U.S. FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

AND

INTERNATIONAL SOCIETY OF PHARMACOMETRICS

PUBLIC WORKSHOP ON

Model Informed Drug Development for Oncology Products

FDA White Oak Campus

10903 New Hampshire Avenue

Building 31, Room 1503 & (Great Room)

Thursday, February 1, 2018

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C O N T E N TS

MIDD Applied Post-Approval: Examples with Ibrutinib, a BTK Inhibitor
Daniele Ouellet, Ph.D. (Janssen)

Panel Discussion

Session III speakers and the following additional panelists:
Lei Nie (FDA), Patricia Keegan (FDA)

Meeting Summary
Jin Y. Yin, Ph.D. (ISoP)

Closing Remarks
Amy E. McKee, M.D. (FDA)

P R O C E E D I N G S

WELCOME AND WORKSHOP OBJECTIVES

Dr. Zineh: We are going to start now. Please take your seats.

Well, good morning everyone. I would like to welcome you all to this workshop on Informed Drug Development in Oncology jointly convened by FDA and the International Society of Pharmacometrics. The organizers have put together an excellent program that promises to an important launch point for further discussions on the role of how to inform strategies in oncology drug development and regulatory evaluation. My name is Issam Zineh. I am the director of the Office of Clinical Pharmacology in FDA and it's my pleasure to open the workshop. I've been asked to discuss the objectives for today and I also want to place this workshop in a larger regulatory and scientific context. The explicit objective of the workshop is laid out here: to discuss best practices in integrating PK/PD efficacy and safety data into the models; to best inform oncology drug development; evaluate disease and mechanisms specific early endpoints to predict long term safety; and discuss potential regulatory implications with these decisions. I have also listed the specific aims of the workshop that are also in the *Federal Register* note and so I won't read those. Many of the folks here are not surprised I am sure about the impact that MIDD has had when it is successfully applied in drug development. There are many definitions for model based or model informed drug development. I personally gravitate towards this modification of the one put forward by Rick Lalonde and his colleagues about 10 years ago where they defined model-based drug development as the "development and application of pharmacostatistical models of efficacy and safety from preclinical and clinical data to improve drug development knowledge management and decision-making" and what I particularly like about this definition is its emphasis on application and as a lifecycle approach. In terms of impact, the literatures were replete with documentation from FDA and other scientists on the role of modelling, for example, pharmacometric modelling on a variety of decisions made as well as efficiencies gained in drug development. This is a nice schematic from the FDA MIDD working group that provides an overview of various internal company decisions and regulatory applications for which MIDD has been particularly helpful. And as you can see, it ranges from target selection and validation. It is in preclinical and early clinical development to late development and

regulatory decision-making on issues of improvability, labeling, just to name a few. So it is really not surprising that MIDD has brought about these efficiencies given that they were models focusing on sources of variability and I think Dr. Woodcock will have something to say about that in a little bit.

This slide emphasizes the MIDD based approach as we have experienced with to varying degrees. On the left, this is on the FDA side, and on the right, I have boxed the regulatory applications with which we have had extensive experience and this includes these modelling-formed strategies for dose optimization for the general population as well as sub-groups. In terms of efficacy, we are talking increased access for patients in the form of population #4:47 bridging and extrapolations as well as supportive evidence of effectiveness. There is an extensive body of work on exposure safety analyses as well as classification of toxic compounds based on chemical structure. We are seeing more activity in the trial design space and IND space as well as using these approaches to inform policy change.

The drug development academic and regulatory community communities have been working on the science underpinning MIDD for decades now, and at the same time, regulatory science provisions in the last two reauthorizations of PDUFA signal a recognition by all involved—the FDA, the advocacy groups, industry, political leadership—that integrating new science into regulatory review and policies is of significant importance. This is just a high level of what is laid out in PDUFA VI under the regulatory decision tools: Provisions and namely there will be mechanisms for drug developers to engage directly with subject matter experts inhouse here on complex innovative designs, all informed drug development where we tend to bring more formality to the biomarker qualification process and faster discussions around real world evidence, real world inference, more structured transparent benefit-risk assessment, and of course, best practices for incorporating patient voice into drug development and regulatory decision-making.

On the MIDD front, I have laid out sort of the specific things that we have committed to under PDUFA VI. These include increasing our regulatory science and review expertise in capacity in MIDD both through training as well as raising the level of the workforce. We have committed to convening a series of workshops to identify best practices in

MIDD. This is the first in the series. This one is on, of course, dose exposure, response and other quantitative aspects of MIDD related to oncology, but we have also convened workshops on PBPK best practices, disease progression, and model development _____. We have also committed to starting up a pilot program on MIDD approaches where sponsors could engage directly with subject matter experts on product-specific issues and add a prominent MIDD component. And we will also either revise or develop new guidances, manuals on policies and procedures and standard operating procedures to advance the science and ensure consistency in the application of these strategies in development and in review.

These efforts are intended to advance the field and integration of the science into our work. There are, of course, enablers and challenges in the application of MIDD approaches. Based on discussions with our stakeholders as well as our own senior leadership, we feel MIDD is enabled by a variety of factors including environment that fosters collaboration using information from a variety of sources which I am sure we will hear about today, acceptance of model-based approaches by multidisciplinary teams, organizational alignment, prioritization and support, methodological advancement and a variety of other factors. There are also recognized challenges and I have raised some of these in a slide here including an absence of best practice for determining a model is fit for its intended purpose, the need for identification and transparent communication of assumptions and knowledge gaps, the need for integration of data from multiple sources, a recognition that there is varying degrees of comfort in adoption of these approaches by end-users and decision makers, clarity on regulatory expectations, and from the Oncology context, a bit of a catch-22 situation. An argument could be made that Oncology is one of the therapeutic areas for which MIDD can have the most impact because the pace of Oncology development is moving so fast that there are knowledge gaps around therapeutic individualization and use that could be filled by the strategies. At the same time, because it is moving so fast, oftentimes we do not have the data that we need in order to fill those knowledge gaps, and so there is clearly a situation to be considered here. Notwithstanding those challenges, of course, there is reason for excitement. There is a global convergence of interest, investment and effort in the MIDD space, and so there is global health authorities, drug developers, academic consortia. They are all actively

promoting and developing the science of MIDD. We anticipate significant progress in the field, and in fact, there is support for MIDD at the leadership level at FDA. Of course, this is just a blog that was put out last summer by the commissioner highlighting the various ways in which in-silico approaches are being used in drug development and in review, and a call really to increase innovation around these tools and their application. And, of course, in a moment you will hear from Dr. Janet Woodcock who has been a longtime proponent of these strategies at the center and at the Agency level.

So with this, I just want to thank the many people that were involved in putting together this workshop. You see these names on the left hand side as well as the speakers and panels in advance. I would like to thank the attendees. At last count, there are nearly 1200 registrants for these meetings. I think that signals a tremendous amount of interest in this space. I would like to also acknowledge the names on the right column. There are many people working on the strategic front here at the FDA both in our center as well as the Center for Biologics in ensuring the success of the provisions that we have committed to go under PDUFA and one _____ as well. So, again, I extend my welcome on behalf of the organizers, and I look forward to a very productive day.

With that, I would like to introduce Dr. Janet Woodcock.

[APPLAUSE]

Challenge and Opportunity of MIDD in Oncology

Dr. Woodcock: Thanks Issam and good morning everyone. Thanks for showing up bright and rolling for this very technical topic. I think there is a lot of excitement in the room and possibly around the world about the potential here. Now, when I took over CDER for the first time, it was at 1994 and my predecessor Carl Peck who is clinical pharmacologist had been advocating for this type of approaches back in the '80s, and I think he is probably somewhere watching this. To Carl, we are finally getting there. In the intervening years, though, there has been a great deal of effort, I think, built up in experience, building a world class staff at FDA. I just cannot tell you the expertise that we have here. I am constantly blown away by this. And, of course, industry with experience in using models of different types in drug development and gradual acceptance of this. So I think the

time is right now, as Issam said, with the PDUFA agreement. We have put a stake in the ground. We said *we're going to do this*. I believe there is a lot of acceptance and understanding in the _____ community which really also had to catch up and we all have to be in this together. So now is really I think the time for us to really informed drug development transform drug development through use of more quantitative information during the preclinical and clinical phases and after marketing.

And why Oncology? How do we find ourselves here this morning talking about oncologic drug development? As you know, the history of oncologic drug development and the theme has been very simple over the years, and this is a very simple approach which is *kill the tumor and don't kill the patient.* Right. [Laughs] And that was the objective and that was the straight line objective—we find the maximum tolerated dose that would not kill patients and then you try to kill the tumor. And because of the desperate situation in Oncology where we have people often with untreatable or poorly treated diseases, there are really very few chances and really little room for refinement, and we will still find ourselves in this situation to some extent where the pressure will be to move forward as quickly as possible. But Issam mentioned the patient voice. We have heard from the patients and we know the suffering they undergo not only from their diagnosis but also from their treatment and we can do better in many ways, and I believe that this type of —— applying this type of knowledge and information to oncology drug development will really help. We know that we have oncology drugs onto the market and they are used without optimization dose. Now it is true for all drugs [laughs], but these are especially toxic drugs, all right? The individualization of dose without optimization of regimen and for *combo*, the *combo therapy*, we are not really sure because there are so many multiple ways we might use these drugs together and the situation is so dire, and frankly it is true for all drug development. There simply is not enough time and resources to answer these questions through empirical kind of trials. We need to have better methods. Now in Oncology, though, we have a changed situation. We have many candidate drugs and we have many approved drugs often for various tumors, and there are many combinations that can be put together and that is a tremendous opportunity for people with cancer and for people who treat cancer it is a stone that there is still this unmet medical need. There is still this sense of

urgency. And so how do we combine these two things? We need to have answers to these questions. How do we construct the optimal region for outcomes? How do we construct the optimal exposure—patient exposure—that will kill most tumors but not cause short term and long term dire adverse consequences? And so we really have to face the fact that what we have done is we just do not answer these questions, and so model-informed drug development offers us a pathway to answer perhaps less conventionally than we have answered questions through empirical clinical trials, but to give us answers that are quite convincing and that can guide therapy in ways that we have not realized before. So opportunities include—and Issam has gone through some of these, but I think particularly germane to this discussion today—modelling before and during early clinical development, exposure, and exposure response. If we can begin to do that in a much more quantitative manner, figuring out how to manage these combo regimens, figuring out how to do a regimen in general. There are vast amounts of information available from previous experiences in these tumors and in these trials. And often in other diseases, we have begun pooling this information to make the same disease models and response models and so forth. There is a tremendous opportunity there, I think, that Oncology to do this.

So can we really optimize exposure response on both efficacy and toxicity for cancer drugs? And can we figure out ways to do that so that when we get the recommendation for dosing on market it is backed up by quantitative information that we understand. Can we achieve more integration of different levels of knowledge? We have tremendous amount of basic science knowledge right now about tumors based on the war on cancer for the last 50 years, right? And so we have tremendous amount of molecular information, target information, all these sorts of things—tumor behavior and so one—but we are still, I see some printout, we are still using the RECIST criteria. [Laughs] We are still in the translational space. In the clinical space, we are still using the tools that we have used for a very long time. So we may need to keep using these tools, but we can re-inform them better with much more of the scientific information. Can we construct models that bring this information together and give us a more global understanding of both behavior of the tumor and then the pharmacology of the drug overlaid on

that? We recently had a sort of workshop here within the FDA on model-informed drug development to inform the staff basically of how far we have come and what the opportunities are. And really in many other disease settings, we have had tremendous, I think, real breakthroughs in understanding for specific drug development programs and also for how we handle a certain approach to the disease based on these models that had been degenerated. They just add tremendous richness when you are able to make these connections. So I think even new end-points that we are considering such as _____ residual disease. There are a lot of people who are looking at circulating tumor cells and how they might be used. There is a lot of biology underlying that. We are still not there yet. There is a lot we can learn. If we can pull that knowledge so that we can learn faster through the quantitative models, I think we can get to a better level of understanding. So it is not going to be an easy journey.

Drug development to a great extent likes to travel well-worn pathways. Why is that? Because there is so much risk for whomever the drug developer is. There is a tremendous amount of financial risk and company risk and all sorts of things in pursuing a drug development program, and so people like to do what has been done before and has been successful because trying other things often as perceived at least adding additional risk to the equation. But we have to take some risks here to get to a better place, and I do not think these risks have to be to a drug development program. They just —— we all have to stretch ourselves a little bit and figure it out. You know, how can we incorporate this knowledge and make decisions based on broader input in something what we find from the empirical trials. I think this is the future. We always hope that we at some point will have enough knowledge of the science of human variability of response to drugs. And in this case, the tumors' variable response to drug as well as the patient's variable response to drug that we can predict the influence of all these factors and actually can predict what the response will be. We are far away from that , but the only way we are going to get there is to incrementally add those pieces of knowledge together and yet our predictions become better and better and better over time. This actually eventually will *de-risk* as they call it drug development considerably because our predictive power which is now pretty poor will become better and we will be able to say with some confidence after we have gained a lot of knowledge about a drug, not necessarily just clinical experience. We will be able to say with some confidence what

we think that last trial will be. In fact, you know, I think today we are talking a bit about the Learn and Confirm model and learn and confirm, learn and confirm. My hope is sometime in the future we will learn and then the clinical trial _____ clinical trial will be the peak, and the trial will be the confirmatory trial. Right now, the construct is we can have a single combo trial and confirmatory model which might from a model from other scientific information, mechanistic information. The future needs to be that we have learned enough mechanistically from Pharmacology and other understandings that we have that when we do the clinical trial we are confirming the prediction that we have made. And confirmation hopefully should be more and more and more predictable overtime. This is for the future, okay? But we are here now taking some of the first steps to that. In Oncology, the complexity of the disease as well as the complexity of the interventions, for example, the immunotherapies and other types of interventions are being conflated. It is getting to an extraordinarily high level. So every tumor—we used to have several tumor breaks—each tumor is its own tumor really, and as far as the interventions, we have only begun to sort of plug the science of what we are actually doing to the immune system and how these things are actually playing out overtime. And of course we have new unanticipated side effects of the immunotherapies. All of these things, at least in theory, are mechanistically predictable if we have enough knowledge, and we have to keep that in mind. We cannot become sort of nihilistic empiricists who believe that, you know, this is so complex that we will never understand it. We have to believe we can understand enough of it to get there, that we will get to a point where our predictions will become stronger and stronger and more reliable. And frankly for handling the complexity of Oncology in the future, there is probably no other choice and to connect all that basic science understanding of tumor, biology in tumor and so forth and begin to connect it up with the pharmacology of the drug that we understand the toxicity and then get to the next level of what is going to happen in that individual patient who has shown that each one of them has so many different factors including their tumor.

So I commend our Clinical Pharmacology Office and the Oncology Center of Excellence for putting all this and our co-sponsors for this. It is a really fantastic starting point. It is a long journey, but that first step is usually the hardest. So good luck on the workshop and I think this

will be the start of something that will really benefit patients in the long term.

Thank you.

[APPLAUSE]

Session I NON-CLINICAL MIDD IN ONCOLOGY

Dr. Jin (Moderator): Good morning everyone and good afternoon for those on the line calling in. I know some of you guys I know it is a good afternoon or good evening. Please join me in thanking Dr. Woodcock and also Dr. Zineh again for setting up a great context and painting us a bright future as a wonderful kickoff of today's workshop.

[APPLAUSE]

I am Jin Jin from Genentech. I also represent the International Society of Pharmacometrics as the current president. It is our great privilege to co-sponsor today's workshop with FDA, and I will also act as a moderator for our first scientific session.

Drug development starts in the nonclinical space and our first session will showcase some modelling applications in the preclinical space, and we will have three speakers covering multiple aspects ranging from using assessment pharmacology modelling approach, the informed immuno-oncology therapy authorizations of _____, use of in-silico modelling to help design up bispecific antibodies, and also use of preclinical to clinical translation and modelling to inform and further optimize the advocacy and the safety balance for combination therapies. We will take a couple of brief clarification questions at the end of each talk, and at the very end, we invite all the speakers to come to the panel joined by a couple of FDA colleagues with the general panel discussion at the very end.

So now, I will introduce the first speaker for this session Dr. Sergey Aksenov. Dr. Aksenov is a pharmacometrics lead in Quantitative Clinical Pharmacology Division at AstraZeneca. Given the interest of time, I will not read through the detailed bios and this will be posted online afterwards. Now, Sergey please come over.

Dr. Aksenov: Thank you, Jin. Good morning everyone. First of all, I would like to thank the organizers for giving me this opportunity to speak here today. I speak on behalf of my many colleagues in office at AstraZeneca and all the _____ partnership. The topic for my talk today is

modelling that we are doing to support evaluation of drug combinations through clinical models and data.

Well, first of all, I would like you to _____ from this, to walk you through the framework that we are using to evaluate potential drug combinations. The approach that we use integrates the PK/PD data, pathophysiology both animal and human. Eventually we use this to make predictions for _____ drugs in humans, and then I will talk about the quantitative systems for oncology model for the immune cycle in mouse, and you will see how we use that model to understand the dynamics of the immune cycle and how it well describes the type of radiation and anti-PDL1 antibodies tumor cycle _____.

So this a general outline of the whole framework. So it consists of two parts: the first part is the QSP - quantitative systems pharmacology model. That is the one from the left. The second part of it is what we call a *joint* model. It is a model that links the output from the QSP model to the _____. So what is a QSP model in this sort of framework? It consists of three modules. The PK module _____ that describe the pharmacokinetics of drugs, concentration of drugs at the test site. The biology module describes the drug targets and the signaling pathways where this drug was designed, and it also describes the way drugs do that biology of signalling there. And finally, the physiology module describes the context for the drug, the targets, the pathways _____. Eventually one of the outputs from the variables from this physiological framework links up to the clinical input and that is the joint model of that. I will not spend too much time talking about it, but that is where we —— just to give you an idea of the thread that pass through all of this clinical work to the post clinical especially the _____ in patients.

Okay, so for the immune cycle, this is what that annual QSP model looks like. This is again as an _____, the PK/PD module here containing PK of the anti-PDL1 antibodies in mouse, other compounds, and how the concentration of these drugs and the effect of these treatments act on the interaction between the immune components of the system. So that is the PK/PD part of it. The biological part of it is again the interactions between the immune components but also the immune system itself and the whole body of the mouse. And finally the physiological part is where the immune cycle, the immune system links up to what we care about which is the wall of every tumor, the tumor size of the mouse. That is the readout for all of our prediction efforts given.

Again, just to show you how this would look like eventually in this framework that we are using. The annual model that I have talked about today is here on the left and the output as well tumor size, tumor girth. So if you will click this, it would re-circle here. So one thing that we are working is an effort to translate this mouse tumor model to human. That is necessary because what we will want to understand is how combinations of drugs affect tumors in humans. In that what we will do is we will develop a joint model of tumor cells progression-free survival and overall survival. And the joint model here—It is a technical term statistically. It just means that we will be modeling multivariable divisions for _____, variable tumor size and _____ progressions and deaths. And so the way we will do it is we will link up predictions from the human #QSP model in which _____ tumor cell response to this joint model that we can build using all the information that is available to us about the cancer—clinical information, clinical trial data—and be able to predict the effect of the combinations on progression free survival and overall survival, so in that way we will be able to make the combinations.

Okay so now about the mouse models. This is a diagram of the model and the key component, the centerpiece is—I have highlighted this with my mouse—the effector cells in the tumor environment, right here in the middle of the cyan blue box. And what these effector cells do is they promote increased death rate of tumor cells, and that is why they are centerpieces. Now, there are three feedback ropes here in the model that together determine the complex that mimics the immune system response through interventions involving tumor cell response interactions. And the first feedback rope describes the downregulation of differentiation and activation of effector cells through the PDL1 axis or pathway. It is right here. The second that we will describe is the role of the systemic antigens in, again, promoting the infiltration of the effector cells into the tumor. Right here. And finally, the third feedback rope here is the antigen, the effect of the antigens on the immunosuppressive components of the tumor environment which would self-inhibit the differentiation of the effector cells. Ultimately these antigens come from the tumor itself. The tumor in the model here—it is an empirical model describing logistic growth of the tumor and exponential death. In wanting to have the effect of anti-PDL1 antibodies through depletion of the PDL1 _____ that is available to act through the components here. Last month, the model was estimated —— the parameters of the model were estimated with using mouse data in syngeneic tumor mouse models. And there were tumor sizes

_____ in response to different treatments, and I will show you this on the next slide. But what I wanted to emphasize is one parameter, one _____ that is circled here on the left. It is the ability of the T-cells to infiltrate the tumor microenvironment. It turns out that that is a very critical parameter in the process in the model, and the _____ was modeled —— the parameter that described this interaction was modeled as a distribution across all subjects. In technical jargon, it is the random effect in the population model, and the purpose was to be able to describe the variability of the variation of tumor responses in individual mouse and the model did this very well.

So these six graphs show you the _____ that were used to estimate the parameters in the model as well as model predictions. So model predictions are the red lines. The red lines are predicted _____. Individual mouse profiles of tumor cell versus time are the gray lines, and the median of those is that dash black line. So the vertical axis is the tumor size. The horizontal axis is the time since inoculation end-points with the tumor cell. So what you see when you look in the control mice, the tumor growth has been watched exponentially and once you apply anti-PDL1 antibodies to mice or radiation treatment with x-rays, you see that the growth, the overall growth rate of the tumor decreases but then it starts regrowing. The bottom row of graphs show you the combination treatments, radiation plus anti-PDL1 _____. And you see the dramatic effect on the tumor size. On the average, the tumor size growth is completely suppressed. Of course, there is some variability between _____ here. What is interesting is that the importance that this model was also validated using external data. So these graphs show you predictions in data for a different set of mice. Draw your attention to the rightmost graph. So that is the graph where the combination of radiation and anti-PDL1 was given together with anti-CD8 antibodies. So these antibodies deplete CD8+ effector cells from the body, and so when mapped to a parameter in the model, it is aligned with predictions with the data as well.

So given all these, we are confident that the models qualify to spread the immune cycle directions in the mouse. That was really the goal. And just to expand on this a little bit, we can do two things with this model. We can address mechanistic questions and try to understand exactly what underpins the response of the tumors to these therapies as well as to make predictions. So in terms of mechanistic understanding, recall where the parameter of that image

probably describes the infiltration of T-cells into the tumor environment. So that parameter it turns out differentiates the quick responders—mice responders—versus nonresponders. So these are the _____ values of that parameter. So remember it was — how we were computing the values for every mouse. And the low values of the parameter right here corresponding to high ability to infiltrate the environment of the tumor correspond to responders and nonresponders _____ have a wider distribution, larger values of the parameter, lower ability to infiltrate the tumor. Then if we follow through this insight to the different components of the model, the variables of the model, you will see a very consistent picture. Responders, quick responders with high ability to infiltrate the tumor also have—I would note the second term here on the top—also have the larger number of dendritic cells that are activated. The same for the overall _____ of the effector cells in view of the response, as well as _____ larger values for tumor effector cells in the environment and _____. So overall, the systemic consequences are the biological differences between responders and nonresponders which should make sense. And to follow through on this element, we also simulated the dynamics of all of these components with two different types of mice, ones with a low ability to infiltrate the T-cells—these are the red rows—and mice with high ability to infiltrate the environment of T-cells. And if you look in the rightmost column, the top _____ that is the tumor size _____ mice with high ability to infiltrate and suppress the tumor very well _____ to 0, and really we get this sort of dynamic insight as to how this happens by looking at the dendritic cells overtime. They reach their maximum sooner than mice that do not respond, stay there for a little bit, as well as here in the fourth panel from the top, the T-cell infiltration happens to a great extent in this mice responders.

