's an active area of investigation not just an industry FDA but other stake holders in the consortiums that are being supported by the pharma providing their information is going to
[02:37:00] be very important in evaluation of that information but clearly there is much work to be done in terms of new endpoints and I think it will be very informative to look at very earlier, much earlier, intermedia endpoints as the response rates start to go up as long as well as the durability, which we have already seen.

Speaker 5: And I'll just point out I think that is one example where, rates, where you are
[02:37:30] already seeing some data sharing, which is nice and talk a little bit about those, some of those consortia where you've got industry that's actually, multiple companies that are sharing data that I think will be helpful to get to some of the answers there.

[02:38:00]

[02:38:30]

I think we're technically out of time, I really apologize for the people standing at the mic. Maybe you can just take one more and for the rest of you folks out there I'm sorry maybe after the panel we can follow up.

[02:39:00]

[02:39:30]

Speaker 6: Guess I better make it good huh? I'm [inaudible 02:40:11] from the FDA and I wanted to go back to the concept of how much therapy is too much and duration of therapy. I wanted to talk about the adjuvant space because we are seeing a lot of trials in the adjuvant setting. Immunotherapy and even combination therapy especially in the GU space and if we are going ... one could argue that there is ... some could argue that there is less to learn from those trials because we don't

have, we can't get as much tumor data, we don't have response rate but perhaps we could learn more about duration these patients are relatively well and they don't have any tumors so maybe these would be ideal settings to look at various durations of dosing. I think that is just a consideration and perhaps warrants further discussion.

[02:40:00] I think that's a great point and I'll comment. I think even empirically as you know I think many companies including Merck have actually reduced the duration from that two year part to one year for adjuvant studies and I, it's empiric but I think for some of the reasons you have alluded to. I agree it would be nice to have more scientific exploration of that.

WomanFDA: Okay, I'd like to thank the speakers and the panelists for session three and call up Drs. Jaffee and Mckee to close the meeting.

[02:40:30]

[02:41:00] Speaker 8: Okay, so on behalf of all our participants I would like to thank AACR for helping us sponsor this. I want to make one quick comment. I think we have really come full circle on dose finding. Actually the genesis of the idea for these workshops was "oh my gosh, why can't we get away from 3 + 3" and as discussed multiple times today we're still at 3 + 3 and so we still have some work to do on that. I think the good news is that now everyone has heard that we want to get away from just 3 + 3. I think the other thing that has been really fascinating about this and I'm not going to use the word that's been repeated over and over again is, really we have so much work to do still and so although this was envisioned as the last of the dose finding workshops for this series, stay tuned maybe in a few years we'll come back and hopefully have learned some more and so I'll turn it over to Dr. Jaffee and thank you.

[02:41:30] I just want to thank everyone at the FDA as well as the AACR for putting this together and I think you are right, I think we need another workshop next year. Thank you everyone.