And the real purpose of this model was to make predictions, and so what you see here are heat maps of efficacy response in mice treated with radiation plus anti-PDL1. The heat map on the left corresponds to radiation treatment started on day 5 since inoculation of mice and the panel on the right is day 12. These are older which are more established tumors on the right. The color corresponds to the degree of _____ response: The moss green is 100%. The red is 0, no response. The rows in this graph correspond to the dose of radiation from 0 _____ to 10 gray at the top, and the

columns correspond to the day when anti-PDL1 treatment was started, again, relative to the evacuation of the tumors. And so the pattern that you see here is that response with a combination is most pronounced when radiation and anti-PDL1 are given close together. So if you focus on the third row from bottom, you see that this green higher indication response where PDL1 was given 3, 5, 7 days with 5 days of radiation. But then it starts to kind of thin out when PDL1 was given much later with day 12 and 19, and this is more dramatic on the right where the tumors are more established. So timing is key and the modelling is for the purpose of identifying the sweet spot for scheduling and dosing of the different combinations or in this case radiation and PDL1. Well, the other thing that you see is that older tumors, more established tumors in the graph on the right day 12 since evacuation. They have a more established immunosuppressive environment. The model captures that and that is reflected in general in the fact that these treatments are not able to induce a good response except with some very specific combinations here. The maximum dose of radiation was _____ very close to that.

So this diagram shows you —— this is a diagram of the more general immune cycle model of the mouse that we are developing. So from the _____ on the model I just told you about, it includes more components, more granularity in the immune components. For example, it does include a myeloid-derived suppressor cells, includes deregulatory cells exclusively. And the purpose really was to be able to start predicting the effect of many different combinations of targeted treatments that we can think of. So in red you see all these different targets that have been considered in drug development, impacting these different immune cycle directions, and that is what we are starting to do here.

So what I will show you next is a prediction from this more general model for some of these combinations. But before that, I am sorry I forgot to say that the one key component is here again the pharmacokinetic models of the drugs and the reason is because you want to be able to make predictions specifically about dosing stages, sequencing of the components of the combinations. That is a very important issue.

So this table shows you predictions with the version of the more general model I showed you for two different types of murine tumors, so two rows in the table. The first row

_____ both have developed immunosuppressive environment. So the tumors in the top row are distinguished by the fact that _____ these myeloid suppressor cells, and _____ that the combination of anti-PDL1 and CXCR2 is predicted to be most efficacious compared to other combinations, again, using the same metric that we have used for the radiation tumor model. And that in some way is so surprising because CXCR2 is _____ infiltration of myeloid-derived suppressor cells. The second type of tumor cells is distinguished by having a large number of deregulatory cells in the environment, and springing through the combinations with the model, we see that the combination of anti-PDL1 and CTLA-4 is predicted to have the most effect. Again, this can be understood given the role of CTLA-4 in the infiltration of deregulatory cells.

We summarize by saying that the first thing that we did is—what I have told you about—we built this QSP model, a quantitative systems for oncology model that predicts the effects of dosing and sequencing in mice. The _____ therapies at first radiation but now we are expanding to a large amount of targets, and the important thing about this first attempt to use this QSP model is that we used radiation and the anti-PDL1 just to make ropes, to move the system in different ways. And if you think of radiation actually, _____ framework of hammering the system in different ways and see what moves that allowed us to understand the key interactions in cycle and have a reasonable concise model that is predictive. Again, one insight here is that we would translate this model to human and then use it in a joint modeling framework to predict progression free survival effect and overall survival effect for the different combinations, and thereby, we will be able to prioritize very early preclinical efforts on all combinations in terms of their likely effect in tumors.

Thank you.

[APPLAUSE]

Audience: My question is how do you model the effect of radiation, which parameters of the model, which _____?

Aksenov: Right, right. So the radiation effect was modeled through introduction of double-strand breaks in the DNA and then those were impacting the death rate of the tumor cells. So the model was breakthrough like I said in terms of logistic growth, exponential death rates, but the death rate was enhanced by the radiation.

Audience: Do you recommend the QSP model that you had built could be used to differentiate nonresponders from responders and applied to predicting _____?

Aksenov: Yeah, absolutely. So, in fact, we tried this as an example in what I talked about, so the beauty of systems for oncology model is that it represents the key systems parameters that presumably mapped to the differences between individuals mice or humans, and so in principle, you would build a population model, a systems population model and then look at the distributions of —— how distributions of various population parameters is different between _____ and try to understand what distinguishes responders to nonresponders.

Jin: Are there any more questions? Please introduce yourself with name and affiliation.

Audience: Okay. I am _____ from Merck. Just to follow up on the previous question. So in terms of understanding the effect of dose and sequencing of radiation followed by PDL1, what kind of input data was used as leading to —— in order to build the effect of dosing regimen? You perhaps need some input data to sort of quantify it _____?

Aksenov: Right. So the data that we used to develop this model consisted of responses of mice to different regimens, to different combinations of PDL1 and radiation. So radiation and PDL1 were given at different times, at different sequences. First radiation and then PDL1 together and then mice got also PDL1 right after the radiation. So we actually moved the system dynamically in different ways to see how radiation and PDL1 affected the system.

Brown: Anthony Brown from Merck. So in terms of mouse model, we know that there are anti-PDL1 resistant mouse models as well. Have you looked out which components are actually functional in those mechanisms as to what makes it resistant?

Aksenov: Right. But not at this time. So, at this time, we modeled mice that have a functional _____ component.

Jin: If there are no more questions, please join me by thanking Sergey.

[APPLAUSE]

Our next speaker is Dr. Armin Sepp. Dr. Sepp is a scientific leader and associate fellow in System Modeling and Translational Biology Division at GlaxoSmithKline.

Dr. Sepp: Good morning everyone. Many thanks to Dr. Jin. What I present today is also the work we have carried out at GSK.

To start with, when people speak about bispecific antibodies and we have been following on the _____ what happened to an antibody when it sees that target cell, and _____ in brief and what should work _____ about an experimental experience we have seen at GSK. So targeting many different targets at the same time is getting more and more fruitful both in _____ and elsewhere. Target selection is not the topic of this talk, but that is obviously the key term. Just a few years ago, there was a nice summary made as to the state of bispecific antibodies that has been developed mostly in Oncology and mostly targeting antigens expressed in different cells but very often also expressed on the surface of the same cell. So we graphed the target we are using here and all the limits with simulation to try to rate _____ evaluated in different approaches available at that time. So in a number of different bispecific antibody formats which had been proposed during that time is just demonstrated by adding on additional domains to existing antibody, chopping it down_____ is a little bit as possible and many of those have been obviously evaluated through _____ please.

Audience: _____.

Sepp: _____. Often the question is do we need a bispecific antibody or we will have just a combination of tumor-specific antibodies to work just as well and that is what we are trying to answer here because we cannot think to replace this with _____ plus the time and effort and so on. So we will be using experimental data. We will be using mechanistic mathematical modeling. We will be using parameters with _____ and other tools to make meaningful predictions about the system, how it might behave in slightly different conditions. So in the first instance, it is fairly straightforward. If we have both targets in solution, then

from the mechanism point of view, it really does not make any difference if we have bispecific antibody or a combination of tumor-specifics. If one of the targets becomes _____, at this point we can argue that a combination dose with two different antibodies might be more efficacious. That is the one therapy that the surface expressed target could connect it from directly the effect. But the most interesting situation on this space where we have the antibody expressed on the surface of the same cell, and if you look at the literature, you can see quite a few different approaches taken. We have some papers taking the approach that we have taken that targets are all well expressed in solution with the _____ insoluble. We have what you see models when they are postulated to be immovable on cell surface, and this presentation actually will be about the approach which takes into account the lateral mobility of targets in cell surface. Right.

Well, every model starts from good experimental data and this model was introducing excerpt computations from Mazor and _____from _____. This was two years ago. They looked at bispecific antibody which was monovalent for either antigen, and the target cell either expressed both CD4 and CD70 or just CD4 or just CD70. We assumed that antibody is in solution stock that targets human trait and symptoms that are on the cell surface. At the end of the day, what we see is that antibody cross-links targets on the cell surface, and in the experimental, it was shown that every target gets cross-linked no matter what consequence they are basically in, and so on and so forth. But trimolecular reactions do not happen in reality, so they are sequentials. So at first, the antibody binds with one or the other arm and that is called cross-linking on cell surface, and cross-linking is very rapid. Here, we are actually modelling this using the Brownian dynamic simulation. We have the cell surface with just a small cube on top of it. It is on the surface _____. It rarely gets around. When the antibody hits and binds the target, it turns into a big _____ and both arms are cross-linked in terms where each step is a few microseconds along, but this can be more than that. We can figure out what happens over a period of time, and just as a surface infusion can be quite a bit rapid in just about a second, a typical surface protein travels above 200 mm. If it was going in a straight bind, it can circumnavigate, descending about 2 minutes. That is plenty of time for the _____ to get cross-linked. And in the model, over a period of time from the simulated experiment, the

concentration of three targets is exponentially reduced. There is no accumulation of monovalent-attached species. What we do see is exponentially increased drug cross-linked species and that was in perfect fit with the experimental data for double-positive cells or single-positive cells, and we have high affinity for CD4 for single-positive cells. With the CD70, the affinity _____ were much better.

Mazor _____ went on to optimize the system. They really wanted to have an antibody which would bind just dual-positive cells so that _____ have gone unchanged and then started to compromise the affinity of the CD4 arm, and eventually they raised the situation where there was hardly any binding to single-positive cells, but there was an almost unchanged binding to double-positive cells. We can capture this also in the in silico, and as I have mentioned, there was no caretaking involved. All the _____ in different and experimental measurements of their mistake. So out of curiosity, in _____ planning experimental with _____, and what we can see here that the end-point reached about 1 hour is actually kinetically limited. There is no equilibrium at very low antibody concentrations, and there is no way that one can actually stand an incubation time much longer than 1 hour that was used, but we can do it easily in silico, and we would actually see increased binding at very low concentration if we put in _____ cells, _____. And from that, we can actually figure out what is the so-called _____ approach. It turns out to be somewhere around 1000 to 10,000 fold when both arms of the antibody did reach the target at the same time, and it manifested itself through reduced _____ rate constant from the ternary complex. Even if one of the arms becomes detached to re-bond _____, the ternary complex just does not fall apart from practical criticism. In real life, it is more likely it would be generalized _____. Looking at it with more thought, we can understand a little better how antibody might interact with cells of these antigens in general, and we think about the conventional antibody monospecific. It has known anti-self-symmetry undertaking Fab rotation which means the fragment sides were unable to _____ opposite directions. If we could turn it on the target in the same orientation, the antibody needs to be stronger for a time so that we compromise the avidity over _____. While in the case of bispecific against a different type _____ on the same molecule, we get a biparatopic kind of antibody that compromise the _____ as well. Anyway that could be likewise with dimerizing

targets on the cell _____. It is unlikely an antibody will be able to engage in a dose on the same dimer. Its problem might be it would actually cross-link with different dimers, and I very much hope that one day we will be able to check out _____ cell that is a resistant cell _____ microscopic cell.

It really does not matter. It does not need to be an antibody which cross-links the cell surface _____ antigen in a sense that if there are any tumor that is screened _____ on the cell surface can bind with the _____ antibody as was shown experimentally and that can be laid out _____ binding. _____ these two targets, we can think of an EGF and INFy _____. In the former point of view, it is the same approach as we just saw with bispecific antibody. It really does not matter if that _____ on the surface of different cells and _____ work in the same cellular immunology TCR-pMHC complex, and there are attached three-dimensional kinetics. _____ the work is two-dimensional, and two-dimensional kinetics cannot be deduced directly from being around the different _____ work. And obviously we have bispecific antibodies which can cross-link, again, in all points of the CD5 framework and of how to express that mechanistic requirement _____ expect this to _____.

Finally, with all those _____ is taken from the mouse plan. Across the species, we can put a target and _____ compartment modeled with _____ what is the penetration rate of the antibody? How much is the target _____? How much documented investigation we might encounter? And that is our GSK experience inhouse with mAb-dAb where you have a collision antibody with domain antibody _____ of the heavy chain, and we have seen a significant enhancement trait in the binding potency on the antibody side, but it is somewhat unpredictable. Sometimes it is there; sometimes it is not. If it is there, it can be actually fantastic. And we have also learned that we have made constant _____ benefits hugely the _____. PK-wise, again, there is a degree of concern that we have that the leads which have antibody-like PK _____ which are compromised PK _____ and it is not necessary —— we have not really like managed the _____ that was the image depicted. It still did not really _____ correct. It is not there. The _____. It very much aligns with our operation from _____ in that there is a similar constant and _____. Such proteins tend to accumulate_____.

Well, just to sum it up, most of the work was done in collaboration with GSK and also with the _____ workshop in silico. For the _____, we have not - we will publish everything later including the _____. The bottom line is that bispecific antibody can be treated as cell specific. It can be very useful. It helps antibody _____, and in models to device, it can at least guide us to optimize things regarding target expression on double-positive cells and single-positive cells. So the challenge is that in experimental protein engineering, linkers, that really everything actually works on paper, but when it comes to real life, the expression of PK does not _____ surprises. Well, more than anything, looking into the results how to understand _____ scenario in terms of let's say what is known best affinities for each other and so on and so forth, I could ask _____ prove it. If they approve _____ parameters _____, some _____ for small molecules, but antibody would be slightly different, so that is a reason for_____ Genentech _____.

And that's it. _____ colleagues from GSK and academics from _____.

[APPLAUSE]

Jin: Are there any questions from the audience? I will ask a question. Do you guys have any experience for the bispecific antibodies in the PBPK space, especially for immuno-oncology service, especially when you have bispecific antibody linking with one targeting new cell, one targeting on the tumor cell, trying to link them together in the PBPK space that hopefully will help the migration and concentration of the immune cells into the tumor? Do you guys have experience with using any approach capturing that aspect?

Sepp: Well, when you look at the _____ in the PBPK space, there is _____ to look at _____ that might make such a similar kind of situation where we have target cells expressing, let us say PDL1 and we have lymphocyte cell expressing something different and how _____ might behave, and one can _____ situations where either one can easily eat up everything there is, and because of the large number of cells there are that _____, and let's say, _____ it can define what kind of systemic concentrations would need to be maintained in circulation, for example, to have any chance to improve their chances thereof for _____ engagement in the PBPK _____ we need _____. Regarding T-cell infiltration, infiltration

probably _____ so the antibody can promote, perhaps stabilize cell complex towards at least a sense of where we are making _____ tumor and will they actually _____ T-cells towards tumor _____.

Jin: If there are no more questions, please join me in thanking the second speaker.

[APPLAUSE]

Jin: Our last speaker for _____ is Dr. Dean Bottino. Dr. Bottino is a senior scientific director in quantitative clinical pharmacology fact data.

Dr. Bottino: Thank you Jin and thank you to the other organizers for inviting me to today's presentation. I'm going to stop _____. Okay, I just wanted to thank the other people who worked on this very collaborative effort _____ pharmaceuticals _____ a little bit _____ techniques and I'm going to show you _____ original concept around this was built _____. So, the current paradigm of at least the way I see it _____ combination that sometimes they just _____. If the X axis here is drug A mg or drug A per day, the Y axis is mg for drug B per day and this is just a drawing and you'll see the real data later. You might escalate drug A where the pipe charts here represent the percent of the patients that have dose-limiting toxicity in red or do not in green and _____ maximum tolerated dose or MTD of 8 mg for the first drug, drug A and then drug B _____ study might escalate and get a maximum tolerate dose of 800 mg and then _____ one dose from MTD and started titrating in for example drug A added to a lower dose of drug B and _____ and for your recommended _____ drug A you have another MTD. And you have a question which MTD do you go forward for your recommended phase 2 dose. Well, the bad news is that not every clinical team _____ realize this at first glance but when you find it in this axis of this, you can see the maximum tolerated dose for a combination is actually _____ many doses of the curve and those X and Y phase here, so the question then becomes along this curve, what is the recommended phase 2 dose or RP2D and we proposed that the recommended phase 2 dose is a dose that gave you the maximum antitumor effect along this constraint curve. In this case, it would be that 110% growth rate inhibition would be around this dose combination here

would be the recommended phase 2 dose. The maximum growth rate inhibition predicted along this curve would be either done from clinical observations if you have the maximum genius phase 1 population which you often do in an _____ phase 1 study or you can use frequent _____ exposures from the frequent clinical species to the clinical situation and I'll show you with justification for that in the next slide. So it turns out for this set of compound study that most models do predict the human tumor response rates when you match the free-fraction exposures to what you can _____ so you have to simulate down _____ months to the exposures that you would have attain if they have been constrained by clinical toxicity. This is something that you can only do once. You have the clinical toxicity data but it is predicted once you do that. As you can see here, if you don't match the exposures and then you just _____ the tumor growth inhibition at the maximum tolerated dose for the mice then you _____ correlation with clinical response rate. Over here, and this is probably _____ internal growth inhibition at the matching clinical exposure, attainable clinical exposure has a nice correlation to the overall response rate in the clinic. So from this point on the presentation, we can use exposures to try both efficacy and toxicity and we are going to eventually at the end of the _____ we can convert this recommend phase 2 exposure back to combination dose _____. If you had noticed _____ this is just a 2D constrained optimization problem. If you remember from _____ those sort of things, the branch multipliers and all that stuff. Basically, what you have is an efficacy service and it is a function with the concentration of drugs X and Y and then you have a toxicity constraint curve here in that X, Y space and then you ask you want to find the point and the probable combination region that maximizes the efficacy service location and for _____ I would say most pharmacologically realistic efficacy services and toxicity curve, the maximum _____ that is somewhere around this constraint curve. So, like this specific case study, this is TAK-117/TAK-228 or sometimes we called the paper combination because it combines the _____ inhibitor which you'll see in this presentation. I used the old names, MLN1117 interchangeably for TAK-117 or TAK-228 which also interchangeably called MLN0128. Anyway, MLN1117 is a _____ PIKTOR and then MLN0128 is a TORC1/TORC2 inhibitor and that here is that you can get a compensatory reactivation _____ that can reactivate the cancer cells and so _____ MLN0128

_____ that, so that's the biological rationale for the combination. _____ from magazines but it helps suppress reactivation _____ last about two years. So the first step in the technical part once we get the data is to start with _____ the tumor growth inhibition data reverting _____ exposures to free-fraction human exposures. So basically what we do is we just _____. We get growth rate for control, growth rate for treated mice and then we use the transformation, we call growth rate inhibition or GRI which is just the transformation over here and then basically just to calibrate your intuition on what GRI means. GRI of 0 means you're doing no better than control. GRI above 200 means you're slowing down the tumor but not causing regression. GRI of 100 corresponds to tumor spaces and greater than 100% GRI is tumor regression. If you remember from the Harvey Wong's slide before, it takes about 60% GRI approximately to cause any kind of response rate _____. The next step is we do this for every single dose combination that we try in the mouse _____ free-fraction exposure in the mouse and what we get is a grade of about 910 points in the points for GRI as the function of 117 monotherapy, as a function of 128 monotherapy, and then the combination space _____. Once we have those points, we use a simple _____. You can pick whatever models you want just fit the monotherapy. So, GRI of drug A on 117 turns out to be linear function and GRI of drug B which is 128 is a saturating function of concentration. So the next step is to use this equation here. Basically, the percent growth _____ is taking to be the growth rate inhabitation due to each of the two growths added together plus the _____ the two monotherapy, there's only one additional _____ that I need to estimate to get the surface which is this _____ and basically what this shows is that there's a slight synergy between 117 and type 228 which is one of the _____ combination into the clinic and so the next step will be to try to determine its maximum tolerated exposure curve. The first step is to figure out what is the PK driver of toxicity and so we considered maximum concentration _____ and was a good predictor for 228 _____ TAK-117 _____ better predicted for toxicity _____ as the toxicity predictor. So these are _____ toxicity, red or patients with those _____ progression. So we use _____ concentration from this point forward. Then the next step is to look at the combination. So this is once we have the phase 1 data _____ represents the average exposure for type 228 and type 117 for each patient in the

combination study. These ones along the axis are of course all the monotherapy patients from the phase 1 studies in the 228 and 117 respectively and again green is the patients _____ dose having toxicity _____ toxicity. Red are patients who do. So then _____ two-dimensional logistic regression on this data. So this is the equation here. It basically just have _____ slow term for S, slow term for Y and then an interaction _____ concentrations of S and Y multiplied together and you get this brown surface where lighter colors are higher probabilities of having _____ toxicity then the maximum tolerated dose is defined to be just the lever curve of this probability surface where probability _____ toxicities are 25% which is more or less what a standard _____. When we _____ the MTE of the maximum tolerated exposure and just for reference, this is what _____ is the straight line here. So you can see that the maximum tolerated exposure curve, like the efficacy curve _____synergy and both toxicity and efficacy. So going back to this theoretical drawing first. The question you can think of it is if you're _____ here where an X is longitude and Y is latitude then as you walk along this fence, the question is this fence was _____ on the map and latitude and longitude _____ where do you reach your highest point and what latitude and longitude you reach your highest point as _____ phase 2 dose combination. So to animate this, you have—you're moving along and what we do is we basically cut the surface along this edge here, well we cut it vertically on this edge here and you get a profile of efficacy as a function—as you _____ basically and moving _____ you recommend phase 2 dose rather than _____ doses that give you this optimum efficacy value. So we tried this with our drugs, X and Y, TAK-117 and TAK-228 and this is just a reminder the _____ we used for this efficacy surface and then we had to change the color coding to red for the _____ exposure curve so that you could see them on the spot but the maximum tolerated _____ exposure from mouse to humans and what that means is when we slice the surface from the side, it looks _____ this. Unfortunately, instead of going upward, what if there were _____ combination, this curve goes downward which means that once you take toxicity into consideration, you are actually better off _____ with all TAK-117 and no TAK-228 is you're better off with monotherapy. We try this with all the different mouse models that were tested and basically one product _____. So we are going to revisit these predictions once we have—so this

was done as a proof—as a _____ of the methodology by using growth clinical data but the _____ move forward while we are working on this and so we do have the opportunity to test these predictions once the phase 2 _____ for this combination. _____. It's very interesting.

[Laughs]

Bottino: This is like a memo where _____.

[Laughs]

Bottino: So in terms of the general methodology if we propose this in the context of a simple problem _____ and phase 1 study with combination, we might want to take this _____ efficacy surface and goes straight up _____ if we don't want to escalate over drugs at the same time or some other sufficient conservative. The idea is to try to get this to the _____ efficacy and _____ so you go up and then actually _____ cohort you could try to refund with uncertainty bands or _____ exposure curve and then ultimately _____ recommended phase 2 dose or expansion for phase 2 _____. To summarize, _____ to the point where you had been _____ in those aspects. So recommended phase 2 dose finding _____ efficacy optimization problem and we have successfully _____ and the model in this case _____ PIKTOR combination would not do as well as the monotherapy once you _____ dosing. We recommend further validation on another combinations. We try to _____. So we're trying to find other ways to validate some of the other combinations. Finally, in addition to all the authors, co-authors _____, thank you. _____ and Brian Cooper for other contributions that you made on these related projects. Thank you for your time.

[Applause]

Bottino: Come in.

Audience: Good morning. This is _____. Nice presentation. So my question as I remember on the beginning of the presentation, this is a _____?

Bottino: Yes.

Audience: Okay. So what kind of _____ that has been observed in the clinic and how do you use this information because _____ any correlation _____?

Bottino: _____ I don't remember the exact nature of the safety events. They were _____ one of the other drug and I don't remember. Anyway, if you look at the _____

which ones were drivers. We did test the events and for the _____ there was no predicted volume Cmax with the toxicity but for the monotherapy 117 _____ of Cmax for the toxicity.

Audience: So, considering the _____ to see how those downstream markers of the _____ PK matrix and how to use that with the model?

Bottino: Yeah, what we did was _____ efficacy surface with the _____ and still with the clinical toxicity constrain, there was no anterior sweet spot or pharmacodynamic effect. The biggest pharmacodynamic effect would be _____.

Audience: _____.

Bottino: Thanks.

Audience: Can you show the slide which shows that _____.

Bottino: This one?

Audience: I wonder if you look like—it looks like most of the combination _____ but it looks like _____.

Bottino: Yeah. So if we cut the surface here. That's a good question. And there's something—if you notice—and then I'll explain what this lighter _____ was as the 5% _____ and you might ask where's the 95%. The 95% could be calculated because they're just weren't enough samples on the outside and that's because of the nature of how we do those _____. Once we have the tolerability issue _____ exploring in the highest dose so there's—here's a sampling _____.

__: _____ horizontal and vertical line _____ kind of region which is still _____. There are no samples on the diagonal region _____.

Bottino: _____.

Audience: _____.

Bottino: Yeah, that's true. There's relatively little support there and you're touching on actually of the darker secrets of MTD finding to begin with and the way we sample, and the way we escalate. If you go back actually a couple of slides here. If you look at even for the monotherapy _____ or the exposure of TAK-117 giving you 25% probability. So we really, in general, across the board

_____ patients if you _____. If you believe that there's even one dose that works for everybody. We're just not sampling enough to really have any confidence in maximum tolerated dose. We did find that _____ maximum tolerated dose and that's _____.

__: _____ thanks for your talking. _____. I would suggest that the one that—that the key problem here is you try to solve the _____.

__: _____ shifting to the next paradigm which I told _____. Are there any more questions?

Jin: I have a question. _____ the common challenge of limited sample size and limited dose has _____. One common challenge we have faced _____ we work in similar phase on _____ combinations and optimizing _____ phase 2 dose. It's actually more than tolerability _____ within the short-term tolerability _____ is basically more _____ limiting and more concerning in longterm clinical development _____ actually not exist from the _____. So you guys have any experience in that phase and how do you _____?

Bottino: We do. We do. Not in this particular model effort, but in this particular combination _____ developing toxicities to make _____ phase 2 and yeah, there's this unfortunate convention of only _____ and so even if you have longer term _____ phase 1 data, they are not actually called _____ first cycle and we have to _____ events if we're going to use this simple _____. The other approach that is not shown here, we have ways measuring all the grades of toxicity model of _____ toxicity. It's a method. It's not _____ regression _____ pharmacologically inspired but anyway you could have _____ toxicity and then you would have _____ based on certain grades that you don't want to see _____. It hasn't been brought in to this framework. It has been brought into the toxicity framework. We did some work combining _____ toxicity measurement _____.

PANEL DISCUSSION

Jin: Thank you. Now I will invite all the _____. We also welcome additional panelist, Dr. Haleh Saber. Dr. Saber is deputy director for division of hematology, oncology and toxicology as part of office of hematology and oncology at FDA.

Jin: So now, floor is open for more general questions especially for using MITD in the non-clinic _____.

Audience: _____. Actually, I have a question for Dr...

Jin: Get closer to the microphone.

__: Yeah. Sure. Can you hear me now? Dr. Aksenov. Very interesting presentation. The general _____ focused on the mouse _____ size?

Aksenov: _____.

__: _____.

Aksenov: Use the microphone.

Jin: Closer to the microphone.

Audience: _____.

Jin: You just need to get closer.

__: Yes. So I think _____ affecting tumor growth, right? You always see a change in growth size. You don't see a change _____. I don't believe that _____.

__: This is _____. This is more general questions. So there's a couple of presentation this morning with a different tumor models in animals. So my questions to the panel is whoever want to answer the question is, moving to the phase 1, we used the data from _____ what is the exposure _____ either 60% tumor regressions or 90% tumor regressions. So, if we have to predict the exposure based on the _____, where we should focus on using the tumor model or _____ now we are talking immunotherapy or _____, how we use _____ versus all those modeling when we move to the phase 1 trial? This is a general question so anybody want to answer.

Dr. Saber: I would like to give a long answer to that, just go back to history starting with small molecules where actually animals _____ a good job predicting toxicities in humans and so _____ human dose. So in terms of small molecules, we do the toxicology in the animals _____ on toxicities and then the non-clinical animal adults are used _____ with a disease used for _____ and activity as a very good place to start to understand _____ activity, etc. However, there are limitations always in animal models _____ and just giving you some examples if—this is xenograft model and you're looking at

antitumor activity and you're proposing to give a drug _____ to the lymph nodes and you're giving that in the subcu _____ efficacy in humans. To me, activity is not the same as efficacy. Efficacy to me is a meaning to have a clinical benefit. So animals _____ are very good place to know the activities, schedule _____, etc., but it's not _____ efficacy in humans. If you have an antifolic—your drug is an antifolic, how _____ is not the same as in humans. If you have a growth _____ esterases, there's a lot of esterases in a growth so that does not equal to that in humans. So, I guess that's a place to have it educated and understanding of activity in humans and then go to humans, study that in humans, and then use the animals to go back for a more tailored question. If you're going to a phase 1 and you see that some _____ patients are responding _____ to go back to your abnormal models and with specific questions you have. So it would be an interaction going into the clinic and then back into the animal. That is the best scenario. Now, going to immunotherapy. That is a more complicated challenge in area. If you think about antibodies, _____ inhibitors and simulators where most of this actually animals tolerating the dose very well. So, we don't have actually a good place for selecting the start dose in humans and then you go into your animal models, you have to think about the differences _____ does it bind to targets in the animals. Even if you use a tumor from the humans or patients, you're still dealing with differences in the FC domain and binding to the FC receptor and differences in IGG isotypes. An IGG1 _____ is not the same as IGG1 _____ surrogate in the animals and if you have a surrogate in the animals, _____ candidate. You need to characterize it. So these are all these complications. Fortunately, _____ is moving towards having better models for these types of clinical candidates and I encourage you to attend our workshop in March 9th because we want to assess these models that are being developed. We attended a workshop in September with the NCI and many academic centers now have very nice or seems to be very nice _____ candidates. _____ industry together. If we can start with the CD models and throw it some safety end points on my markers of activity that is of interest to the regulators and see if _____ uses it. So, the _____ workshop will be March 9th. _____.

Audience: Thank you for the long explanation. So, _____ model to go to the phase 1. Now, looking to your phase 1 data,

_____ clinical data and to I would say we optimize the _____ is that correct?

Saber: Yes. Do a good job starting with your non-clinical, but _____. There are—at some point, you would probably say, okay _____. I know the dose, I move it to the clinic, but if there are questions to be answered _____ to the lab and study with a more _____ questions.

Audience: Thanks.

Bottino: _____, I think we need to start thinking about doing a way with the phase 1 is for MTD, phase 2 is for efficacy _____. So, ultimately, we wanted to continually learn about both as _____ but right now _____ are being used in phase 1 is answering the question how _____ but still using the same number of patients and the question is how _____ before investing in the next level of development and that's a very different question but you might be _____ to properly define the dosing strategy but at the same time, you should be learning about efficacy as well. So this idea of _____ phase 1 _____ and phase 2 when you have more patients you could be testing different doses but _____.

Audience: _____ University. I have a question for _____. When you are presenting your _____. How much of that was because _____. I'm sure you can sort that out.

Bottino: Yeah, yeah. _____ efficacy was ultimately less than just _____ toxicity so then when move along _____ so you get an effective loss of efficacy just because you can't get to the doses you need to _____.

__: So for sure, there was _____.

Bottino: _____ toxicity. Yeah.

__: _____ single mouse you can find the synergy _____ but there has been _____ when you get the benefit from combining two doses is because maybe some patients will respond to drug A and some will respond to drug B _____ you get the response. _____.

Bottino: Yeah _____. Yes. _____. So the findings of the model that is shown is continued on the fact that patient tumors are like seen in rats when really they could be

mixtures of multiple tumors. In this case you might get benefit from the combination. It would seem _____ model and I'm trying to remember the name of the presenter _____ who showed exactly that a lot of clinical studies that in all synergy can actually be explained _____ patients.

__: Adam _____ .

Bottino: Adam _____. Right, right. Yeah, _____. But ultimately I believe, the finding _____ started wondering whether we were doing the wrong thing by chasing down synergy _____ exactly for that reason. I always _____ proof of that.

__: _____ paradigm. What is the MTD to how confident do I need to _____. As a model and that's the concept, that's intriguing to me and that fits in with _____ about deviating from those _____ and seeking towards more individualized therapy so we can actually have optimal therapies at the time of approval _____ studies. _____ paired with clinicians and regulatory scientists who might say, oh, we can do it just by using the MTD _____ approach where we can actually be answering in our clinical studies. _____.

Bottino: That's a nice question. So my first answer will be _____ at the right time. We have to start _____. This is our confidence region around the declared MTD. Let's call _____ probability of phase 3 success. If you _____ starting as early as possible and this is really hard because phase 1 is _____, but if it could be done, you _____ of this is a spread of possible phase 3 outcomes and it goes from _____ 1.4 because we only have 17 patients so far, but as we find—we'll keep looking at this dashboard to see if our certainty increases. That's _____ right now.

__: And it would seem that we would need to have more advanced models to put into that dashboard so that we can have _____ in relationship of the changes we're seeing _____ in patient and how that relates to the ultimate outcome that _____.

Bottino: I think someday _____ and things like that. If there were some would be relevant in driving tumor size changes and that if you have a strong dedication, that dedication

that you believe is _____ and overall survival or _____ benefit, then even with those first two patients, _____ you can start making those projections _____.

__: Okay.

__: _____.

Bottino: I will answer that. _____ it's a financial-type modeling on how much delay can you tolerate in a program if it means 2% increase in probability _____ and it turns out to be greater than 0 and I think the _____ in phase 3 but a few months in phase 2 or 1 in terms of _____ value can be very much _____ if you increase the probability _____ came up with this _____.

Jin: Maybe a last question from the audience?

Audience: Can you hear me? Okay. Thank you. My name is _____ we do provide _____ companies. My question is similar to some of the previous questions and may need to _____. I think for a fixed combination even from the small molecules _____ fixed suggesting one single fix. So again if some patients, if we need to _____ or some other patients we need to _____. How in your early research and you know phase 1 given clinical work through simulation modeling. You can generate sufficient data and insight to support the flexibility _____ to get to phase 3 or _____. If you have only one fix _____, you need to be very careful with the patients _____, but if you have, you know, _____ combo versus _____ combo, you maybe targeting two, somehow, different segment patients. That means a lot, right? _____. So I think this is _____. If you have a combo submission _____ another type of the combo by _____ differently component A versus component B. Thank you.

Bottino: Alright. Thank you. _____ in terms of predicting one-time baseline factors _____ are predictive of response _____ to that and if you _____ you can start considering the effects of combinations _____ and basically what baseline _____ are predicted of— what kind of combination of _____ particular patient needs. _____ and then look it up in a table or something and say whether or not the patient _____ dose combination for which dose combination is best for the

patient. I think it could be done right and I do not know _____ patient's data based on _____ simulations of which those combinations are best and then _____ of whether or not a patient responds to modified data _____.

__: _____ for visualization.

Bottino: That's another _____ on baseline when really you should be refining your predictions based on _____ initial response _____.

__: _____.

Saber: We don't have a requirement for pharmacology—what type of pharmacology studies you need to do. You just tailor it based on what you want to show, to prove. So if you believe that those pharmacology combination, pharmacology studies will help you to convince our physicians regarding certain schedule or adjusting the doses up and down _____, sure, go ahead. That's _____ to decide. But again I want to mention that, when it comes to biologics, combo studies are very tricky even if they have monotherapy, it's not that easy. Sometimes the only _____ species is the _____ and you're talking about modeling in the rodent species so that means you will have surrogate probably in the rodent and how _____ of the clinical candidate is that. Thank you.

Jin: For the rest of 10 minutes, I would like to ask a general question, hoping for some additional panel discussion especially we are at FDA and we are kicking off to start _____ initiatives. So I would like to hear some thoughts from all panels. Any idea how, especially drug develop _____ regulators better work together. We help each other. FDA helps _____ also help FDA. _____ initiatives tackling especially some other challenges we have _____.

__: _____ safety. So with that degree, _____ there is a way to _____ to help correct _____ to make those models a success _____ studies.

Saber: So we also recognize that there are gaps and we do _____ drug development and _____ patients. We don't want to expose patients to some therapeutic doses and this is what, I think we're actually doing with some of our _____ specifics and that's why we felt that there was a need to collect data to guide us to see how we can do

drug development better and if you _____ from 2016, 2017 _____ and based on that, there has been actually some adjustment in phase 1 clinical trial design that is _____ therapeutic doses _____ dose is so low. Also in addressing the _____ representatives from industry _____ from NCI _____ March 9th is an attempt to address some of these gaps by bringing every one together in _____ these models. It seems to me that they were not talking to each other and certainly industry was not aware of these models. NCI is funding these programs but they do not know what their regulators need. So _____ discussion to see how we can address some of these gaps.

Bottino: _____ different institutions within the larger industry in academic and regulatory environment is that it helped offset what _____ something like that and then you know _____. So we need to identify that when it happens _____. I like your idea with the clinic. Clinical team wont' go for it. _____ you have to restrict objections to new ideas to people who can actually speak for who they are and not _____.

Jin: In addition to the cross-institution collaborations, _____ is the importance of new _____ are developing minimal models. At the same time _____ scientists are developing _____ models. _____to hear there is a coming workshop in March _____ attendees of the workshop. Do you foresee anything we can do _____ I don't know _____ workshop. I'm actually curious _____.

Saber: _____ will not have a kind of attendance but the first set I think is to make sure you do have the right model before we _____ how to use those models. Yes, certainly that is in the back of my mind. Now, it was the back of mind in September when I attended the NCI meeting and I've asked on that question but I released that we are far from that question because _____ there.

__: _____.

__: _____ comments.

__: No. _____.

__: Any audience would like to _____ comments?

__: _____ with Dr. Saber. _____ that there are some reviewers who _____?

Saber: No, it's not really _____. It depends on the toxicities or expected toxicities and where the dose is in your phase 1 trial. If this is very low _____ minimally anticipated biological effect level, I believe, indeed, is subtherapeutic and patient will not benefit then the trend is do an _____ but if the toxicities are such as there might be a benefit from a pre-design because you want it better access, those toxicities, and your dose is not too low than that's really for the _____ to decide but what I'm trying to say is that once we put the _____ out, the clerical team actually realizes how low we are with some of these _____ when it comes to the actual _____ dose and that's when _____ started on _____ dose escalation.

Audience: Is there somebody at the FDA are being responsible for _____?

Saber: I think _____.

__: _____. There were concerns about biologic products, _____ of the fact that often the toxicities maybe delayed and then somebody said there's really no reason to be working _____ toxicity _____ products or the _____ flexibility there. If it's not necessary in order to assess of some toxicity over multiple cycles, dose escalation has been permitted. However, because in that previous treatment and particular dose level made altered with responsiveness to a higher dose, we would not use that data for _____ to get a higher dose in cycle 2 or 3 or 4. That data could not support a dose inhalation _____ because of that _____.

Saber: _____.

Jin: Okay. We are few minutes ahead of schedule. This will end our _____ session. We will take a break, 20 minutes break. So I'll ask everyone, please come back at 10:35 for our start _____. Thank you.

SESSION II CLINICAL MIDD IN ONCOLOGY

Dr. Dutta(Moderator): Good morning. My name is Sandeep Dutta. I am from Amgen and I have the privilege of moderating the next session on the _____ Model-Informed Drug Development

in the clinical phase. We have a _____ session of _____ type of treatment in patients followed by _____ and then come back for six short presentations on examples of _____ of MIDD in _____ development which will be followed by panel discussion on _____ speakers and _____ panelist from FDA. I would like to remind all the speakers to use a mouse because of _____ and not use a laser pointer. Our first speaker is Dr. Stuart Bailey who is Vice President of Biostatistics and _____ on Novartis and he will be presented on Beyond MTD Integrating Non-safety Endpoints into Oncology Dose-finding.

Dr. Bailey: Thank you Sandeep. _____. This is a joint presentation on our team. We are presenting _____ team statisticians _____. Dr. _____ mentioned that _____ we need to _____ annual _____ transition _____ presentation _____ I began with the presentation _____ presentation as well. Certainly is that better? Fantastic. Okay. Please _____ before _____ that again. I asked you about these questions _____ just to let you know that some of the details _____ will be _____ office and _____ represent _____ specific _____ and rather than _____ my presentation _____ red flag _____. I think it is actually be _____ if we do not forget the _____ studies of the first _____ drug for combinations into patients so what we think about how we should optimize the endpoints we will use _____ translating activity into efficacy. _____ we must not forget that _____ so they are still _____ safety of the patients. However, we should think about designing studies in a much more detailed way, learning from what we see _____. To me, it is about, on the preclinical side, understanding what we believe the drug do and then generating data to try to validate what we have seen _____ look for difference between _____ and _____. Now, you could imagine _____ mentioned having _____. I think we struggle with that. I would like to see _____ just between what we have seen _____ the ability to validate translation of that information. _____ gained information and _____ which means having real time _____ use for decision-making _____ and not specifically try to _____ design _____ retrospective use that data to answer different questions. We should have _____ mind those

questions _____. There is a lot that should and could be done to incorporate _____ data either from taking preclinical _____ human but _____ human _____ into combinations, translate data from the _____ information with preclinical _____ synergy _____ translate that into what we expect to see in combinations. We also need to think a little bit better how we translate data between patient populations _____. Often we think of _____ studies only once we determine that _____ activity of the drug in adults, and I think that tends to _____ and we need to be a little bit more considerate about how we can potentially generate _____ activity generate data _____ populations and how to _____ translate that _____ to _____ across regions. There is a lot of discussion between Western and Japanese _____ running _____ studies out there _____ go to specific region in _____ diversity giving way between Western _____ Japanese _____ concept. We do not understand diversity to predict the differences in how patients _____ differ _____. Additionally the use of _____ volunteers, we are moving into area where _____ drugs developing may not have the same level of toxicity that _____ in the past and there are questions as to how _____ use potentially healthy volunteers _____ information _____ regions. I think additional thinking is _____ as well as _____ translation between _____ and this is just _____.that increase interactions between statisticians _____ and not just _____ the interaction of oncologists _____. It is no longer _____ how the statistician _____ forward. _____ that every time _____ trials, we are using information _____ as well as _____ to understand the information _____ make the best decisions _____ so traditional challenges. This is why people elect to _____ drug _____ determine _____. Hopefully wise people _____ from that _____ safety has been used. _____ some studies using _____, but it is still important that we do consider safety as controlling _____. I do not see the previous approaches were _____ safety potential so you wanted to be able to _____ avoid overdosing, but there are complications _____. We need to be within a certain or very narrow window where the MTD will be _____ activity or efficacy, so therefore, _____ and _____ timely

fashion. _____ because it goes to why we want to maximize the use of information _____. _____ that we should not be _____ introduce _____ with the same number of patients. We should be looking at the designs that we have put in place, understanding the value that that would bring, the data that we will generate from, so I think we need 50 or 100 patients within the study that would _____ learnings that we understand the value of the data it will bring back to us, so to me it is about finding the best doses and not just necessarily _____ for _____ we talk about that _____, so we need to have studies that allow flexibility in _____ patients into _____, so again, just to look back, generally we have to _____ toxicity data. We use that to establish a starting dose. We have estimated exposure _____ that we expect to see _____. There is discussion about _____ of the preclinical trials and negative predictive value, positive predictive value and they tend to be a little bit of negative _____ some toxicities _____ everything, but we may _____ information _____ dose toxicity relationship. Sometimes _____ sometimes not, but _____ convert it into _____ predefined dose range so you do not have _____ sequence or organizations move to less _____ 100% _____ steps _____ toxicity _____. _____, so if _____ be able to use it _____, then you can do much better than to simply say _____, so _____ relationships, _____ commented on the fact that these were traditionally introduced _____ you could still apply _____ and the goal is to really try to target MTD _____ introduced is kind of _____ challenges _____ qualifications. _____ going back a little bit to this discussion around the fact, for example, _____, it is interesting to know that _____ approach introduces _____, so it is not any _____. It actually is _____. We do not _____ specific in making decision _____ and I think that one of the big differences is the fact how we integrate with clinical we investigate _____ patients. _____ helps to define this window potentially _____ doses that minimize the risk of _____ to _____, so _____, but we actually use _____ from within that range _____, so I may have _____ 20. The ones in the 20 _____ acceptable. I then used my assessment _____ those levels from the _____ the view of the

PK related to _____ where the preclinical data was indicating exposures to toxicity _____, so actually in _____ as to whether we should make this _____ whether we should _____ investigate _____. I _____ of that, but the nice thing around this is that you can incorporate _____ if you have differences between _____ species in terms of the projections for MTD. We incorporate _____. You can allow for a variety of _____ to allow you to slow down to approach _____ as long as you have _____. _____ you are not specifically defining upfront every single dose that you will define maximum steps because we do not want to encourage undue _____ so you would not be _____ dose, but then you have this window _____ data. We have the flexibility to incorporate _____ between populations, so if I have some understanding from the _____ differences between populations or if I want to study _____ differences between the same trial, I believe that maybe some differences _____ I can incorporate _____ data _____ difference _____ demonstrate _____ and this can also then instead of being used as _____ study _____ optimize MTD _____ to integrate with the other data that you have _____ make a decision which dose to use. _____ drug _____ case of an antibody _____, the weight of that other data will then transition as to _____ about _____ if I reached an area of _____. _____, so I would not make _____ steps _____ away _____ I expect to see _____ activity. There are additional approaches that integrate _____ we can incorporate _____. We can do _____ and then _____ approaches I have seen _____ recently _____ extensions of that _____ extensions again. The paper talked about the ability to _____ MTD, so _____ with this is it is a very nice approach to use, but to use it _____ increasing our _____ between _____ safety but then not necessarily _____ a decision and then _____ do this so _____ we have in our team who _____ combination approach. _____ combination _____ safety _____ with _____ exposure relationships based on the _____ interaction between the two and then counting for that within the _____ decision _____, so _____ have to augment _____ left-hand side which is the case where we have studied a few different _____ dose. We have not seen

any _____ and _____ potentially increase up to _____ potentially _____ control to some level, but when we actually _____ for _____ platelets and we are _____ platelet counts over time, so you can imagine we may have seen some _____ changes in platelets. Actually _____ using _____ platelet. We can actually now look at the risk of _____ within a specific time _____. You can _____ potential _____, so if we are to make this _____ slight higher risk of _____ and we get this _____ risk _____. At least, it will be incorporated in the decision making. It may tell us overall _____, so that is _____ safety assessment with other data. _____ actually not expecting to see _____, so _____ therapy, so examples _____ based on the study _____ safety issues with this. _____ patient to 15 from _____. Really it is a question here that it is not just _____, but we may see events later and how to deal with this _____ when we are making _____ decision from _____, but we are _____, so there are a few different form of approaches to do that. We could incorporate _____ data _____ further and then we have an internal _____ reference _____ what we go by cycle the other end, so _____ and it is still _____ introduces the ability to look at those changes that occur within the _____ as well, but it is very challenging when you are in a situation _____ escalation is that _____ developing _____ to keep the patient long enough on that treatment to be able to see _____ investigated in terms of pushing to try to escalate _____ because they do not see _____, and these patients _____ how to be _____, so this formal approach is _____ changes that _____ still have information _____, so another topic around this will be the studies when we are designing a clinical trial, we should be designing it in a framework that allows us to change into _____ reactions of information _____ trial without the need for mention to _____ around the _____ estimate _____, but to perform _____, the number of people _____ the number of _____ so it is a custom to _____ to _____ the time the patients have to wait to get this, but the companies decide to do _____, so that is the smart design to allow to make these changes and this goes back again to the work that should be done preclinical _____ cases _____ only _____,

but we already have studied _____. We should be able to incorporate within _____ flexibility to switch to _____ reaction and example _____ the compound _____ thrombocytopenia and we are able because of the way we approach _____ to introduce _____ treatments _____ because we have not _____ told us _____ at the same time inform us that we should not see any change at least in the activity _____ sense to how about we translate _____, so we know _____ we have _____ that we have exposures related to _____. We know that we also have models that will help us understand _____ changes, the dynamic changes _____ or _____ that would be related to clinical events, so _____ presentation _____. _____ presentation _____ talks about the assessment of finding an optimal efficacy outcome when I am on my safety boundary. We have to understand that safety boundary changes over time, but the challenge can come if the safety endpoint _____ is also related to the clinical outcome, so _____ this case, the _____ also affected by these treatments and we see changes in _____ we may see the occurrence of _____ and there is _____ to be able to look at the relationship between _____ potential _____ and there is also assessment of the _____ that predict patients _____, so how do you look at trying to optimize the outcome, whether going back to investigate _____ treatment to mitigate some of the _____ treatments if that is what is _____ because we do not want patients having _____ but still _____, so understanding _____ to go back to the _____ trials _____ on how to change the frequency of dose _____ and it should not be seen _____ event that we go through _____ should be able to integrate to effort within a company or organization as we are collecting data _____. _____. Just to _____ if that is okay. This was an example for a compound where we had multiple _____. We integrated _____ three different _____ platelets. You can see the reference _____, but this we used within the study to help us understand how to _____ integrated by _____ study design and this also goes how we could consider to support those selections in safety efficacy _____ on assessing the relationship between circulating _____ necessity and ability to inhibit the target with certain _____ within the _____ based on what we can measure in the circulating _____, so

just the same, _____ safety _____. We should design trials that _____ support decision making while safety is in control, but we should not try to assume we could design _____. _____ discussion is that I think we may need to look at _____ studies _____ not just looking at how _____ but _____. Thank you.

[APPLAUSE]

Moderator: So, we _____. If there is one more question? Or questions? If not, thank you. We'll move on to the next speaker. It is Dr. Tito Fojo. He is a professor of medicine, Columbia University , and he will be presenting on _____.

Dr. Fojo: Thank you. Thank you very much and thank you for the invitation. So, basically what I'm going to describe to you today is a novel method _____ analyzing tumor kinetics and this is the summary of it. It actually rose from a disagreement that Dr. Bates and I were having, and we turned to _____ and we resolved it in her favor, and basically what you see here is in blue, what we generally measure in the clinically arena. The patient's tumor regresses and they eventually _____ cannot be achieved in the majority of patients with a solid tumor. What is truly happening during that period of time is that the fraction of tumor here shown by the red dotted line, it is regressing in size here and it is gonna disappear _____. The fraction of tumor which is shown by the green dash line which is the persistent fraction of tumor which is…

Audience: would you please speak into the mic…

Dr. Fojo: Okay?…and the green which is the green fraction of…it is the resistant or relatively resistant fraction of tumor which is gradually growing. At any point of time which you see in the clinic, this is a combination of the sensitive fraction, and this is gonna disappear, and the resistant fraction that's gonna grow. This could all be described by this equation down here at the bottom where the fraction of tumor at the time it's seen, is the exponential of the growth rate times the _____. The exponential result is negative if _____. This is exponential. If you go on Google, what you find is that exponential growth and this is mostly _____ population kinetics. Exponential growth is _____ by Ex and decay by E-x and that is exactly what we are using in our analysis. And we know that tumors grow exponentially and regress exponentially. We're doing

that since the late 1950s. _____ paper by Howard Skipper describing the exponential growth without fault. But we come back in this situation. What you have then is the basic formula, a basic equation which we've shown here. In some cases, you end with a situation where there is no growth at all _____ regression. In that case, the formula's simplified for this. In other cases, you end up with a situation where there is no regression at all, you get only growth. In that case, the formula is simplified again. And some of you may be saying you know we've made it something which is very important when you talk about the fraction of tumor that is sensitive and the fraction of tumor that is resistant but is not here. Actually you can describe a formula which takes that into consideration, where phi is the fraction of tumor that is sensitive, where the sensitive fraction is decaying at this rate, your resistant fraction which is _____ minus phi is growing at this rate, and so, you can better define and incorporate the tumor fraction you feel that is sensitive and resistant. The problem is that this has _____ unknown which is phi. You, therefore, need more data or more robust data, and this we know in clinical trials oftentimes that amount of data is not available. I can't tell you why. I think that a lot of very, very, very smart people think about this. In turns out that knowing phi or not has very little impact on knowing the precise growth of regression. You can get comparable lesson in this, of growth and regression, but the simple formula doesn't incorporate phi. Now, some of you might be thinking, no, that tumors don't grow exponentially. They do, and it's not only the exponential equations that we have looked at. We've looked at countless numbers of other equations. Some of your papers are probably in here and some example of tumor that might be growing exponentially on the surface, is not growing in the center or any model that you might have, we'll be happy to derive an equation, and we'll be happy to put all of our data into it and see how much effective your equation. All of these equations, usually about 1% to 3% of the clinical data will fit any one of these equations, whereas in excess of 90% of the clinical data fit the exponential equations. I've no doubt in my mind the tumor's growth will regress exponentially when treated with essentially any therapy. So this is from _____, and this is from a clinical trial. It's called the Velour clinical trial that used aflibercept in combination with Folfox to determine the efficacy of aflibercept. As you all probably know, aflibercept improved _____ based on this clinical trial. The overall survival had increased 1.4 months. I point that out here because I will show you a lot of data based on

this, and so you know I've not picked any sample that had an amazing result. I've actually picked that have a very, very, very modest result, and whatever I show you works _____. I'm gonna be working for everything else. So here are three examples to treat patient 1, 2 and 3. Their data has been measured using _____. What you see here in red defines the natural measurements generated by the group. Blue or black in this case is a pick of the data to the best _____. We used to take this data and wait to let it have the opportunity to fit Dd formula, the Gx formula, the Dx formula and the Gd prime formula, and the program that helps you which was the best fit. Sometimes you should fit to more than one formula or program that helps you provided the best fit, and what you see here, additional randomly selected and wee picked the better ones to show you here today. This is the amazing tips that you can get for today. It is not that we chose to draw these lines, so we're gonna go through all these points as well as the test. Every point of this line, not just the ones. Every point in this line is defined by a G, and a D and a phi. In this case, it was best that you define the equation at the number of days here. As you can see, the actual measurements adhere to that quite closely. Here's another set of examples, another three individuals. Again, you need dimensional measurements by dimension level. Oftentimes what you see is the fit of the biometric data is the best, in which we end up with a lot of key values. You might ask how well does it fit, how well these data fit with this G value and we basically cover the key value the best. Initially we could start _____ with a phi value of less than 105 which was pointed by _____ talk about data from one individual patient, not from many patients, but in any case, as you can see here, the fit of the value is incredibly, incredibly _____. So this is the summary of the data from this Velour trial as performed in collaboration with the _____ group. In this initial look at the data immediately indicates to you that, in fact, aflibercept was an effective addition. Actually what did is, we _____ experimental arm and which was the control. We figured out that the D was the experimental _____ better or the fact it was. What you see here is the percent of the data applied from the file. This is the unit _____ dimension and the volumetric measurements. I'm gonna show you as we go along, the volumetric is a superior measurement. I'm not proposing it be used in the white robe of Oncology, but it is for research purposes, and I think that drug development will probably be the optimum way to assess tumor measurements. So, what you see here is the percent of the data which is usually 10% or less, and this is true regardless of which they present

_____. While we can't get meaningful data, sometimes it's just one point beyond studying data. Sometimes, it's just two points, and in those two points are more than 20% difference. We all consider them meaningful, and we chose this over a decade ago when we started doing this, so that we would be accused of taking data that we since might think was inaccurate in measuring data. I think with our more sophisticated measurements that _____. What you really want to know is once you've eliminated the data that does not exist, 1% of the data does not fit any of the month, and that usually is something between 5% to 10%. The rest of the data fits something. The rest of the data fits 1 of 4 of Dx, Gd, Gd5 or Gx. You could see by looking at this, with gray representing the bars, the distribution of the rate of models _____ what's happened to the experimental arm, and immediately you begin to see this _____. Specifically, engraved here at the percent of samples that fit the Gx model the best. This is actually the one you don't want to fit in the drug which has exponential growth, but you can see the pattern of growth percent in green. Regardless of how they're measuring, there are fewer fits to that model, and what you see in red is that there are more fits to models that have a decay rate as part of the equation, so what we're seeing here is that we've taken it away from tumors which are growing to tumors that are now "growing and depressed". When you look at the G-values and this is the median values, you can see here the G-values for the experimental arm and the G-values for the control arm. You can see the ratio of the experimental control. As we go to the volumetric, you can see that that ratio is much less. The volumetric is in fact able to detect the differences between these two experimental…between the experimental and the control arms much better. Now here is a depiction that I like but not everyone likes it, but what you see here is to the left are the slower G-values and to the right are the faster G-values. In blue or teal is the control arm. In pink here is the experimental arm. What you can see is that the experimental therapy has in effect brought in all of these tumors that were misbehaving in the past three values and reduced their rate and as a whole made it for the entire arm to have a lower G-value. Again, as you can judge from that, the experimental arm isn't the performing value. Here you can see the median key value and you can see that there is basically no difference between the D-value and the experimental arm. This is what we see time and time again. Experimental therapies, the ones that we use today, did not accelerate the rate of tumor decay. Now, remember this is a rate. I'm not saying that they don't kill more tumor, but the rate at which tumor decay occurs is not

being impacted in the experimental therapy. Here, it is rapidly depicting, in this case _____ description of it, just so you can do it _____. You can see the experimental in pink and the control in teal are actually comparable in terms of the distribution of the D-value. So what does this type of analysis allow us to do? If it could allow us to do all of this, then the answer is yes, and I'm sure that these months at a time. Does it discriminate between two arms? Absolutely. What you see here is a depiction of the rate of growth for the control arm and for the experimental arm. _____. You can see that the median for the experimental arm is less than the median for the control arm. This is unidimensional data. Bidimensional data, instead of seven zeros for the key value, it's now nine. The volumetric data is seven. The key value is eleven. What you're seeing is volumetric actually magnifies the differences between the two arms and that's why I think this would be a valuable way to measure clinical data so that we can move forward even faster in the development of drugs. Theirs is a correlate with PFS. What I've done here for you is we've taken the D-value for the entire data set and divided it into four types, and then passed as a correlate with PFS. There is some pink here. It's the G-value of the slowest growing tumors. This is the G-value of the next slowest. This is the G-value of the next slowest. Over to the left, you have the fastest growing G-values. As you can see, a remarkable correlation with PFS. This is the unidimensional measurements, cleaned it up a little bit more. We go to the five dimensional and even more we go to the volumetric. Now I know what you're all thinking. You say, boy, that sounds really good correlation of G with PFS. Actually you're wrong. PFS actually correlates really well with G. The gold standard here is G, not PFS, and I have a bias. _____. There is a correlate with all this. At the end of the day, that's what you really want to know. Again here are the _____. That's the slowest _____, the next slowest. That's the unit measurement, gives the biodimensional. You can see a remarkable correlate. Again this is data that was obtained exclusively while the patient has been enrolled in the clinical trial and we captured the data that was obtained at the time and only during the period that the patient is in the process and we're able to remarkably predict the overall survival for these patients. Now you want to say, okay, so maybe the Volpak people are really good. You don't have to mention it, they know very well. This is true anywhere else. What about comparison to PFS? We tried to do the same with PFS and it was very difficult. Actually you can get pretty good regression between PFS and OS and when you get it down

to about 150 patients and you've eliminated data from PFS or OS, PFS and OS are the same. As you can see, this is just a few hundred patients and the data that I have shown you had over 500 patients in analysis. Is this something that is unique to Volpak or unique to colorectal cancer? No. We had shown this previously in prostate cancer and we published it last year. If you go the Project Data Sphere where a lot of data is housed, they have a warehouse, you see the correlation in pancreatic cancer between the G and the overall survival. The key here is that this is data from three separate files and it has been blended altogether. You get a G-value in pancreatic cancer. It doesn't matter which trial you were on. It correlates with overall survival. This transcends clinical trials. What about breast cancer? _____. Not only does it transcend clinical trials, here you have a combination of both control and the experimental arm. _____ prediction of overall survival. This is renal cell cancer. This is Sunitinib and interferon combined. You need to see that it doesn't matter whether it is a targeted agent or immunotherapy. It all combines to give you robust data. Here's Sunitinib alone, and here as a surrogate for immuno-oncology products. On Project Data Sphere and certainly with the Volpak group especially, we'd be delighted to get immuno-oncology data analyzed. You can see again a remarkable correlation between G and overall survival. So the one last point. We use it to decide which phase to study to move forward. Could we benchmark other clinical trials with the use of guide therapy? And the answer for that is yes. What we have done here is we have taken the data from the control arm as the reference or as the benchmark. We have been taking the data from the experimental arm and gradually pulled up one at a time, at which point that commonly patients, the data from having patients have been pulled, doing a thousand resamplings with _____ and the number of patients with unidimensional data is four. If you take the data from the bidimensional measurements, you only need 33 patients. If you take data from the volumetric analysis, you only need 27 patients. What I'm telling you here is active into this clinical trial that had a 1.4-month survival advantage. We used a benchmark, 27 patients, _____ this was the superior treatment than the control arm. And then finally this is the last _____. Does this apply in the real world? Absolutely. So _____ also worked at the VA in the Bronx in New York where we have our laboratories. And actually you can go into the VA data which is called _____. It's the largest free source of data in the world. This is just a small portion of it. This is in prostate cancer, and I will just tell that this is one

therapy and this is another, and what you can see here is that by just looking at 36 patients who seek one therapy, I can tell you that it is statistically inferior because it has a faster growth rate than this patient over here. The reason is because we have 928 patients in this patient population in this comparison, and that becomes such a large robust and reliable dataset that you can benchmark against it, so soon, when we get around the publicists, we'll be able to tell you an individual, for example, how well the patients did. I could probably be able to tell you how well patients that are 85 years old did compared to the rest of the population because we are going to have a dataset that is several thousand, actually over 5000, and you can ask any question that you want for any small set of patients. So you can see the benchmark, you don't need _____. So finally what we plan to do in collaboration with the Volpak group is to make this even better by incorporating _____, and then here at the end, at the top or five of us who have been fanatical about this for the last decade and poured blood on it, and then at the bottom highlighted in red, new colleagues in Volpak who are incredible and whom I'm delighted to be working with, and all the other people _____. I want to thank you for your attention.

[APPLAUSE]

_____: You kind of assume that you have resistant and susceptible cells initially. Does it make sense to incorporate and plot the distance? Have you tried that and need it?

_____: _____ after some time in some patients.

Fojo: So sometimes the data, we analyze and form data when they actually get cured, then you find that there's no existent population. That sort of data fits the DX model, _____, so otherwise you will find that there's a growth rate in every model that you mentioned with detection very early on, and it is a constant that you emphasize, so it's the same growth rate _____, but what you are really measuring is the growth rate of that _____. You don't have the resistance. I'm sorry?

_____: _____.

Fojo: Yeah, so what you're asking is…right, so what you're asking is could we see emergence of resistance? And the answer to that is that the data suggests that they're pre-existing, so yeah, it might a very very small fraction.

Audience: _____ Answer to your question. So thank you so much for the last…the first question is, what do you think about the duration of the tumor band? Does it mean we're getting actually a decline in the tumor's anatomy and we're retaining that duration, so can we summarize, you know, the complex tumor dynamic with a single parameter which is the slope of the growth? That's my first question. Because it does not actually capture the duration of response. My second question is going to the premise about using our model for the growth. We know eventually things plateau off, so the best answer is maybe plateauing off or an e-max, so maybe a more appropriate model would be better than _____ growth of the tumor and how can you handle the lack of measurement, because after BFS, there is, you know, patients actually switched and we're not tracking them for progression, but tracking them for survival. So measurement is actually a sensor in solid tumor.

Fojo: _____. We only use the data that's available from the frontal product, and yet we're able to _____ the overall survival. So with regards to your company, I'm not quite sure I understood either of your questions, to be honest, but how I understood it. So, I mean the rate of growth is a constant and it continues, continues, continues, continues, and in fact, we have data on some patients especially for example the Sunitib trial where they stayed on that study for years until they had progression and I'm talking over a thousand cases, taken over a thousand cases. The rate of growth remained constant. What that says, which is why I thought you were going with your first question. In fact, maintenance therapy seems to be effective with some growth in some cancers because it maintains the rate of growth intact.

Audience: So clinically you think that the tumor dynamic can be summarized using a single parameter.

Fojo: Absolutely. Well, it can't be summarized using a single parameter. You need a growth and you need a regression rate constant, but clinically for patients, the only one that's important is the rate of growth. _____ tomorrow, next week, next month, or next year. As long as it stays the same. All you care about is how fast is the one who has had benign growth.

_____: So if the tumor is not growing, you know, which means the duration of response is prolonged, that actually can give benefit in terms of rate of survival.

Fojo: Absolutely.

_____: What I'm trying to say is, these models are not capturing the duration of the response but actually the depth and the growth rather than maintaining…

Fojo: Except that the growth predicts overall survival. Actually we've done that, but we have very granular data. We can actually predict an individual's overall survival with uncanny accuracy actually, to be honest.

_____: Thanks.

Dr. Roy: Amit Roy from Bristol-Myers Squibb, thank you very much for your very nice talk and also for the decades of work that we've all followed with you.

Fojo: Thank you.

Roy: I had a couple of questions as well. One relates to the use of all the data. In the example that you showed, the percentage of subjects who only baseline measurements were there were roughly the same. I am surprised they balanced out. But I just wanted to sort of make the point that oftentimes data, only baseline measurements are available

in patients who progress very very rapidly, and then there's an imbalance between the two arms, so there is informative censoring, if you like, so that might be important to take into account in particular. That's the first question. The second one is, I was wondering if you'd look to see how sensitive the growth estimate was to the number of data points that you actually have because especially in early-phase medical trials, there is a lot of very very _____ patients have grown sequentially. The estimate of the growth may depend or may change as you get more and more data, so how reliable is that estimate based on how many samples are there?

Fojo: Alright, to answer your first question, so fortunately the majority of trials have equal number of patients who have data that is inadequate, but obviously there is a greater balance here and we have to take that into consideration. To answer your second question, so, you know, if you give us two parts, we'll draw a straight line for you, so that's that. So you need a minimum of three points really. And by four points, usually you've nailed the growth rate. Actually what you've done is basically have enough up to three, up to four, up to five, up to six, usually up to three and for sure after four, the confidence interval of that fully encompasses the confidence interval of the more mature data _____. So with three or four parts, you can do it. You know, it's actually…if you really want to do this and do it quick, you just need to get points a little more frequently, you know. You don't have to say, well, I think if four points are two months apart, it's going take me eight months. If you get 12 points a month apart, that's good. You know, you need to see how noisy your data is basically, about three to four months.

_____: Thank you.

Dr. Zheng: This is Jenny from Pfizer. I really like the topic. _____ is that the three-dimension measurement of the tumor size is important. My question actually is related to the previous question. Your model _____ clinical trial actually more frequent than tumor size is actually measured, _____ so basically all information is unable for you to define rather than the tumor growth as seen in a

later time. So I'm just wondering, theoretically speaking, knowing the trial, knowing a lot of data, there is supposed to be better measurement and more precise measurement than seen. How do you explain which is actually better? _____.

Fojo: So I think, to answer your question, so there's two things. One, the rate of decay is always much faster than the rate of growth by several fold. That's why we're concerned that the tumor has regressed. Actually we can calculate a rate of growth before there's growth of the tumor, and you know, if you think that three points, the first one's here, the second one is here, you draw a straight line, the third one should be where that straight line goes down. The fact that that third one isn't and has veered away from the trajectory that it should have been following is because there's a hidden component to the tumor that is growing and pushing that out, so usually by the third time point, even if it's declining, we can calculate already the growth and advances. We actually compare it to prostate cancer quickly. How mature if you do this would there be PSA growth, PSA velocity? It's basically eight months on average if you can do this or calculate the growth rate _____. It is faster in decay.

Zheng: _____ information, in my experience. I think that maybe that primary care needs more information about the people. Maybe that's why you _____ but from an observation perspective, I think it would probably be a small precise estimate. Thank you.

Fojo: So I'm not quite sure what you were saying, so the G-value actually has information about the drug effect _____, so you do get a lot of feedback, which is why I think it's overall fine.

Zheng: Thank you, thank you.

Turner: David from Merck _____. Quick question for you. Do you use these G-values in care of an individual patient? Would you ever tell a patient his or her G-value?

Fojo: I would be willing to do that and I think we're going to get at that point. You know, I mean, we tell patients a couple of times, you know, and so PSA velocity, and really discuss these things. Not really, but, you know, we factor them. We start to tell patients what your CA 19-9 or your CA 125 is growing, so we're trying to show you data in pancreatic cancer and showing the same thing, so patients put a lot of faith in them. At some point, we're going to have to tell them not only, you know, it's going up, but what is the rate it is going up. Eventually it'll be less about telling the patient than about knowing it, and the decision of benchmarking it with what will become an enormous amount of data that we'll have as a reference. _____.

Moderator: If you can hold your questions because we are _____. There is a panel discussion at the end. Please do come back for questions. It is generating a lot of questions, that's great. Our next speaker before we break for lunch is Jeremie Guedj. He is a research scientist with the French National Institute of Health and Medical Research, and he will be presenting on _____.

Dr. Guedj: So thank you first to the organizers for giving me the opportunity to present today. So let me start first with a sum…short terminology of what we call survival analysis or time to event analysis. So what is a time to event? So even some things that happened at about a long time ago _____, it can be the appearance of new lesions, or it can be also a positive, even like a cure. The main methodological issue that comes back to the question that was in the audience is that of course this event is sometimes observed, but it can also be sometimes not observed in many contexts that we are interested in. That's what we call the absence of it. It means that no patient lived until a certain time. _____, but we don't know what happened after that, okay. So that's the main methodological hurdle that we have in this sort of survival analysis. So in survival analysis, the instrument

tool that we are using is the hazard function, okay, so that the function H(t) that defined the instantaneous rate of experiencing even a time t, knowing that the patient has not experienced yet even the x t. So from that function H(t), one can derive the survey mode _____ and one can also adjust the variables to evaluate the effect of the baseline covariant on the hazard function and basically how covariant affects the hazard function and that's what it's used in proportional hazards and Cox's function. So we have typically in our framework longitudinal and survival data. So we have time to event data and we have longitudinal measurements. Typically the longitudinal measurements that we have are PSA…excuse me, I'm sorry. So we have longitudinal measurements. It's typically tumor size or PSA. I'm sorry, I don't know where they have it. Give me five minutes.

Moderator: I think while we wait because it's a little past…maybe we can take some questions for the previous speaker, if you don't mind.

Moderator: _____ argue within the audience.

_____: _____.

Moderator: How about then in this case let us break for lunch and we start——

Guedj: I am sorry. I think that with the jetlag —— I got some charts. I am sorry. So let me resume my presentation. So we have longitudinal measurements. Typically it is the tumor size, but now in this presentation what I will focus on is the PSA. Okay? And typically what we are interested to know about kinetics, PSA kinetics that is nonlinear. And you know that in pharmacometrics, we like nonlinear models which are defined by ordinary differential equations because we believe that these models carry all better representation of the biological mechanism that we try to address. So we have basically longitudinal measurements any time it will be needed. And we can have two slightly different objectives that sometimes people do not really distinguish. So the first objective is how can I characterize my nonlinear kinetics, my PSA kinetics, my tumor size kinetics in the presence of a time-to-event? Okay? How can I characterize the fact that I have this PSA kinetics that I want to attempt to model, but I know that

there is also time-to-event data that I need to take into account. And we will come back to that issue that is informative setting. The other objective that can exist and that we can have which is often the most important is how can I characterize the impact of this kinetics on my time-to-event? How can I characterize how the effect of my PSA kinetics, of my tumor size kinetics on the risk of experiencing the event and especially survival time and time to death.

So the easiest and crudest approach to do that is to use a Cox Model with a time-dependent covariate. Okay? That is something that you can already do, easily do. In our package, we can —— we have software to do that, and basically you incorporate, you plug —— in your survival model, you plug the observed PSA value and you make the assumption that the PSA is a piecewise constant function. The problem is that —— this approach posts two problems. The first one is that theoretically it is problematic in a Cox model to incorporate an endogenous variable. So a variable that is virtually in the individual and that is directly dependent on the time-to-event because basically if the is patient experiencing event then you will not observe this variable anymore. So it is an endogenous variable. The other more technical issue is that as I have said you assume constant, piecewise constant function and you do not characterize really what happens between different time points, and second, if you want to make a proper estimation, you need to have a lot of data and you need to make sure that you have data for the measurements in all the patients at all event times. Okay? So that is often incorporated. And it is not for very long, actually since the '80s that this approach can lead to spurious parameters to it. Another more sophisticated approach is to use what we call *two-stage* approach. So basically in two-stage approach, if we come back to this #3:43_____ symbol of PSA kinetics. You can fit the PSA kinetics of the patients for instance using a nonlinear mixed effect model, and now what you really plug into the hazard function is directly the prediction from your model in the hazard function. So that reduce the values, but it does not enumerate all the values that comes, that you could have in the Cox analysis, and that again is not for quite some period of time. Actually to be a little bit more balanced, I would say that this approach works pretty well when you do not have much missing data. But the problem as

again was submitted in the previous talk, comes from the fact that —— actually in #4:33 _____ you have missing data and you have informative missing data. And what I mean by that is that the probability to not observe the biomarker directly depends on the truant biomarker value. So let me try to exemplify that a little bit more clearly. Okay, we have this #4:53_____ patient. Typically the PSA declines and then regrows its condition. In that phase of regrowth, it is very likely that the condition of the patient deteriorates or that he experienced directly the event or that he is considered as nonresponder to the treatment anymore and then he decides or it is decided that he has to drop out of the study. So for one reason or the other, the probability that you will not to follow this patient probably now is high. On the contrary, to compare with the patient right here in green that starts with a much lower PSA and let us say responds much better to the treatment, the PSA entity remains low, and in that case, it is much more likely that you will follow this patient for longer period of time. So what that means in practice is that poor responders are more likely to drop out of the study even while good responders will become overrepresented as time goes by which means at the center of which you are doing your two-stage estimation becomes less and less representative as time goes by.

So basically, the problem is that as I have said some parameters in two-stage of kinetics will be identified only in survivals or at least will be precisely identified I should say only in survivals and that may create a bias in survival parameters and what we will try to bring forth in general in my opinion is that it tends to underestimate the impact of the dynamics of interest, the PSA, the tumor size on the survival. Okay? So there are some other issues that —— we can keep them for the other panel later. Now, again, regarding the other objective which is what about just characterizing my longitudinal kinetics? What about just characterizing my PSA kinetics? That is what I am primarily interested in. I do not want too much to understand the impact of this kind of things on my survival. Here, I would be careful, but when I try to look into the different examples comparing two-stage versus more sophisticated approach, it seems to me that again some people may comment on that, but in my opinion, I could not find convincing examples of the very strong bias that would be induced by two-stage analysis on the longitudinal

parameters. Okay? So I am not talking about the survival parameters but longitudinal parameters. But again, be careful when you are doing two-stage because the typical diagnostic plot that we can make like typical VPC are of course misleading because of this informative censoring.

So what I would like to introduce in the talk is a joint model. So basically in a joint model, we try as indicated by the way to combine together the longitudinal part and the survival part. So we have the longitudinal part a nonlinear mixed effect model, okay? —— this random effect —— and the survival part. The most simple combination that we can think about——we can imagine more complicated stuff——but just for the sake of simplicity, I kept the same framework as before. We have the hazard function, baseline hazard function, and then here, we have a function that——[all right. Please. Please. Okay. Sorry.]——and then directly incorporate in the hazard function the prediction from your longitudinal model. Is this better, Jin? Okay. So here, you really can have the longer PSA for instance or you could have the AUC or it could be the derivative of your PSA, whatever function related to the PSA. So what has long limited the use of joint model in pharmacokinetics is the difficulty to estimate the parameters. So, again, I will not go into the details, but when you calculate a likelihood of a joint model, you can see here the contribution of the longitudinal and the survival part, and both share the same random effects. Okay? And then if you want to calculate the likelihood that means that you have to calculate this complicated integral whose dimensions directly equal to the number of random effects. Okay? And the main difficulty is that for long we did not have really good numerical tools that is able to calculate and therefore to maximize this likelihood. So in the recent years, there has been an extension of the SAEM algorithm in Monolix that allows now to do that, but there are also some ways to do that in NONMEM. Some people can comment on that. And that's the approach that we used into that project.

So for the sake of illustration, we have 600 —— we have 600 patients from the phase 3 clinical trial in prostate cancer treated with docetaxel. So we split the sample in two: first 400 patients that will be used as training dataset to concentrate in our model and then the validation that I said on 200 patients that will be used for individual dynamic prediction, #10:13_____ effect _____.

So you can see here the two startup data that we have in the longitudinal measurement. Patient increased before treatment in black and then declined initially under treatment in red and then they stopped treatment, but in that the starting PSA continue to endure, and we can see the increase in PSA on the time started. In here, you see the survival in the Kaplan-Meier curve in that population. So in the Infectious Disease model —— I do not have much experience in Oncology #10:46_____, so when I was asked to supervise the project and to analyze its data, well actually I used what we do typically in Infectious Disease when we want to model the effect of treatment. We have two populations: those that are sensitive to treatment and those that are resistant to treatment. So I have tried to apply the same concept to PSA kinetics, and so we have cells that are sensitive to docetaxel and cells that are resistant to docetaxel. So when you start a treatment, the treatment will block the proliferation of the cells, but it will not act on the resistant cells. Okay? And what you measure —— the PSA that you measure in the blood —— is the sum of the PSA produced by those that are sensitive and those that are resistant. So I will not enter into the mathematical model that is pretty standard in the field. I am just going back to the question that was asked before. Here, we have some carrying maximum capacity precisely to avoid that the PSA kinetics will try to interfere with as time goes by. So the survival part, as I have said, we have a baseline function at 0 which is called the Weibull function, and then we tried several link functions, so several possible ways by which the PSA can have impact on the survival. So we can assume no link or that just the initial PSA really matters or determined PSA or the slow growth in PSA or the area under PSA or something a little bit more interesting which is the sum of the sensitive and the resistant cells. And, again, that comes back to the previous talk where the previous speaker nicely illustrated that probably when we look at treatment sensitive cells, the impact of treatment sensitive cells and treatment resistant cells on survival that might be very different, and that is exactly what this model tells basically when the PSA will regrow after the end of the treatment that will be treated by this R cells. So we expect this beta prime to be larger than the beta, okay, to be consistent with the previous presentation. So what I think of this joint model is that actually it does not complicate much the approach. I mean once we have the good

software, we can choose to more or less reuse the same methodology that we are used to in longitudinal traditional nonlinear mixed effect model. So you can calculate the BIC of your different model, look at which one provides you with the best fit. And here, we could find that the model providing you with the best fit was the one considering a differential effect from treatment sensitive cells and treatment resistant cells on the PSA, on the PSA kinetics. So basically that is how the prediction would look like. The gray area is the parameter during —— is the parameter of treatment, and before treatment, you can see the PSA increased. Then the PSA starts to decrease when treatment is initiated, and there is in some patients an escape from the treatment that leads to an increase in the PSA. And the nice thing with joint model is that you can directly predict the hazard function of your patient from time's view to the initiation of the treatment. Okay? And you can see here the decrease in the current capacity. In fact, at some point, the PSA would stop increasing exponentially and will start to plateau.

So then, if you remember, we had split the samples in two: one for the training and one for the validation. So now what we said is *okay, we fixed the joint model.* We fixed the population parameters, and we just looked at the PSA in my validation sample. So patients that we have not used up to now, and just using the PSA of these patients, can I reconstruct the survival of these patients without looking at it? So that is what we did, and we predicted the PSA and used this PSA into joint model to calculate the survival that we predict for these 200 patients. And what you can see here is that this red prediction nicely overlays with the Kaplan-Meier in this population. So, again, I mean let us not be too over optimistic. It is an internal validation and it is clear, but at least it illustrates how a joint model when it is working allows you to actually reconstruct the survival just by looking or just by analyzing the longitudinal kinetics. So now, the last couple of slides, we are interested in dynamic prediction. So what we mean by dynamic prediction is this difficult situation where we have the new patient that enters the study. We have our joint model. We have an idea of how PSA and survival interact or how PSA impacts on survival. We have a model of PSA kinetics, and now we ask, *Okay, I'm following this patient for a certain period of time. I have three PSA measurements, and now what can I*

see from this patient? How —— what can I predict after the three observations for the survival of my patient? So basically what we are interested in is to calculate the probability #16:16_____ of survival in that patient individually. So to do that, we used the same approach. We fit all the parameters on the joint model and then try to calculate the individual parameters of this new patient. To do that, we do not want just to have one estimate. We do not want just to have the EBE, the empirical Bayes estimate of that patient. We do not want to have a median prediction for that patient. We want to take into account uncertainty and the fact that if the patient just entered the study there is probably a lot of anxiety that needs to be taken into account while we make the prediction for that patient and that on the contrary over time when we incorporate more and more data, this uncertainty will shrink. Okay? So we need to take this uncertainty into account and that is what we did here by calculating the full *a posteriori* individual parameters of this patient using Hamiltonian Monte Carlo in STAN. Okay? So basically that is how you —— let us compare these two patients. Okay? This patient will die in month 24 and this patient will be censored in month 24. Okay? That means he is alive month 24 at the end of the study. So we find that just to include the initial measurements, we can see that in predictions for the PSA are roughly the same. That makes sense because the only information that I have included is the usual PSA. In survival, they are very similar. There is some difference, of course, because they do not have the same initial values and so that impacted the information. But more or less it is the same. Now if I incorporate more information, you can see that the fit of my PSA improves and that the interval, the prediction interval tends to shrink over time. And if I am following this patient for a sufficient amount of time, what we call the *landmark*, at 12 months here you can see that I make a very strong prediction of what will happen one month later on. At month 24, for that patient, we predicted the survival will be very low while for this patient the survival is much higher. So again that is example that shows how that could be used in practice that we need to take into account absolutely the uncertainty that we have and the fact that this uncertainty depends very much on the amount of data that we have accumulated. It is a very simple idea, but we need to keep that in mind. So now, what we need to evaluate with the predictability —— that is just an example.

We need to have the metrics to evaluate really the prediction and the capability of this model. So to do that, again, there is nothing really new with that, but statisticians have developed tools for decades. One —— and it distinguished generally the capability of the model for discrimination and the capability for calibration. So what we call by discrimination or what we call the area under the ROC curve is the capability of the model if we have two patients that one that will experience the event during a certain window of time and one that will not experience this event during the same period of time. Is the model capable of saying which one is at risk and —— which one is the more at risk and which one is less at risk. So that is the discrimination and that is something that we need to quantify if we really want to evaluate the model capabilities. The other one is slightly different. It is what we call the calibration. To do that, we can use the Brier score. So that is entirely different. Now we do not try to really discriminate and compare the ability of making the good prediction between two patients, but we would like to evaluate the capability of the model to really predict the event. Okay? And to really predict when the event will conclude. Okay? And so that is a blind spot and no way to detect. And now what you can do is evaluate the property of your model. And again, the property of that model depends now on two parameters. It depends on the long MAC and so how much information you accept to completing the model and your #20:27_____ how much into the future you want to make your model to be able to make a prediction? So if we stick to AUC to keep things simple —— here, if I just incorporate the initial PSA, you can see that the AUC for short period of in time, so very rapidly after the initiation of treatment is pretty high. But very rapidly, the AUC reduce and gets to a very low levels, so close to 0.5 which means in a single —— if I only have the initial regimen of my patient where really the ability of my model to make this connection is extremely small unless I am really focusing on a very short period of time at the very beginning of treatment. However, if I incorporate more information, if I have the 6 months or the first 12 months of treatment, then you can see here that the AUC tends to be much higher and is close to 0.7. Okay? So if I incorporate the year of treatment, now I start to have good capability for discrimination.

So just to finish, on the use of joint models, we can see this recent review that was published in BMC. It is clear that, I mean, it starts to grow. I am not sure that we can really talk about an exponential growth in the place, but there is more and more interest from the industry and from the academy. I wanted also to have like that —— cancer is not, I mean it is one area of research for a joint model, but there are others like HIV, transplant, or cognitive decline where it is also used, and the reason for joint modeling —— again, there are different processes for joint modeling even though I focused here on how to characterize the impact of my kinetics on the time of treatment. There can be other interests for doing joint models.

So in conclusion I hope —— at least I have tried to convince you that joint models are needed for two purposes: to characterize the longitudinal process, increase #22:32_____ informative dropout, to assess the relationship between the longitudinal process and a time treatment data. Okay? And it has long been limited to do in our models, but we now have the tools to use it in pharmacometrics even if there are still some technical difficulties that you will face if you use it. There are _____ you could see that there are still some difficulties sometimes to calculate the likelihood when we are working with models that are too much complicated or defined by the length of time it is used. Also there is an order —— I mean joint model as I have presented here has also the drawback of its virtues. It is a fully parametric model and we need now to really evaluate different parametrization, how the parametrization impacts on the prediction that we make and so on. Okay?

So what is the future of joint models? I think that we need now, now that we have to choose, we really need to evaluate that properly. There is a lot of expectation that joint models can be used to improve and to optimize drug development. I think there is a lot of interest in particular on how we can make the best use of phase 2 to optimize swift phase 3 trial, in particular probably increase the #23:50_____ of phase 3. Can we early demonstrate that phase 3 trials are in danger or on the way of a failure? So there are a lot of descriptions about that, but now we need to address that properly and really evaluate if joint models bring something and to what extent it brings something. I think also that we will need also to be more realistic, to take into account the fact that in

general there are not only one-time treatment but there are several. I did not talk here, but you could also think about new lesions from #24:28_____ modeling, treatment approach whereby you can _____ after dropout, after change of treatment. So a lot of these things need to be taken into account, and again, there are also things to do outside drug development. It is the benefit in the treatment individualization outside any issue of drug development of therapeutics. It is how we can really use this kind of dynamic prediction to help distinguishing in the patient to early detect the patients that are the most at risk, those that would really benefit from change of treatment. Okay? And again, to do that, we believe — I think just you know make a risk evaluation and the best way to make a realistic evaluation is to make a randomized clinical trial in which you will evaluate whether this sort of dynamic prediction will really bring something.

And with that, I would like to thank my former PhD student who collated all that work Solène Desmée who is now an assistant professor in France and this work was supervised by myself and France Mentré, and it was funded by Sanofi France.

Thank you very much.

[APPLAUSE]

Moderator: Alright, please take your seats. We have a really tight session. We have six speakers in 90 minutes. In this session, we are going to talk about some inspiring examples of MIDD clinical development. We are going to kick off. Every speaker has 15 minutes, so if you can keep your thoughts down to 10 to 12 minutes, then you can entertain a question or two. Otherwise, please hold any questions until the panel discussion at the end. So we will kick off the session with Dr. Michael Maitland from Inova, and he's going to talk about…give us a clinical perspective, which will be followed by case examples.

Dr. Maitland: Thank you. So, to help ease you back from lunch, we're going to give you a presentation that's a little less heavy on the quantitative analysis and instead focus on clinical perspective. The title of the talk is bringing the community fair setting into the learning versus confirming paradigm. I have to thank the meeting organizers, most specifically Rene Bruno and Yanan Zheng. Arguably Dr.

Zheng's paper at VIA in 2007 is the inciting event of being here today. We were wrestling at that time with ways to shrink the size, shrink the timeframe of phase 2 clinical trials, and it was his modeling analysis suggesting that change in tumor size in lung cancer patients at the earliest time of assessment on clinical trial might be a quantitative marker to be used to predict whether drugs would ultimately improve progression to create overall survival. So that was the inspiration. Then what kept me going in this field was Dr. Bruno approaching me at ASCPT several years back and saying, you know, conditions don't really understand what all of us are doing in the modeling space and we had a few ambassadors to sort of preach to your community. So I've been converted, and here I am today to give you some insights on perhaps some new ways. Apropos Dr. Woodcock's comments at the beginning of the session, we might bring about this new paradigm of not just incorporating fully into drug development but actually directly into patient care with greater effect. So I came up with all these lofty ideas when I was in the ivory tower of the academy at University of Chicago, but two years ago, our team took a leap of faith to come here and work at a place most of you have never heard of, the Inova Health System, so now when I give these talks, I have to introduce you to Inova. We are a hospital and health system. You are here today at the FDA in the state of Maryland. You likely flew in through Reagan National Airport in Alexandria or Dulles Airport in Loudoun County, and our Inova Fairfax Hospital flagship is located right here, about a 30-minute car ride from FDA. Each of these green pins represents either one of our major community hospitals or a major ambulatory care center. The relevance of this is increasingly we find if we want to personalize therapeutics and have real impact on patients over time, we need to get away from our drug development and clinical trials paradigm into a more of a real-world evidence and implementation paradigm. Inspired by that, the leadership of Inova committed nearly eight years ago to building up its own translational medicine institute, to beefing up the heart, vascular and cancer institutes by recruiting several of my senior colleagues away from major academic institutions that represented these. Most recently, the health system has established its own strategic initiative and brought on site its own venture capital team to function as an accelerator of technology-enabled health care services as well as devices and other methods of

trying to improve the care of patients in our system. Not coincidentally, this great opportunity arose in 2014 when an Exxon Mobile, which had been directly across the street from Inova Fairfax Hospital, decided they were moving back to Houston and left this 120-acre campus and about 2 million square feet of office space available for some buyer. The Commonwealth of Virginia along with Inova Health System purchased the property and has begun to fill it with plans that included our having an ambulatory cancer care center, a laboratory building directly adjacent that is now committed to being cohosted by Inova and the University of Virginia, and then to have next door to that this facility for biotech and health IT. In the meantime, since that's due to open in 2019, I moved my practice to this rather humble-looking community medical office building across the street from the hospital. It's here over the past year and a half that I've had the opportunity to practice in a less academic, more community-oriented environment. Related to the request of the meeting hosts today, I now will just address for you some real-world examples of a couple of patients who I actually interacted with in clinic this week. So patient 1 is an approximately 30-year-old woman who presented in 2014 with prolonged menses. She underwent an endometrial biopsy which unfortunately revealed endometrioid adenocarcinoma. Patient 2 is a woman in her 30s who also presented with similar symptoms after she initially had an abnormal screening cytology. She underwent her D&C in January 2014, also with a diagnosis of endometrioid adenocarcinoma. They both sought gynecologic oncology surgeons to have unfortunately at such a young age hysterectomy. Patient 1 proved to have stage IIIC2 disease. Patient 2 had stage IIIC1 disease. Given the high likelihood that those diseases would recur, both patients underwent standard of care adjuvant therapy, patient 1 with cisplatin and doxorubicin followed by radiation therapy with progesterone, patient 2 with adjuvant carboplatin and paclitaxel followed by radiation. Both had no evidence of disease for more than a year during routine surveillance. Patient 1 in March 2016 had recurrent disease and received carboplatin and paclitaxel, patient 2 in October 2015 with carboplatin, letrozole and doxorubicin, etc. Both patients again had some evidence of disease control. Patient 1 in August 2017 was found on CT surveillance imaging to have recurrence in the retroperitoneal lymph nodes. Patient 2 had been chronically on bevacizumab through September 2017 and now

is having some bleeding problems and is definitely in need of change of treatment. As it is not 100% common in our community environment but increasingly so, both patients now have access to relatively full molecular testing. This patient's tumor sample notably returned with an MLH1 nonsense codon leading to full stop of MLH1 expression. In fact, interestingly at the time of resection in another country, the patient had had immunohistochemical testing that showed MLH1 deficiency, but in the United States, I would not be able to get her insurance to approve treatment for MLH1 deficient disease without having a US CLIA-certified laboratory identify this molecular variation. Patient 2 also had some molecular determinants suggesting a particular treatment strategy. However, in her case, the clinical trial that was open most oriented to her disease which has this known functional mutation PIK3CA R88Q as well as apparent deficiency biologically so of PTEN would likely benefit from a PI3K inhibitor, but the clinical trial that we were running at Inova through the GOG NRG with copanlisib was on hold to further accrual. She did not have her MSI testing. Her overall mutation burden was determined to be intermediate whereas patient 1 was found to have a high tumor mutation burden. So ordinarily we would be thinking about enrolling these patients, for those who might not be familiar, on an innovative trial called TAPUR, Targeted Agent and Profiling Utilization Registry Study. What's novel about this study is it's sponsored by our professional society, American Society of Clinical Oncology, and not anymore an industry sponsor. The trial facilitates patients who have molecular testing to access what might be appropriate treatment regardless of the organ of etiology of the cancer, provided that as one of the drugs that has been donated to the trial by any of eight industry sponsors. So patient 1 would have been assigned to an arm involving a checkpoint inhibitor, but we didn't need to enroll her on that trial because the FDA a few months earlier had approved pembrolizumab for this broad indication of deficiency of mismatch repair proteins. So in August 2017, our team, after applying for some paperwork, was able to begin treating her with pembrolizumab. Unfortunately patient 2 did not have the same experience. Although there are many PI3K inhibitors available, none commercially approved, we know a lot about their pharmacokinetics, we know a lot about their safety profiles, but the only way I would be able to access this compound for this patient is either through a clinical trial, all

clinical trials that I'm able to open at Inova are not open to accrual, and so the patient proceeded to receive commercially available paclitaxel in September 2017. So patient 1 has had a very good experience so far. Her October 2017 CT imaging revealed decreased retroperitoneal adenopathy. Our team has had some experience managing patients on checkpoint inhibitors, so we are actively monitoring her liver function tests. We found some unexpected elevations, but she was asymptomatic and they resolved. We have been serially monitoring her thyroid stimulating hormone. We learned through years of collaborating with our melanoma colleagues at the University of Chicago that once you see a rise in the TSH followed by a precipitous fall in TSH while the patient still is asymptomatic, it is wise to begin some supplemental L-thyroxine therapy, expecting that the patient will become hypothyroid as a result of mild autoimmune thyroiditis. The patient continues to work full time and, except for some mild fatigue, is living an optimal quality of life right now for someone with an incurable disease. Contrast that with patient 2. In October 2017, although her vaginal bleeding was controlled, her pain persisted. She has developed progressive manageable peripheral neuropathy on paclitaxel. Her pain and her fatigue continued. Although I am by no means a right to trial law advocate, our team with lots of experience in coordinating with industry to obtain what we used to call compassionate use INDs now called single-patient INDs, completed all that paperwork to have a willing partner sponsor, but we still as of January 2018 have not had approval to receive an agent ministering to this patient who, by all estimates of her molecular profile, is expected to have some possible opportunity for definite response to those drugs. So it's putting us in this rather awkward era between prior paradigms and the exciting one as implied by this session today and Dr. Woodcock's conference this morning. It highlights some problems we have and _____ articulated the positive elements in this editorial a couple of years ago where some of our drugs are being developed so effectively, largely through some use of model-informed drug development, that they're becoming commercially available before we actually know as much about them as could be helpful in the clinic. So this classification certainly had a major influence on many of the clinical pharmacology fellowship graduates at the University of Chicago. You all are familiar with it. Time

is short, I won't go over it, but suffice it to say, this paper is 21 years old and a lot has changed since that time. We're getting quite good at characterizing parts of this response surface. We have, therefore, a new set of issues and problems to deal with. So if you look at a pharma foundation brochure from just 2013, this was sort of a sob story for all of us in drug development of how much testing and how many resources are put into the development of a single FDA-approved medicine. My colleague Tina _____ has characterized how in oncology care, we've really benefitted from a lot of new approaches and are rapidly developing agents having a more fluid concept of how to develop drugs for commercial use. I think it's no exaggeration we are quickly getting to the point where this diagram really looks like it's the new paradigm, and that's creating a whole set of new problems. Not to poke fun at any colleagues here, I just highlighted how impactful an immunotherapy drug can be on a patient who is the appropriate match for it, but we are now effectively generating too many slots for too few patients to answer the many good questions we all have. I think here lies the solution, and this is why our team was so willing to take this flying leap to a community health system with these lofty ambitions of conducting research because our information technology today is giving us the very real capacity to conduct relatively rigorous clinical investigations with a very limited description intensity protocol and to then literally within our electronic health record system incorporate this level of data acquisition and have our routine treating clinicians function as effective self-investigators in the new environment. We also had the opportunity to incorporate new technologies in ways that are less and less intrusive to the patient. In the community health system, unlike our clinical trials, we have the opportunity to collect long-term longitudinal data. On one of my lung cancer patients who we've treated at the University of Chicago for a span of about five years, we had serially collected her plasma samples over the course of three of those years. We now are able to use some quantitative plasma DNA detection methods and we could trace the concentrations of her mutated PIK3CA and BRAF mutated status DNA in her plasma over the course of different treatments. An interesting thing we found related to what Dr. Fojo was talking about earlier today is when we assess the total tumor burden by taking volume measurements of her many tumors, we have a more reliable

relationship between the imaged sense of the patient's tumor burden and her plasma DNA kinetics reflections of the tumor burden compared to if we had stuck to plain old RECIST-based single longest dimensions of a few target lesions which suggested throughout this entire time that she had rock-stable disease when she did not. We have most recently been able to coordinate with one sponsor to try to take these new technologies into a reductionist approach of can we actually do meaningful and novel subject trials? I think this single patient's result on this study where we had this pretreatment tumor growth trajectory, was on treatment tumor growth trajectory, withdrawal of treatment tumor growth trajectory, and his restoration of treatment tumor growth trajectory, to say that we potentially can do this and should in the future, but we have a long way to go to treat patients with pancreatic or biliary tumors and none of them survive long enough for us to be able to perform these full assessments. But my case in point in my last slide is that we really need to focus now on this world of a new paradigm on developing the methodology and the resources to perform these types of analyses in this post-marketing post-approval setting. We can access many more patients. We will have better generalized ability as a result of studying patients in this environment. We know we're moving into a new era of life cycle management where increasingly we will be focused on value. This is seemingly impossible to establish that value with the size of the cohorts we are now studying in standard phase studies. We're in this new era of regulatory management where our colleagues here at FDA are going to have to think about ways that they can oversee the data and the conduct of these types of investigations to ensure patient safety. But I think overall we're going to have better capacity to enhance and extend value of these compounds for the folks who manufacture them, for the folks who use them, for the patients who receive them, as well as for those who are actually having to foot the bill. So this is really just the beginning of a conversation. This is my email. For many of you who will have much brighter ideas than our team has so far, we want to let you know that we're sort of open for business and collaboration as we all explore the new paradigm together. Thank you for your time.

[APPLAUSE]

Moderator: Our next set of speakers are from _____. The next speaker is Dr. David Turner from Merck.

Dr. Turner: Thank you very much for the introduction. It really is an honor to be here today. I think we have an excellent panel of speakers, and it seems a lot of us are very keenly interested in endpoints that really is a hot topic of, you know, oncology right now. Now, I am indeed from Merck. I am in the quantitative pharmacology department. I am also a member of a cross-functional working group at Merck that's been tasked with better understanding in describing the relationship of surrogate endpoints and overall survival. So today I have the privilege to show you some of those results. So pembro is obviously very important for Merck. It is also very important for patients. The early approvals came on the basis _____ melanoma and non-small-cell lung cancer, and we've obviously expanded across the many different tumor types and have been in the market since then. So now that we have this data from KEYNOTE-001 _____ we're sort of going back to the well, so to speak, and beginning to query that to better understand some of those relationships. So we have this sort of hierarchy of questions here, starting with…these all could be the same. Are there subgroups of patients with progressive disease that have different outcomes? And then, as alluded to from previous speakers, we took _____ as an aggregate measure, but in a sense, we're sort of borrowing some of these data from the individual lesions, so there's a question as to whether or not that gray area might add something to our understanding. Then of course most importantly, what does this mean in terms of clinical practice? What's treatment failure and what clicked? And what we do when a patient progresses by RECIST criteria? Do we keep the patient on the drug or do we remove the treatment? So all of these are important questions, I think. So we started this journey with KEYNOTE-001 as sort of a learning analysis and then we expanded this into KEYNOTE-052 that also looked at bladder cancer. So I'm showing you here data from KEYNOTE-001. This is some lung antagonist. _____. You can see from this clearly that we have a number of patients who have an excellent response to the treatment. There are a number of CRs and PRs, we have those. Look at the tumor shrinkage. These patients are highlighted here, so this is a disease control group. We also obviously have some patients who have regressed who have SLD growth greater than 20%. I think what's interesting is the sort of middle ground where we have patients who are still have progressive disease by RECIST. Again they don't meet the

threshold on an SLD basis for progression, so this suggests that they either have growth of a non-targeted lesion or formation of a new lesion, yet still you can see a lot of these patients have shrinkage in their target lesions, so these patients are actually benefiting, and so this really begs the question of how do we treat these patients and should they be labeled the same as the other patients on drug? Now to sort of further complicate matters, if you look at individual lesions, so here, each vertical column represents a single patient, you will see that some patients have a combination of growing and shrinking lesions such that you have patients who actually progress when you have a shrinking lesion and you have some patients who are responding to growing lesions, so there's a lot of gray area here. Obviously we sort of reassess them to make sense of all this information. Just to start out, the purpose of this presentation, we came up with a stratification system. I will show you here. So on the far right, we have our typical aggregate growth and these are patients who have SLD growth greater than 20%. Next, the mixed growth are our patients who have single lesion progression, so they have progression of one lesion but not enough to meet the threshold for SLD progression. Then we have patients who regressed with no growth in the target lesions either with or without a mass, so plus and minus. Of course, we have our disease control group on the left. We will come to this schematic after a while to look at some of these results. So again we started with KEYNOTE-001. This is our random dataset. We have a fairly large dataset here, and when you go through all the filters, you see that approximately 60% of our patients have progressed prior to treatment discontinuation. When you look at the general breakdown here, you see that we have a fairly good representation across these different subgroups that we define. So after analyzing KEYNOTE-001 would be a fairly perspective analysis to apply the rules to KEYNOTE-052, again bladder cancer population. When you look at that data, you see generally the same proportion of patients belonging to individual subgroups. So I think, in it of itself, that's an important finding because it is a very different complex and you see that patients are progressing for different reasons and have underlying differences in their disease status, but it really begs the question, what is the outcome of these different subgroups? So here we start with a Kaplan-Meier plot of KEYNOTE-001 again and this is our disease control group. You can see

that survival quite great in these patients who belong to the disease control group, as you would expect. Now when we layer in patients who progressed via non-drug targeted, you see that there's a slight difference in here. I think it's interesting that the differential between the mets plus and mets minus is not unusual in size, suggesting that formation of new lesions might not be as important for survival, but still reduces some of the survival gap. Now when we go further down inspection in patients who have targeted lesion growth, either at the sort of the net aggregate level or at the signal lesion progression level. You can see that they have significantly more survival compared to our disease control group and high group. So you can see there's sort of a spectrum of outcomes here, and typically when we summarize things like response rate and PFS, we will be grouping all these patients into a single measure. Again interestingly when we look at KEYNOTE-052, we see the same pattern of graded response, starting with the disease control group and the patients being targeted with growth kind of the worst outcome. I think again, just to emphasize, the patients with single lesion progression are not progressing due to targeted lesion growth, but they still have similar outcomes, suggesting that if you have one tumor that escapes, it certainly _____ the survival of your outcomes or more closely resuming in patients with met SLD growth. So I think Kaplan-Meier plots are a great way for visualizing this data, but we're dealing with unsteady phenomenon and we have do things like minus because these events are occurring at different times. We want to ask questions, for instance, what is the impact of treatment discontinuation? So to do so, we put an extended Cox model which is similar to traditional Cox _____, and yet considered covariants as time varying, so all patients started at baseline at an unknown status, but then after the first progression, we locked their status and then we also accounted for when it was continued, so it's essentially a subgroup of a subgroup. As time progresses on the study, dynamically we allocated to different subgroups, as suggested by the figure on the left. This allows us to tease out the individual impact of either belonging to a group or being on a _____ in that particular subgroup. So when we look at the hazards now associated with being on drug in any of these particular subgroups, it more or less captures the trends that I showed you in the Kaplan-Meier plots, so here, our

reference hazard is the disease control group, and you can see that as we move down this spectrum that patients with no growth mets minus and then mets plus and then to the target lesion, the hazard increases as we move down the table. Now, again, as we look perspectively at KEYNOTE-052, you can see again that the patterns here recapitulate the patterns that we saw in KEYNOTE-001 and also the patterns we saw in the Kaplan-Meier plots, so we see an agreement between the non-parametric and the Cox model results here. Now I think sort of the take home point and more interesting aspect of this is when we estimate the hazard associated with discontinuation and belonging to any of these particular subgroups. We start at the top. You can see that the hazard ratios for each of these subgroups are significantly greater than 1, suggesting that there are patients within these groups who stay on drug and there's an association, a positive association with survival. We can see the disease control group, the hazard ratios _____, the hazard ratio for our no-growth mets minus group actually more closely resembles the hazard in our disease control group. Then you see a pattern of decreasing hazard such that patients with aggregate growth have perhaps a lesser benefit and yet they still have…there's still some patients in that subpopulation that could benefit or potentially benefit from staying on drug. Again, as we applied our learnings to KEYNOTE-052, we see the same pattern of hazard ratios where most of the patients show…some patients who are staying on drug may survive longer. So my quick summary slide here is that in KEYNOTE-001, we showed that there was a difference with survival in lung patients who progressed and so we typically treat these patients as all being a member of the same group, perhaps that's misleading. The perspective would confirm that KEYNOTE-052. The general feeling was that patients who have non-targeted growth tend to survive longer than patients with growth at the targeted lesion level, including patients who don't meet the threshold for SLD growth but just growth in a single lesion. I think most importantly we found that there was an association between staying on treatment post progression and survival, and again we confirmed that in KEYNOTE-052. So there's sort of two competing hypotheses here. Either pembro itself is _____ patients or alternatively commissions are selecting patients with better prognostic features to stay on drug. I think if we assume even a sort of worst-case second scenario and this suggests that RECIST alone is

doing a poor job of capturing the disease severity in these patients, so this…I think these are interesting questions. One thing we want to do next is potentially look at these trends and chemo treat patients because we think we could better tease out some of the causality here. So that's all I have. I just wanted to…just a quick acknowledgement. Seth Robey, who is in the audience, was a key in a lot of this work and has been an incredible player here. We have collaborations with our stats colleagues--Robin Mogg, Brian Tomko, _____ and many other people.

[APPLAUSE]

Our next speaker is Dr. Yanan Zheng from MedImmune.

Dr. Zheng: Thank you for the introduction and it is really an honor to be invited to the _____ workshop and I hope to take this opportunity to talk about our _____ MedImmune in modeling of the tumor kinetics and overall survival but verify prognosis including durvalumab's efficacy for _____. So as many of you know, durvalumab is an anti-PD-L1 monoclonal antibody that has been developed for cancer immunotherapy. Its mechanism of action is to block the interaction between the PD-L1, its effects on both tumor cells as well as immune cells can lead to these factors as described on T-cells. Blocking the interaction between PD-L1 and its receptor will result in enhanced T-cell activity as well as T-cell mediated tumor cell killing. Therefore, leading to tumor shrinkage. Just earlier last year, durvalumab has been approved for patients with locally-advanced or metastatic urothelial carcinoma that have progressed following not even maintaining chemotherapy. The approval of durvalumab _____ using the patient, as many as supportive data from the study 1108, which is at phase 1/2 dose escalation expansion study in solid tumor which includes using expansion for _____ 10 mg per kilogram Q2W. So in that study, durvalumab has demonstrated favorable efficacy with concurrent objective results with a 17.8 in a total population in 27.6 in the PD-L1 type sub population where the _____ high was defined as greater than 35% of PD-L1 expressions in the tumor biopsy. At this time, it corresponded to a median survival of about 18.2 in the overall population and 20 months in the PD-L1 type population. Now, the question about we would like to address is how can we further improve the efficacy, how we will benefit and impact patients who are likely to respond to durvalumab treatment

so that we can use that to greater _____ and also to guide the physicians' decision to identify who are the best patients to treat. So to answer this question a pharmacologic modeling approach is _____ because better than the traditional approach which looks at dichotomized response to date, the pharmacologic modeling focused on the entire longitudinal tumor responses to each individual patient which contains a lot more to each information and also it allows us to evaluate the biomarkers in a continuous fashion rather than looking _____ receptors. Further it is a powerful tool to have a systematic way to evaluate the multi-variant/covariant analysis. So, using the pharmacologic modeling approach, we developed a tumor kinetic and overall survival modeling framework for immuno-oncologic therapy. So first, we developed a tumor kinetic model to describe the longitudinal tumor response over time which enhances the tumor growth as _____ K_g as well as the tumor killing in response to immunotherapy which is _____ K_{kill} and then we then developed an overall survival model which uses the predictive tumor dynamics from the tumor kinetic model as the input function and predicts the survival from _____ over time. In addition, we also developed a dropout model to describe the relationship between the tumor response and the likelihood of patient dropout from the study. Lastly, we performed a multi-variant/covariant analysis on all of these models to identify significant factors not only for tumor growth but also for tumor killing, the dropout as well as survival. So, using this modeling framework we have analyzed data from using patient in the study in _____. So, here on the left-hand side you can see only a third of individual tumor kinetic _____ from the study. Here, the tumor size is defined as the sum of the longest parameter. So you can see that there is a modeling agent _____ individual responses and when you look at each individual responses closely, that is the _____ essentially three different type of tumor dynamic profiles. So the first type is one that has continued tumor progression whereas the second one shows that the last tumor shrinkage rather than _____ and then reaches a steady state over time as opposed to _____ and the third type is characterized by initial increase in tumor size. So, _____ has little progression and then followed by tumor shrinkage which suggests a delay in the tumor response in these patients. So in order to describe these

different types of tumor kinetic responses, we developed a model that describes the tumor growth as first _____ models and K_g here and then the tumor killing in response to anti PD-L1 treatment and the scores as added killing rate constant K_{kill} and here the growth rate is modeled as first order kinetics as done in the standard models and the killing rate is modeled as the same order kinetics to represent _____ reaction which will be the immune cells and the tumor cells and also allows the system to reach input again over time as consistent with _____ data. Also, in order to describe the delay in tumor response in some of the patients, we also incorporated a delay in the immune response which is modeled using a transit compartment model, a model rate with K_{kill} so that in some patients the killing rate increases from zero is maximum value over time and allows to delay tumor response. So with these structural model with each individual the ability in incorporating the population to the tumor kinetic model, we are then able to describe all the different types of tumor kinetic _____ in the study. And another important aspect in the tumor response is that there is a strong relationship between the tumor response and the dropout. As you can see from the individual profiles, the patients who do not respond and progress with the study tend to drop out of the study early. So very limited data from these subjects, whereas the patient who responded to the drug tend to stay in the study for a longer period of time. Therefore, we needed to develop a dropout model to track the range _____. So here, it shows the different tumor kinetics in the study using the final tumor kinetic model coupled with the dropout model. Again we can see that the model is finally _____ fairly well, both in terms of mean response as well as the durability among individual patients. So with the model, we can then perform model-based covariant analysis to identify significant covariates for a tumor kinetic _____. Specifically, with both the tumor growth rate constant K_g as well as the tumor killing rate constant K_{kill}. So data in gathering _____ action of anti-PD-L1 therapy is to induce the T-cell mediated tumor killing. Therefore, the factors that impact the tumor growth rate are considered as prognostic factors as those who even have another treatment whereas the factors that affect tumor killing are computed as related factors because those should be related to the treatment effect. So for the K_g, the growth rate we evaluated around the potential

prognostic factors as you can see here. For example, neutrophil _____ standard ratio, _____ spaces, line of therapy, the ECOG's health performance fitness as well as the baseline levels of LDH, hemoglobin and albumin which have been reported in the literature as potential prognostic factors _____ types. So the model as in the _____ spaces as the most significant factor for K_g where the patients with liver metastasis are associated atypically with greater than 50% increase in their tumor growth rate.

On the other hand for the tumor killing rate, we evaluated the PD-L1 expression as _____ specifically in the type two different scores here, one is the TC score representing the PD-L1 expression in the tumor cells. The other one is IC score which represents the PD-L1 expression in the immune cells. So the model actually estimated that the IC score is the significant factor while the TC score or the tumor killing and increased IC score into increased killing rate which leads to greater tumor shrinkage as consistent with what was found in the _____ data. Also the model predicted the baseline tumor size as the significant factor where a smaller baseline tumor size are associated with a great killing rate which the definite smaller tumor is easier to treat. So more interesting is how we translate to the tumor response rate in _____ we used the models in remission to predict the tumor response rate by various _____ groups and then you can see here that model predicts a high response rate in patients with higher IC scores or with baseline tumor size as well as the _____ liver metastasis, without liver metastasis compared to those with the liver metastasis. We can also use the model to predict the response with different cutoff values for PD-L1 expression _____ PD-L1 high population is defined as either TC or IC greater than 25%. So here, using the model simulation, we predicted that increasing the IC count to 25% to 50% and further to 75% will lead to increase the response rate and the TC score does not have the obvious impact. So of course this is based under the result of one study and we will continue to validate this in future trials and once this is confirmed, this could help in improving the patient in terms of clinical application of PD-L1 _____ using patients with durvalumab treatment. So then, we want to see how the tumor kinetics is linked to the overall survival. So here this graph shows you _____ curves expected survival from the study type and the last tumor

response. You can see that as a clear separation between these _____ which suggests that there is a strong relationship between the two where the patient who has better tumor response had a longer survival compared to those who have poor tumor results. So given that we further have to balance the overall survival model where the hazard of survival is modeled as a function of the predicted tumor dynamics from the tumor kinetic model as well as other baseline factors and predictive survival probability over time. So on the model actually you can see that it captured the observed _____ monitored the survival very well with regards to the overall population as well as the sub-group of patients by various response types. So you can see that the model predicts the responders, either with delay or no delay has the longest survival, followed by the non-responder and non progressors and the progressors have the worst survival which is consistent with its _____. And finally, similar to the tumor kinetic model, we also performed model-based covariate analysis using the survival model to evaluate the significant factors for survival after the tumor kinetic has been accounted for. So we identified a number and various _____ of TC and IC score, liver metastasis, hemoglobin as well as albumin as significant features and here it shows several examples of the simulated overall survival occurrence, like covariance interest. So for example you can see that similar to tumor kinetics response, the increase in immune cell PD-L1 expression of these two increased probably besides survival but not the tumor cell PD-L1 expression. And in addition, we also showed that the model also predicted increase for _____ survival for patients with a higher baseline albumin levels as well as those without different metastasis compared to those with the metastasis. So with _____ these prognostic factors can also be used in addition to PD-L1 expression to help select patients for future clinical trials and also help the physicians to identify the likely responders in the clinic. So in summary, we developed a relation in tumor kinetics for overall survival and dropout modeling input to describe both the longitudinal change in the tumor size as well as survival in cancer patients treated with durvalumab and as a modeling framework as a useful tool to study the tumor cells in combination with _____ as well as the fact of multiple prognostic _____ factors in the multi-variant analysis and ultimately, the results from this type of modeling can be used to try patients with

_____ and enrichment strategies and to optimize clinical trial designs for our therapies plus various responses in patients. With that, I would like to thank everybody who have contributed to this _____ including entire financing and _____ and last but not the least, all the patients and investigators who have participated in the development of the trials.

Thank you.

[APPLAUSE]

Moderator: Okay. Our next speaker is Amit Roy from BMS.

Dr. Roy: Let me start by thanking the organizers for inviting me and let me say some of the role that we have been doing at BMS along the lines of _____. I would like to start by stating somewhat more explicitly the _____ role in dose selection that had been alluded to in some previous talks where we had been talking about using tumor response in making decision on dose selection and why that is really, so unlike any other therapeutic area, the oncology endpoint in the early phase of a trial is different from the phase III ipilimumab trial anywhere in most cases where the endpoint is somewhat single-based, either it is tumor response rate or its PFS at baseline research whereas its is based oftentimes on survival. It has also been alluded to you like the necessity being pointed out by Dr. Woodcock the assessed number of ORR. Our research actually does not use all available data. Usually, it requires a minimum new recent followup, let us say, for six months, let us say, and they have before that ipilimumab use and this is _____, so you have duration of followup with every situation response _____. More of our… And there is also exponential study in a limited number of subjects that we have, so the point being that what we want to do is… This is actually what is reasonably well despite all the talks starting, you know, this morning, but I think there is a lot more that we can do due to university setting of necessity and data are so precious and only fragment use of all the available data. We will disclose selection becomes more complicated overall honestly.

So the proposed approach that we have been following is very much along the lines from the other speakers here. We got across the tumor growth dynamics and overall survival for tumor genotype. Maybe the assumption that these tumor growth dynamics and overall survival is more agnostic with nivolumab. That is to say, the more you characterize the

tumor response profile, and I am going to talk about it very generally, does not necessarily mean someone is dying with it over time. It could mean other things as well. Only that is what we should look at. That once you characterize the tumor response over time that essentially represents an official efficacy for the effect of drug. Ready to press now which drug which may induce that response once you characterize the response which you are going to do pretty similar as to something _____. And then once you have this, the more you characterize the tumor genotype it is going to reflect to the clinical data that you might have from other phase trials with limited number of subjects with new followup to be able to make predictions of survival and make judgments on whether that overall survival you would like to be further detailed _____. So you can form both no-go decisions or go decisions as that is the informed dosage.

So that I can motivate these concepts with every case done and effectively with this, quite recently, it was published with _____ utilizing a few number of TGD-OS model _____ on nivolumab applied to break overall survival with ipilimumab. So the advantage, these are both immune-checkpoint inhibitors, but actually, the mechanism of action is actually complementary. Ipilimumab stimulates the activation of and proliferation of T-cells whereas nivolumab primarily reactivates quiescent T-cells in the tumor microenvironment, and there is evidence that these mechanisms of action are complementary comes from a peripheral file we have regarding advanced metastatic melanoma which shown that complementing the two is better than having it alone, so somewhat they are adding something to each other.
We actually have a very interesting set of data set within inhouse to evaluate this because what happened was that ipilimumab was approved for 3 mg/kg once every two weeks for four doses, and other than from the basis of a phase III study that was initiated prior to BMS becoming involved in the development of the drug and then in the end we got involved in the development of the drug, there were several phase II studies that were conducted, one of which was of two-ranging phases. In these two-ranging phases of the study, we found that the 10-mg/kg dose given once every two weeks had better tumor response, RECIST response, than the 3-mg/kg dose. Soon after that, the phase III study led up. It was positive for ipilimumab solely received _____, but we also have a postmarketing commitment to the phase III study to evaluate free-growth system, free-growth study _____.
Subsequently in the meantime, nivolumab came along and it has a short benefit in overall survival for metastatic melanoma as well as other genotypes. This is an aside to those that were initiated for three weeks of the nivolumab versus the

once in two weeks with a flat dose of 240 mg. So the essence of it, it is unusual to have phase III data from two different agents with the same treatment effect which can actually do this _____.

We now address to the approach to tumor growth dynamic modeling. We have decided to sort of move to an initial model for describing profile, and it was shown over here significant loss from ipilimumab and what you can see usually are three distinct profiles, types of packet of response, and these had been classified based upon initial model approach that had been given nivolumab. And what you can see clearly is that… Okay. I think I said that. Just to make sure, the tumor growth dynamic model was based upon a model that was published by Young some years ago. We did some modification to actually make sure the model had one component that has no growth at all because otherwise everyone has growth with this that has been present over time. And that was not the fact that we had seen. We had enough stable tumor growth that we had seen. And also as an aside, we make a point that in this case tumor shrinkage model was exponentially decreased. The tumor growth is of linear increase. We also think exponential increase to growth rate models that we have taken very comparable. And as you can see given the limited amount of data that we have for patients who are progressing, a linear growth model recently discussed that recently at least after that.

Into the view of looking at this, maybe you can say, "Okay. The subjects in this no-growth group of subjects are lacking growth better in terms of overall survival" whereas the progression-free overall survival _____ we have linear growth survival. So a few points to make over here, we decided to use that data profile because again _____ even though we may not get a deep response we have a long durable response and this is a thing. A single fine-point example, we can get tumor shrinkage and maximum tumor shrinkage. You might get some subjects who have high shrinkage that involve generally overall survival. So that is the reason why we chose the shrinkage model.

So here are some key results from this long study. Interestingly, the progression-free survival was very similar for the three _____. I am showing the reference that whereas there was a highly significant difference in overall survival. So there was about 6% to 7% difference in maximum survival at one year. So the approach that we have taken actually is to accumulate a setback. So the approach that we have taken in terms of overall survival modeling is to include all the baseline prognostic factors that can include

all the features of a tumor profile to include the shrinkage rate, growth rate and time key to include baseline _____ to include absolute and relative tumor sizes as well as include new lesions that may appear at times, so from time to time, the model… Importantly, we also recognize that there are subjects who drop out early. That is the highest factor that has been included in the model as well as in the… That is it. I mentioned that one.

So here are the results of the study, a complete list of study, a completely different drug. We did _____ in describing the 3-mg/kg dose and the 10-mg/kg dose. The effectiveness had turned out very good. Despite this, the model has captured some of the benefit, additional benefit, with the 10-mg/kg dose. So what we are showing here is how can we actually use this model to limit the data and how can we actually do. So if you take a limited data from this phase III study with ipilimumab, 35 subjects turnout with six months' followup and you use the model for free-tumor growth survival, can you relate the better overall survival with 10-mg/kg as better treatment for the patient? This shows exhaustive direct horizontal line that is showing the observed differential in survival percentage at one year and in two years, and the _____ show the distribution of clinical trials that show an advantage. So approximately between, you know, 70% and 75% _____ would show that the 10-mg/kg dose has been shown better even though PFS was essentially identical in percentage.

So in summary, the TGD-OS model developed with one drug, nivolumab, _____ rate of survival for a different drug, ipilimumab, providing proof principle that this set of approach could be agnostic to the drug in terms of tumor shrinkage and the tumor response profile may be sufficient to break the overall survival on the drug. This set of model can be used to leverage data from all new clinical data from _____ receptors to form a program of _____ modification and several set of improvements to the TGD-OS model can be made and maybe discussed at the _____.

Moderator: Alright _____. Our next speaker is Dr. Rene Bruno _____.

Dr. Bruno: Thank you, and welcome to the FDA _____ ISoP _____ find interesting _____. So _____ breakthrough _____ is a drug _____. In fact, there is a link between _____ treatment _____.

The beauty of that is that you can develop a model using clinical studies, and then you can use _____ is used as a biomarker to capture treatment effect and predict _____ benefit. Then when we have developed this type of model, then we can learn about TGI data and therefore _____. There is a variation of this where we can apply this type of modeling _____ entering phase 2 _____ studies or in phase 3 studies when we are _____ then we can _____ tumor data _____. So when we are talking _____ and recently we have _____ actually today TGI-OS models _____ phase 2 data that have been used _____ phase 3 studies _____. From there, we have two studies. The POPLAR study was a phase 2 study for varying dose effects _____ single agent in patient with _____. Those are the data. You can see that atezolizumab is doing better than docetaxel. _____ is the team that developed docetaxel _____ and I think _____ successful phase 3 trial in _____ patients _____. So that is very, very interesting.

Okay so then we developed a model based on those data _____ model _____. The tumor growth inhibition _____ using is _____ that is being presented by _____ except that instead of _____ patients depending what you see, we used a population approach with that. Patients _____ we could estimate _____ for each of the patients. We then _____ population approach _____. The only thing _____ at least _____ baseline, you can _____ that in the POPLAR study, we had 277 patients; and 91% of the 277 patients _____. What I am showing here is the typical profiles of the _____. What you see _____ is docetaxel, and you see that docetaxel _____ initially _____ than we would expect; and then there is _____ compared with atezolizumab _____. So if you got any of the matrix _____ overall survival, you will see at least that _____ as we are using earlier is not going to predict the benefit from atezolizumab. Same when we have the _____ using in the past. Of course _____ and we want to predict the _____. So you will see that those things _____. Now let's see what's happening in those patients that we defined as _____ those patient who are _____ right? _____ and here you see that there is _____ between docetaxel and atezolizumab

_____ with the atezolizumab _____. Of note, we did not find any evidence of _____ drug effect kind of _____ studies. We did not find any _____.

Now we are going to _____ of the patients, and we developed _____ models _____ two baseline characteristics _____ met sites _____ so it is not a good assessment _____ patients _____ number of sites that are _____. When we use _____ treatment effects _____ but when you _____ explain the _____.

Now we are _____ model in simulating the POPLAR study, and this _____ here. We are simulating _____ study _____ distribution for each of the _____ and what you see here is a prediction of _____ we predict the _____ we did that for all of the patients and we did that by baseline biomarker expression. So patients that expressed _____ PD-L1 at baseline _____ tumor cells or immune cells _____. Those patients are benefitting a bit more _____ when the patient not expressing PD-L1 _____. In addition to that, we have a marker or a gene expression of the T-effector and interferon _____ genes _____, and we could show _____ predict the model _____ benefitting the patient with high _____ gene expression _____. Now we can _____ further and we predict that in phase 3 studies _____. This study _____ docetaxel _____ but still we can predict the phase 3 study based on the tumor dynamic data _____ in patient by data of the biomarkers. Here you will _____ the patient with no expression of PD-L1 benefitted. Patient with _____ gene expression benefitted _____. Here we have the _____ here we got the phase 2 study _____ when the _____ phase 3 _____ comparing atezolizumab to _____ but still we see the same thing in the _____. Here we have the _____. Here it is a qualification of the model _____ but we have the two groups of the patients. First group were first-line patients, cisplatin _____ group were second-line patients who _____ and you see that _____ patients _____ first line versus second line= _____. Now we go to that model and we predict the _____ that is comparing _____

docetaxel _____ this group and we _____ which is comparing atezolizumab with _____. Same thing _____. So now what we do is _____ except the _____ phase 3 studies _____. Let's see what we can do to help selection of _____ combinations _____. Okay, so we know that _____ predicts _____. This is a typical profile. This is the one you have seen in KG growth rate. You see that the _____ predictions here. We can see that _____ single agent or even _____ growth rate _____ 20% _____. So then based on _____ you can _____ show you studies that _____ recently because they can be _____. You have to _____. Here what we are doing is that we are comparing the growth rate estimated in those patients _____ single agent _____ patient characteristics _____. Then we compare what is the difference in growth rates _____ patients. From there _____ growth rate _____ we see that the _____ of the growth rate is _____. According to the OS model, we would expect _____.

[APPLAUSE]

Moderator: Next to the last presenter is Dr. Jenny Zheng.

Dr. Zheng: Yeah, I would like to thank the committee inviting me today _____ approach and _____ to guide in decision making _____. So before I give the presentation, I'd like to emphasize that the previous presentation is all about phase 3 information _____ but here we are talking about the situation _____ information. So this _____ actually has been discussed by the previous speakers, but I'd like to emphasize _____ is quite challenging _____ is low. Actually many factors may _____ successful rate of phase 3 trials _____ it may be made into the phase 3 trial is _____ informative. Very often they have a single arm _____ to the patients _____. So knowing that this design from phase 2 _____ decision making for phase 3 is associated with great uncertainty. So the best way to handle that, of course, is to _____ increasing the number of arms of treatment in the trial _____ feasible. So the next _____. What can we do actually to mitigate the uncertainty? So what I am proposing here actually also discussed by the previous speaker is _____ maximize the _____ from phase 2 trials

_____ we can use _____. Secondly _____ we should learn from prior knowledge _____ the quantitative relationship between _____ and long-term clinical endpoint using _____ approach _____ prior data _____ indication. The third is using the _____ relationship from the _____ project the clinical outcome using the data obtained from the early trials. _____ I think the tumor dynamic is a good approach to _____.

So I want to talk about _____ tumor size data. Tumor size data actually is _____ trials. Tumor size actually _____ so those information can help us to bring the _____ tumor size _____ contains a lot of information _____ the drug effect difference caused by _____ or caused by _____ tumor size _____ information. _____ it has been diagnostic _____ tumor size _____. So that relationship can be quantitative _____ relationship actually _____ to project long-term clinical outcome using the _____ tumor size _____ information. So in this aspect, FDA made a huge contribution to _____ this exercise _____ from the FDA _____. So the objective of _____ presentation is to present two cases to demonstrate the value of using _____ data and prior knowledge for decision making, and specifically _____ first-line treatment for metastatic renal cell carcinoma. This presentation _____ the impact of the proposal so I am not going to go _____. So the new treatment assessed here is axitinib plus avelumab. Another _____ combination X+Y which is masked treatment _____ as a first-line treatment of sunitinib. So the first step is to pull _____ data from the new treatment sunitinib and then _____ dynamic model. Data from axitinib plus avelumab come from _____ patients. This actually is _____ considering this is a phase 1b study. Data from combination of X+Y come from _____ data only from 10 patients. For standard of care data, _____ information. So the drug effect, as I said, can be estimated using _____ study; and the drug effect _____ from the model _____ and compare the two new treatments versus sunitinib. This comparison _____ focus on two parameters. One is the tumor size _____ which is _____ this presentation. Another is drug effect on tumor shrinkage rate. The reason

to _____ tumor size _____ of the treatment so that parameter _____ can be estimated _____ much information about the tumor growth. So this is the tumor dynamic model we use in _____ proposing _____. This model basically has _____ assumptions. The first assumption is that tumor growth _____ growth rate of KL indicated in this equation. The second assumption is that tumor shrinkage _____ in this equation. The third parameter is about described resistance. Eventually it is assumed that the tumor _____ meaning the tumor will regrow _____ actually describes how _____. This slide shows the tumor reduction after treatment of axitinib plus avelumab _____ patients. As you can see, tumor size shrinkage is quite a lot, and this reduction is good. However, we don't know how good is good enough for _____ combination model. So this slide shows the comparison between two treatments off axitinib plus avelumab versus sunitinib. So all the _____ represent tumor size reduction from sunitinib, and the right line represents tumor size reduction from combination. So as you can see, combination did cause greater tumor size reduction as compared with sunitinib. However, I think _____ so the tumor size reduction rate is actually more _____ compared between the combination versus standard of care sunitinib. So as you can see, the combination did _____ greater tumor size reduction rate as compared with the sunitinib. The difference actually is statistically significant. This slide shows the tumor size reduction _____. So as you can see, the combination caused more tumor size reduction and the difference is statistically significant. So the same _____ we will actually apply to treatment X+Y, and this I would say _____ data for the second combination _____ tumor size reduction. When compared with sunitinib, the reduction does not _____ better than the standard of care. For the tumor size reduction rate, this is actually really _____ so no surprise. For the tumor size reduction _____, the second combination is _____ sunitinib. So based on that, actually the second combination _____ move forward not only based on this exercise but _____ to this agent. So this _____ support _____ of the combination of axitinib plus avelumab _____ for the second combination, and I hope the case convinced that a modeling approach can be informative _____ knowledge for that.

So I would like to acknowledge the team _____ without their support, this exercise is not possible. So that's it.

PANEL DISCUSSION

[APPLAUSE]

Dutta: Thank you all. We have _____ presentations, the first few focusing on methodology _____ examples. I now would like to ask the other speakers to come _____ to ask questions, as well as _____.

So I think we are settled. Before we start _____ from the FDA. Dr. Atik Rahman is the Director of Division of Clinical Pharmacology, and Dr. Jerry Yu is a team leader in the Division of Pharmacometrics. Before we entertain questions, I would like to give the floor a little bit if Dr. Rahman or Dr. Yu has any _____.

Dr. Rahman: Thank you for giving me an opportunity to say a few words. The first thing I would like to mention about what we have done at the FDA Board with MIDD _____. The first thing is that we have started to use MIDD drug development as well as in drug approval and in drug labelings. We have used MIDD approach for validating the selected dose or approved dose retrospectively through this tool. We have also _____ marketing trials so as you know that most of the data that comes and as you have seen that sometimes the PFS and OS do not have the same outcome, and we have issues related to dosing which is universal not only for Oncology as Dr. _____ mentioned. We have used phase IV approach to PMR post-marketing trials, and we have used modeling to kind of help select dosing comparison in the post-marketing settings. We have also used a community-based modeling approach to informed dosing for combinations especially for drug interactions in the labels. So these are just a few examples of modeling approaches we have used in the FDA. All we plan to do is to further help move this bill forward and in order to do that, we need to have training within the FDA to understand how this technology is developing and how we can have early resource allocation to have early discussions with the pharmaceuticals to provide our knowledge to help move their particular drug development program. Also we need to

collaborate internally among our pharmacometericians, statisticians and the pharmacogenomic folks as well as the nonclinical scientists to understand how we can approach this modeling _____ development from the get-go to the end _____ setting. So these are the few words that I have _____.

Moderator: Thank you. Dr. Yu?

Dr.Yu: So I actually have _____ oncology products _____ delayed effect. So when we _____ an assumption with using the model is that the _____. So as we see _____ modeling _____ today, we can use _____ tumor response. _____ is always on tumor, and the _____ if it is tumor and actually contains _____ that is when you use all data, tumor sizing data, you can actually get more information. This is important in the early stage because in the early stage when we look at _____. We look at the detail of tumor size data, it really provides more information _____ tumor modeling will work _____.

Moderator: Thank you. I think Dr. Roy has _____.

Roy: Thanks, Sandeep. I just wanted to correct an omission I neglected to advance to the _____ the work was done _____. The tumor marking was done largely by colleagues _____ was done largely by colleagues at _____ Research Group, and we _____ collaboration. I just want to mention we actually _____. Thanks.

Moderator: Thank you. We will take the first question.

Audience: Thank you so much. _____ from _____ Pharmaceutical. My first question is for Dr. Amit _____. In your example _____ if PFS was the _____ of the study or overall survival?

Roy: Overall survival.

Audience: Overall survival. So hence I do understand that the goal of this session was to present _____ but I think it will be interesting to see something _____ because one of the examples when we presented data for 3 mg and 10 mg was _____ to see if _____ the same way _____. This is really what I saw as missing in all of the presentations so I do not see the _____ metrics how this _____ endpoint if we look at the tumor model. So what has happened between the time we do the _____ process versus _____ whether or not the clearance has

changed overtime, and I think one of the examples is that _____ immunotherapy that clearance has changed overtime. How this affects the endpoint _____ of the process.

Roy: Yeah. So in the _____ we presented, we did not include the exposure response part. So the doses _____ will be investigated with 3 versus 10 _____ increase in dose. The _____ of monoclonal antibodies _____ is quite small in comparison to that full increase in dose. It is still about 20% _____ additional 25% overtime _____ the change in dose. So _____ change coming from the dose is _____. Our focus here again, as I have mentioned and as Dr. _____ also mentioned, is that _____ dose actually inducing the tumor shrinkage, the idea was let us capture _____ tumor shrinkage and _____. If we can capture that, then you can get, as the next step, the ratio of exposure and tumor _____ profiles.

Bruno: _____ just to comment actually it is _____ I think it is important to realize that exposure _____. So it is not exposure but _____ survival. It is _____.

Audience: Yeah. Thank you for that response because—or maybe I should…

Guedj: Can I add a comment on what you said? I think that the old presentations that you see, I think that we are still _____ by the traditional proportional _____. Therefore, we expect _____ dose. We expect that if the biomarker responds better from the higher dose, let's say, we expect that this should translate into overall survival. I think we need also to be prepared now, maybe in future situations where the higher dose might very well affect the _____ marker that _____ that this differential effect _____ marker does not translate even at all in some situation to overall survival. We could very well have a situation where the high dose improved the _____ but does not improve at all the survival. So in that case, what could be the interpretation? We need to think about whether this is due to the way that we modeled _____ the biomarker into survival _____ take into account all the factors such as toxicity for instance. So I think there are a lot of things that we need to think about in that area.

Turner: I'd like to _____ a comment as well. So you mentioned exposure. We have actually done a lot of work with exposure response and looking at _____ tumor size and survival. Just as you mentioned, clearance is really _____ with response so it is not the typical pattern. We think about exposure _____. It is actually exposure is a trailing effect of disease status where when you look _____ dose, you see a very clear relationship of exposure response, but then _____ this dose ranging, you can clearly deconvolute and see that actually clearance _____ for disease status. It is not the typical causal relationship of exposure driving response, so I think we have some _____ of exposure response.

Moderator: We'll have the next question.

Audience: _____ all the speakers, there's really a neat collection of so many _____ approaches in tumor sizing. _____ everything were saying, there is some commonalities but also some differences so I think like in some slides, there were references to new _____ being important for overall survival but then _____ it wasn't that important compared to overall change in tumor size. In some talks, there was mechanism _____ tumor size _____ survival _____ like in the first assessment, you compare doxy and _____ a little bit. It actually is _____ into account. I guess with so much leadership here in terms of ISoP and FDA, I feel like something really useful would be an effort to kind of synthesize all this information into just _____ everything like what are some few _____ we do agree on and _____ states that need more investigation and also _____ way to do that _____.

Yu: Just a brief response. I think, I mean the question asked _____. I think it is the definition of _____ and there is what you call immune-modified disease criteria so we have _____ progression. _____ definition as a new definition specifically for the _____ therapy, kind of implying that _____ it is important _____ long-term benefit as _____ said before. So I think also we have modeling _____. There is also _____ data _____ so that's _____.

Bruno: Just to comment on your comment. I think you're right. We could may be kind of _____ collaboration to see what

the best approach is _____ conception, and we are thinking of doing _____ collaboration across _____ drugs and studies.

Roy: If I can also just quickly comment _____ quick. So I think _____ and clearly the tumor data is much, much greater than that. I think what you saw _____ target lesions is quite different from having it from one large lesion. The _____ will be different. The implication _____ survival will be different. Where the lesion occurs _____ some references to liver metastasis, for example, _____. So I think new lesions can have _____. I think there is room for improvement and really digging down deeper into _____ aspect of it. _____ actually need more information from _____.

Audience: Lily Turner from _____. First, I have a comment on this general discussion on the relationship between exposure and response endpoints _____ response and survival. I think it's important to be clear that the comments that were made about the relationship between drug clearance and things _____ tumor burden, that really an antibody or an immunotherapy scenario, you might have other _____ or drug classes where you could have a relationship with the concentration and change in tumor size, and then an independent relationship _____ survival. May be we will hear more about that later, but now I have a specific question for Dr. Zheng from AstraZeneca. In your model, did you test for correlation between the baseline tumor size and the shrinkage or the delay in treatment to see if the reason for the delay is just due to bigger tumor or if there is a delay just based on tumor size?

Zheng: Yes. We did test the baseline tumor size as a _____ for the _____ constant, and actually it is a significant _____. As I showed in the results, the patient with a smaller tumor to begin with has a higher tumor _____ rate. As far as the delay time, so we did test the _____ for the delay time in a post hoc fashion so after we have accounted for the _____ factor from _____ as well as tumor _____ remaining correlation between _____ and delay time, and we didn't find any significant _____ at that point.

Audience: Thank you.

Audience: _____ I have a question regarding the influence of post-progression treatment to overall survivor. I think in most cases, the _____ treatment either surgery or medication may influence the overall survival especially when overall survival is much longer than the _____. In randomized _____ trials, the post-progression treatment is not always balanced between the control arm and treatment arm. Therefore, in this case, the efficacy and _____ results may be affected by such imbalance. So I just want to clear the panelists' opinion regarding this issue and _____.

Turner: So I think it _____ presentation material that we saw. We weren't comparing necessarily the treatment versus control. We were comparing treatment versus treatment. So here we see _____ progress _____ discontinuing or they remain on the drug. We are not advocating for a causal relationship here because there is clearly an issue of _____ for those patients who do stay on the drug post progression, compared to their peers who received the same treatment but discontinued, it was associated with longer survival.

Audience: _____ excellent presentation. I actually have two questions, one regarding the _____ which is basically we are moving from making an inference _____ personalized medicine, and that's where we want to be in terms of the biomarkers especially for _____ so the idea here is how can we do a better job identifying those patients who are responding due to therapy _____. So my question to the panel is what are we doing about the biomarker? Especially most of the work is more of post hoc, and what we're doing is we have _____ so the literature is _____ this is prognostic and it is all over the place _____ as a clinical pharmacologist _____ to understand better how these biomarkers behave and how we can _____.

Roy: Since no one else is speaking out a comment on that, I think my sense is that most, if not all responses, have a very active biomarker _____. Unfortunately it is not _____ identify _____ biomarkers. So for example, for _____ has a very nice _____. It really activates and proliferates the T cells _____ dose response _____ does not always lead to improvement in tumor response or survival. Although we have looked very, very deeply _____ for over a long period of time because there is _____ who likely respond do not even

find _____. So it is not always possible to identify a biomarker. In addition to that, the notion that we want to have a method that is treatment agnostic to predict survival _____ sort of converge on this tumor response profile _____ talk about it in very general terms, it does not _____. It could be volume. It could account for different number of lesions and so on and so forth, but that ultimately I think has the potential to be agnostic to the drug where as a biomarker is likely to be connected to the _____ of the drug.

Bruno: Just to comment on biomarkers. We are trained to do biomarker gene expressions _____, right? When we do that _____ we can see that some of those biomarkers are very strongly correlated _____ they would also have _____.

Zheng: I would like to comment _____ immune-oncology actually is _____ but in terms of _____. I think the challenge here, in my experience, is the _____ how we _____ biomarker, what biomarker needs to be _____ because in immune-oncology, we work with so many pathways so a single biomarker for prediction of outcome, I think, is _____.

Moderator: _____ willing to ask your questions _____ then we will have _____ questions _____.

Audience: This is _____ from Genentech/Roche. _____ speakers who are telling us about what they have done and _____ data sets for phase III and so on. We have learned a lot of insights from these data so we can connect tumor growth to survival _____. We heard quite a bit about _____ but _____ actually be able to bring this to the table in a tangible way that we are actually helping patients in our clinical trials or ultimately helping patients Dr. Maitland was talking about. So I would like _____ the panel to think about _____ challenges still that what could be some of the things that we could do and whether FDA would help us with _____ because this is part of expediting the development part of using model-based decision making. So what are some of the _____ that you see and what could we do as an organization ISoP _____.

Audience: Actually I also want to tackle this question _____ FDA. So thank you for this brief presentation. We saw a lot of _____ from the industry side _____ and

there are some _____. A lot of times, you do not have clinical data and traditional _____ but why will you use this tumor growth model to address this question, but do you see these kinds of things? So that _____ may affect _____ survival _____ immunogenicity but if you have reliable tumor-growth model and you can integrate to that immunogenicity to adjust _____ it can affect the overall survival. So those kinds of _____ questions _____ need to address _____ regulatory agents.

Maitland: I think those are great points and from the clinician's perspective, you asked about low-hanging fruit and collective opportunities. As fantastic modelers with great teams, you are used to doing the most you can possibly with the available data. I think one of the compelling issues I see is we are still collecting data at fixed _____ with regard to tumor burden based on conventions from assessing cytotoxic therapy. We have tried to breach this in individual pilot studies at different institutions. It is enormously challenging because _____ appropriately will not allow us to just perform extra CT scans at will, and similarly patients are only so willing to make the extra trips back and forth to a radiology facility, but I think a concerted effort to better define what are the optimum time points of collection to assess tumor burden, even new models to new technologies, there is nothing they could do that might make a difference in the near term.

Zheng: Yeah. I just want to concur that this is really very important. I think the example presented here demonstrated and hopefully convinced _____ tumor size information could be _____. However, what is the best time to collect those information _____ they all kind of make a contribution in the _____ in this area. I think the important thing _____ information.

Bailey: To comment on that as well, in terms of the _____ phase _____ how we decide to switch _____ I think one thing is the _____ in the early stage of _____ phase I trials. We intend to actually move forward with those _____ exploration with any other trial. So on the slides, I touched on very briefly at the very end _____ looking at how to look for _____ when you have no _____ data. It does not really _____ target and estimate what is happening in the

tumor based on what you see on the blood. To be able to look at simulated predictions or which doses would give you suspicion _____ under different schedules _____ within that trial. So to be able to _____ and use of that data _____.

Guedj: I think _____ we need to have the same systematic approach in survival _____ in clinical pharmacology. That being said, people _____ to come up with alternative models _____ show why they chose this model rather than another one or evaluate ways to have a combination of models, so we need to see that and we need to see how _____ to change the assumptions that are made _____. So I think it is something that needs to be done.

Moderator: So I think we are 6 minutes overtime. I just _____. So I think the questions that were raised today _____ in terms of fixed dose versus _____ doses. There is still a long way to _____. First, I'd like to thank all the organizers for _____ this workshop. It has been _____ interesting _____ and the industry _____ part of this community. Then last _____. There has been bias, a lot of bias _____ immuno-oncology presentations, and in order for this to gain wide acceptance, the clinical community has to _____ kind of decisions has to be applied across all _____ therapies that are being _____ Again, they could have _____ there is a lot of _____ a lot of data _____ overall survival. There are many reasons for it and we want to _____ reasons, but we need to understand that and apply a concrete _____ this to be applied more frequently _____. With that, I would like to thank all the speakers _____. Thank you.

[APPLAUSE]

SESSION III MIDD BEFORE AND AFTER APPROVAL

Dr. Wang (Moderator): Okay thank you for sticking around. This will be our last session of this workshop. As you can see, we designed the workshop to cover the entire _____ from preclinical to early clinical, all the way to its approval. That is why the third session today, we will cover when the whole drug in our data are collected and the sources are ready to submit the whole package for review and the financial approval and how model informed analysis can be used by sponsors to support _____ of arguments

_____ and how FDA reviewers review this type of analysis or when you apply additional modeling informed analysis to support approval or laboring or potentially towards marketing targets so then we have three speakers to cover this news and our first speaker who is Dr. Kellie Turner-Jones from VIP and that she is a senior research scientist at Eli Lilly where she is the _____ leader for one drug that she will go into details to discuss at the stage of submission, how model informed development, the informed analysis were used to support most of the disease.

Dr. Turner-Jones: Thank you to the moderators for the invitation to speak to you. I am honored to represent the Event Cycle Team. Please shout if you cannot hear me well. Today I will tell the story of abemaciclib and how model informed development and collaboration, computation and communication. So this afternoon, we will release just the tip of the iceberg. There is a whole lot of model stimulation detail that lies at the base so briefly I will go through who the team is, some background of abemaciclib and the model informed development and _____. So first off, this work was highly collaborative. You can see a list of cross functional teammates who worked together to tell a story of abemaciclib and ultimately I would like to also extend a special thank you to the patients and their families and the site and clinic staff who participated. Without their devotion and time and samples, we would have nothing to tell you. So abemaciclib is an inhibitor of CDK4 and 6 that was approved in hormone-receptor positive HER2 negative advanced for metastatic breast cancer based on the results of the registration studies of MONARCH 1 and MONARCH 2. It is important to remember throughout this talk that abemaciclib is such _____. It is metabolized to the active metabolites that are equal potent to parent and then represent an approximately 45% of plasma exposure. With the dosing, with the abemaciclib, this is used as single agent. This is orally 200 mg twice daily. In a combination setting with fulvestrant, it is dosed at 150 mg orally twice daily and it is also important to know that dose reductions are permitted per individual tolerability at 50 mg units to a dose of less 50 mg twice daily. So when we were building the models to hormone development of abemaciclib, we always have a purpose in mind for the models or a question. The seasonable questions that we would ask that relate to dose justification broadly. We used the models as input or PK/PD models or exposure response models. We want to understand the therapeutic window and ultimately our goal was to justify

the starting dose and the dose reductions. So there are four types of models that I am going to tell you about today. First a preclinical PK/PD model, next PopPK models then PopPK/PD model and ultimately a PD/PK model as well. So starting off at the early stages of development where in the preclinical phase and we would like to find out what doses we should study in humans and how we should be able to tell if doses are working or they might be active. So we built a model based on data in lines PK/PD data and we were able to link the possible concentration in lines to biomarker model where we incorporated the data from possible RV, temperature output and possibility of _____ which we are all downstream of the targets CDK4 and CDK6. We linked those biomarkers to inform the growth of the tumor or _____ and also model and there was also a concentration dependent off that was still cytostatic and cytotoxic. So the impact of the preclinical PK/PD model was that we were able to demonstrate its sustained inhibitions required for durable cell cycle arrest. These models supported the plan or the strategy to use a chronic dosing paradigm for patients who take abemaciclib daily with no time off or no prescribed time off. It also helped us to select the PD biomarker that we would study in patients, namely that was _____ and then it also helped us to identify a target study stage trough concentration that was needed to maintain drug or cell cycle arrest and this was a trough concentration of 200 ng/mL, and again here as a reminder these are the sorts of questions or purposes that the models were built. We are going into dose justification and we have identified the target exposure that we want to achieve in humans. So next, we were first in the human study in cancer patients. This is called JPDA and the question here is what exposures can we achieve in humans and are these exposures leading to target inhibition, and ultimately based on the results of the study, what dose should be carrying forward into registration studies. So we published the results of this publish in PK modeling last year in clinical pharmacokinetics. This was collaboratively done by Sonya Tate and Damien Cronier and others so I want to show you the results of the PK analysis. On top, we have concentration time profiles for a dose of 150 mg twice daily, on the bottom is 200 mg twice daily and that these results we are seeing that we are achieving at this dose level that targeted trough concentration at 200 ng/mL, and then we were able to get the target phospho-Rb in cancer patients. These were based on skin biopsies taken at baseline and that study state and here we are finding the change in the phospho-Rb

from baseline versus the total daily dose and so I told you we have a data at 150 twice daily and 200 twice daily so this 300 mg represents the 150 twice daily and then 400 this is the 200 mg twice daily, and so based on this analysis of biomarker data from patients with cancer, we are seeing target inhibition, it is maximized at those levels of 150 or 200 mg twice daily and ultimately in this study, the maximum tolerated dose was identified as 200 mg twice daily and that is one of the dose levels that was carried for into the registration study but we also used the dose of 150 mg twice daily and so the modeling and simulation work that we did in the study helped to support carrying those doses forward into registration studies. So now we fast forward to the time when we were preparing to see the data from registration studies MONARCH 1 and MONARCH 2 and we need to develop a population pharmacokinetic model because we need to do covariant screening to determine if there are any patient level cofactors that would require dose adjustments but we knew that we are going to have a lot of data from a lot of patients because we are incorporating data from that first study I just showed through JPDA. The data from MONARCH 1 and an extensive clinical pharmacology package when we have data from our C14 study and _____ study, a clarithromycin interaction and rifampicin interaction study so it is a lot of data and knew it would be a computational intensive exercise so we developed an intermediate model and that is the structure of the model I am showing you here. It is a two-compartment model and this is full of _____ only and we used this as a tool to screen the covariants that we were just to see things impact dosing and with this small _____ we screen for those covariants, those that came out of it or if we tested in our ultimate model population pharmacogenetics so _____ where we incorporated that in the metabolites as well and here is the structure of that model. It is a mechanistic model and we wanted to be able to describe the exposures not only of the parent but the active metabolites and to _____ and that is important because given their activity, they could be contributing to both advocacy and safety, only needed a way to output exposures to determine if anyone _____ was driving either efficacy or safety and we used all of the data and fit this model to it and this is what we used as input for other exposure response analysis and modeling. So the impact of this model, we were able to describe the disposition of the parent and to active metabolites highlights and it was useful for exposure response analysis and it helps to understand the relative

contribution of the parent and the metabolites to respond at length and we were able to understand the covariant effects that could impact those, and one of those _____ is weight. So here we are finding that trough concentrations of abemaciclib M2or M20 versus weight and there is no appreciable impact of weight by any exposures. Therefore we do not need to have dosing based on weight and that supports the paradigm that we have used and these were all we so expect and may need _____ presented last fall at _____. So one past forward to the time, we have the results from MONARCH 2. This was a phase III study randomized control _____. Patients received either fulvestrant plus placebo or abemaciclib plus fulvestrant and these are the results from a plan _____ analysis. This is the standard analysis we have seen at this time throughout the drugs that we see something that we know FDA might expect to see. The good news from these results are that for any _____ of abemaciclib exposure, there was longer progression for a survival compared to the control group for those who received placebo plus fulvestrant control group is here in the bottom line and here you have the _____ of the abemaciclib exposure, and if you have seen on, we might have already noticed that the lowest _____ of exposure here is on top and there is a miracle tendency towards longer _____ for patients who have the lower exposures. This presented a problem for us because you might conclude that we should not be using that maximum tolerated dose approach and maybe our efforts to achieve that trough concentration of 200 ng/mL were misguided but here one of the challenges we are facing is time because I told you about dose reductions that are permitted for abemaciclib. The longer a patient is on study, the longer PFS they have, will also the longer opportunity to have for dose reduction so we were looking at a single summary metric for exposure and we are calculating that based on average exposure while on study, there is correlation or a confounding between low exposure and long time on the study. So that is one problem with time but this is where modeling has a unique advantage to be able to help us to understand the impact of time because this sort of _____ analysis is really more suited to understanding the impacts of factors that exist before a patient moves on the study, not only suited to address time varying _____ like what we are seeing here with exposure but another problem with time is that we have these top claim results and we need to submit quickly. We would normally like to take three months or so to build the model to help us to

understand the relationship between abemaciclib concentrations and the response _____ but we do not have that much time. It is our own effort we did it quickly and we got our result. We started off for the change in tumor sites model and we have abemaciclib concentration dependent fact and there is also fulvestrant impact here because we have data, all the patients in the study were receiving fulvestrant. We have a transient compartment model, where ultimately the concentration and impact leads to cell death, and here is a spot of the results from that model. Here we are seeing a positive slope where higher abemaciclib plasma concentration results in faster tumor shrinkage so we are starting to trip away at that initial conundrum where we saw the opposite relationship. When we took those step further and we built a model for the hazard of progression and this hazard model includes not only a concentration dependent that directly on the hazard of progression increase survival but there is also that we have that concentration dependent fact of the change in tumor size so progression-free survival versus time in weeks, the abemaciclib plus fulvestrant group is depicted with the gray line, the observations of the line and the shaded areas are the model prediction of the data so you can see that the model that we have built predicts the data well, and here the relationship between concentration and hazard is that higher concentrations lead to a lower hazard so again we tripped away at that initial conundrum and this ultimately supports the dosing paradigm where we need to start at the higher dose, in this case it is 150 mg twice daily in combination with fulvestrant and we can lower the dose for patients who needed for individual tolerability and we have simulations that showed the relationship between the median progression groups survival's line and the dose. The simulation was from the model are predicted here in black and there are two groups, two abemaciclib groups, the green represents the patients who started at a dose of 200 and by amendment a short time into the study, we reduced the starting dose to 150 mg due to unacceptable fall rates of diarrhea and then the next group of patients started out 150 mg twice daily. There was not a significant difference between these two groups but there was a significant difference from the placebo group. So this PK/PD modeling approach where we incorporated individual dosing changes as a concentration change in tumor size and survival confirm the appropriateness at the starting dose reductions that were used in registration study. This is very important and might have the results from the static _____ analysis and this

helped us to define efficacy portion of therapeutic window which could be used to evaluate scenarios such as the impact of the true defect or drug interactions. So as a safety side of the therapeutic window, neutropenia is one adverse event that we see so we took the neutropenia data and we wanted to understand the relationship of abemaciclib exposure on that. We have fit the free bird model to the data and we saw a concentration dependent effect. Here we are seeing the inhibitory effect on neutrophil progenitor cells versus concentration. There is a positive but non-linear relationship and this helped to confirm our understanding of the low frequency of this adverse event and how just you define the safety side of the therapeutic window which we could use in evaluation in different scenarios. So finally I wanted to tell you just a little bit about the PD/PK model that we developed. Remember that was _____ and its metabolized to the active metabolites M2 and M20 but the fraction of the _____ of those metabolites are also metabolites _____ but the parent has a larger fraction metabolized than the metabolites _____ and so when you have a drug interaction that would _____ for, the effect on the parent is bigger than the effect on the total active species. So when we built this PD/PK model, we could understand the impact of scenarios on abemaciclib and the total active species and that helped us to make dosing recommendations for drug interactions that we have in study. We put that clarithromycin and rifampicin but we were able to make recommendations for the label for drugs like diltiazem and verapamil and _____. So by way of summary and conclusion, we tabulated the types of models that we used and the decisions that we were able to make or how these models have turned informed the development of abemaciclib. It is important the dosing paradigm of continuous twice daily dosing. It helped us to identify and confirm the target systemic exposure. It helped us to figure out which biomarkers we should look at in patients, what does with _____ violation in dosing. Very importantly, it helped us to confirm the acceptability of the starting dose which started out as a bit of a riddle. It helped us to understand the risks for adverse events that might be associated with changes in exposure and it helped us to note the dose adjustment recommendations that had not been studied in clinical studies but we were able to simulate. Thank you very much.

[Applause]

Moderator: I think we have time for two questions.

Audience: Yeah. I wonder _____.

Turner-Jones: So if I understand the question, you're saying here's the model to see if we could reproduce the original quartiles from the static analysis when we took the static. That's something that we haven't tried, but it would make sense that it should be predicted—

Audience: We're not really interested in _____ because here essentially _____ divide into groups and _____ predictions so if you're saying that this model is _____ prediction, it would be able to reproduce the _____.

Turner-Jones: Yeah, thank you for the suggestion.

Audience: I was wondering since you modeled _____ whether you tried to incorporate toxicity or at least _____ entities in your _____ model.

Turner-Jones: In terms of if you have a neutropenia event, would that then trigger dose adjustment?

Audience: No, whether that would change this _____ because I mean at the end of the day, the x_____ of the patient is a balance between the efficacy and toxicity so…

Turner-Jones: That's right. I guess another way to frame that would be is it required to dose to neutropenia in order to achieve longer progression-free survival.

Audience: Yeah. Just wondering if you could try to model that.

Turner-Jones: Yeah, I think it would be…we could try it, yeah.

Audience: Also a suggestion. When you did the _____ survival analysis, if you remove _____ because it could be that the higher the concentration _____ seeing dropout effect so sometimes when _____ this analysis and then remove _____ then we see actually nice curves which by the way _____ because again it is _____.

Turner-Jones: So one of the details in the _____ we did handle dropout in the model so it should be taken care of here with our dynamic model.

Moderator: Thank you. Our next speaker is Dr. Chao Liu. He is a current team leader in the Division of Pharmacometrics, and

he will discuss how we as reviewers apply modeling _____ analysis to NDA review.

Dr. Liu: Thank you. Good afternoon. My name is Chao Liu and I'm from _____ at FDA. It is my great honor to do this presentation at this session. Today I would like to talk about models _____ NDA/BLA review for presenting two review cases. Before starting my presentation, I'd like to make a disclaimer that the views in this presentation represent my personal opinion. We are presenting these two review cases. I will show that _____ the analysis of _____ response relationship may _____ assessment of efficacy, safety as well as dose. In addition, modeling-based analysis _____ can be used to _____ two cases can provide some insight to _____ in terms of the relevance of the modeling _____ analysis for NDA/BLA review.

I will start my presentation _____ case of rociletinib, an EGFR inhibitor for treatment of non-small cell lung cancer. The second case is about lenvatinib and everolimus combination therapy for the treatment of renal cell cancer. In this case _____ analysis was used _____ trial. It shows _____ of each case.

Let me first provide some background in the first case, rociletinib. Rociletinib is an EGF receptor inhibitor that was developed for the treatment of T790M mutation-positive non-small cell lung cancer. The efficacy was primarily assessed by _____ dose levels from two clinical studies. Based on _____ 625 mg b.i.d. for approval. Hyperglycemia and QTc prolongation were the two major adverse events of special interest. During the clinical study, patients across different dose levels were not randomized. The pharmacokinetic causes of rociletinib are shown here. Rociletinib _____. Therefore in the clinical studies, rociletinib was administered _____ rociletinib is converted to two major metabolites, M502 and M460. These two metabolites are responsible for hyperglycemia and QTc prolongation. Hyperglycemia is primarily attributed to M502, and QTc prolongation is attributed to M460. During review, we _____ relationship over a dose range from 500 to 1000 mg b.i.d. _____ non-compartmental analysis on the left, and the population _____ analysis on the right _____ each part represents a steady-state AUC of one individual

patient. The _____ analysis on the left was based on the _____ data collected from a subset of the subject _____ AUC of day 15 of cycle 1 is flat, suggesting _____ over the dose range of 500 to 1000 mg b.i.d. The plot on the right shows the dose exposure relationship based on _____ analysis of over 300 patients. The _____ plot represents the distribution of the individual exposures. _____ results from the _____ data. Subjects with 500, 625, 750 and 1000 mg b.i.d. doses showed _____. Thus, based on the _____ analysis, we concluded that dose exposure relationship as flat from 500 to 1000 mg b.i.d. We also evaluated the exposure response relationships for efficacy and safety of this drug. Exposure-efficacy relationship between rociletinib _____ response rate was explored using data from patients who were treated _____. The relationship was _____. In the plot, the mean _____ 95% _____ of the observed response rate of _____ rociletinib exposure _____. The actual plotline _____ represented _____ is 95%. _____ represent the distribution of rociletinib steady-state AUC at each dose group. The plot shows that within the smaller range between 500 and 750-mg b.i.d. doses, the effect of the drug exposure to efficacy _____. Using this model, the predicted ORR for the 500, 625 and 750-mg b.i.d. dose _____ risk factors were identified. Based on the exposure-efficacy analysis, the results _____ efficacy across different dose levels. No meaningful different in efficacy would be expected by increasing the dose level about 500 mg b.i.d. _____ M502 is primarily responsible for hyperglycemia. The plot on the left represents the exposure-safety relationship between M502 steady-state AUC and the instance of grade 3 or 4 hyperglycemia as evaluated by the FDA. _____ 95% _____ of grade 3 or 4 hyperglycemia _____ M502 exposure are represented by the _____ represent the _____ incidence of grade 3 or 4 hyperglycemia _____ represent the distribution of M502 steady-state AUC at each dose group. For exposure-safety analysis, there appeared to be a correlation between increasing M502 exposure and the incidence of grade 3 or 4 hyperglycemia, suggesting that a patient with high M502 exposure has a greater risk of grade 3 or 4 hyperglycemia. _____ M460 is responsible for QTc prolongation. As shown on the right, a model predicted correlation between M460 exposure and QTc prolongation but the _____

concentration of M460 and _____ from baseline. The solid _____ represents the predicted change from baseline _____ QTc _____ correlation between prolongation of the QTc interval and the increasing M460 concentration. Finally _____ similar exposure from 500 to 1000 mg b.i.d. _____ from different dose levels will provide _____. In addition, based on the identified exposure response relationship from 500 to 750 mg b.i.d., patients with higher rociletinib exposure are unlikely to have further benefit. However, subjects with higher metabolite exposure are at greater risk for QTc elongation and hyperglycemia. Thus we _____ proposed 625-mg dose was not adequately supported based on available data. FDA's analysis was _____. Along with other issues _____ approval based on available data. A complete response _____.

In the second part of the presentation, I'd like to talk about _____ collaboration with _____ analysis _____ marketing trial. In addition, the novel analysis strategy was used so that drug toxicity _____ can be _____. So that _____ tyrosine kinase inhibitor _____ approved as a first-line therapy for the treatment of differentiated thyroid cancer. In 2016, lenvatinib was approved for the treatment of metastatic renal cell carcinoma as a second-line therapy in combination with everolimus. The approved dose is 18-mg lenvatinib plus 5-mg everolimus q.d. In the _____ trial, patients in the lenvatinib/everolimus combination _____ shown here in the _____ shows significant improvement in progression-free survival as compared with arms of lenvatinib or everolimus _____. However, 89% of the patients in the combination arm had dose reductions or interruptions due to _____ drug toxicity. Thus, safety was one major concern about the approved dose _____ issues by the FDA to optimize the dose _____ a post-marketing trial. For the selection of an alternative dosing regimen to study _____ exposure-based model simulation _____ dosing regimens to find out the most promising candidate. _____ analysis at each case is how to handle the dosage _____ dose adjustment and one subject _____ trial. In this case _____ overtime. It is challenging to define _____ at the subject level _____ response analysis and _____ representing the drug exposure derived from average dosing intensity over treatment _____ estimate of the E-R relationship. For example,

assuming the progression-free survival was used as an efficacy endpoint. For a subject who progresses soon, the duration of the treatment will be short. The patient may have no chance to experience _____ dose reductions and thus still remains at a higher dose level _____ average exposure could then be higher. On the other hand, a subject who progresses later stays longer on the trial and thus has a higher chance to experience more dose reductions and _____ exposure. The _____ average exposure and efficacy would be appear to be flat or _____ estimate of the exposure _____ relationship.

To address these challenges _____ model strategy was adapted. The standard of using a constant exposure matrix subject level _____ exposure matrix was used _____ tumor size was used to assess the drug efficacy. In terms of _____ safety _____ AE was associated with _____ exposure. Finally in the simulation _____ to address the _____ dose adjustment _____ trial _____ to incorporate the dose exposure-safety interaction. The exposure-safety and efficacy relationship between lenvatinib and everolimus _____ tumor size was explored _____ trial. _____ tumor growth rate _____ to the natural growth rate minus the suppression effect from lenvatinib plus everolimus. _____ from the three arms of the previous study _____ to estimate model parameters. Tumor _____ growth rate was referred _____ study where a placebo arm _____ renal cell carcinoma _____. Meanwhile through communication with FDA, a longitudinal _____ AE _____. AE is _____ dose adjustment were treated _____ and this model will be used to predict the dose _____ regimens to form the dose adjustment cost by _____. So in terms of selecting the alternative dosing regimen _____ dosing regimen were simulated to predict the efficacy and safety profile. At each dosing regimen _____ dose adjustment _____ adverse events was _____ overtime based on the _____ E-R _____ of a single-agent dosing history overtime where each dose level is represented by different _____. Finally based on the generated dosing history, the tumor dynamics was simulated _____ efficacy at each dosing regimen. This slide shows the simulated tumor dynamics. At each graph, the X axis is the time of the treatment up to one year, and the Y axis is the relative tumor size compared with baseline. _____ is a single agent _____ values of the tumor dynamics.

The dosing regimen of 18-mg lenvatinib plus 5-mg everolimus served as the _____. We first evaluated _____ lowering the lenvatinib dose would provide comparable efficacy. Dosing regimens of 14, 12 or 10-mg lenvatinib plus 5-mg everolimus were validated. None of them was able to provide the same magnitude of tumor suppression compared with _____. Upon further simulation, we found that implementation of _____. In this scenario, a patient could be uptitrated to a higher dose level _____ if the patient did not experience any _____. The dose cap of lenvatinib was set to 18 mg. When up-titration option is provided _____ lenvatinib starting dose could provide comparable tumor suppression compared with the control. In terms of _____ lenvatinib, _____ requirement was _____ to optimize the dose, and 14-mg lenvatinib plus 5-mg everolimus was selected as the alternate dosing regimen _____.

The end of this presentation will just be a revisit of the take-home message. The modeling-based analysis _____ relationship facilitates FDA's assessment of efficacy and safety. In addition _____ review, drug exposure-based modeling can be used to form the trial design for the post-marketing study _____ frequent dose reduction _____ should be perfectly incorporated. Last but not the least, I'd like to thank my FDA colleagues _____. I'd like to especially thank Dr. Yaning Wang who led to _____ and Dr. _____ who performed the pharmacometrics analysis _____. Thank you very much.

[APPLAUSE]

Moderator:_____ question? If not, we will move to the third one. The next speaker is Dr. Daniele Ouellet. She is the Senior Director _____ group leader under the Global Clinical Pharmacology from Janssen, and she will talk about _____ from the post-marketing perspective.

Dr. Ouellet: Thank you, everyone. Thank you for having me present today and for putting together this workshop. I think everything has been really interesting so far. So as Yaning said at the beginning, the purpose of the last session was really to look at model-informed application for late stage _____ it was nice to hear the regulatory perspective, and here it is really post approval so trying to find an example where we use a model-informed decision to support _____ post approval. So the example we are going to talk about is with ibrutinib, a BTK inhibitor. _____

the context of _____ activities that we do also in terms of the post-approval stage of what is going on. So most of you are familiar with this figure that comes from the paper that was done by the MID3 workgroup so _____ model-informed drug discovery and development _____ and really talking about the impact that it can have at the different stages of development. So we have heard a lot of different case studies, but what is really important is what kind of decision do we make based on that. So really _____ her in development, it is all about selecting the target, selecting the dose, optimizing the study design and things _____ tumor model will be nice _____ really start to integrate that and optimize some of those decision we make _____. Then I think Kellie showed a nice example of understanding the risk-benefit characterization for when we submit, and then post approval _____ to see here the darker green, the questions are a little bit different, right? So it is about extending to different patient population and it is about _____ drug combination, how do we support the combination after the first approval. So looking at the _____ we have and the activity we spend supporting these projects that have been approved _____ and the idea here is that we are lucky that we have a lot of different information and understanding of those relationship between dose and exposure. We have done a _____ model _____ package and also between exposure and efficacy and safety, and it is really capitalizing on that knowledge to inform and be efficient when we go to this other _____ population. So part of what we do is really bridging _____ and the question we ask ourselves is always, okay, so what do we do when we go to a different tumor type? Should we go with the same dose? And then the question we have to answer upon treating _____ manner is verifying the assumption that we have. Is the patient population really similar to what we have? Is the tumor _____ similar to what we have studied or are there any difference there worthy of concern? Is the tumor burden _____ so thinking about these things and seeing what can we do to leverage the knowledge we have. A lot of the activity post marketing is also on pediatric. I think there has been _____ workshop there to show the value of model-informed drug development in dose-specific indication, and I think it is well accepted in that particular aspect. The other one is really supporting some of the labels. Someone this morning mentioned that especially in oncology,

the drug development and approval is really fast and sometimes we do not have as much time to optimize perhaps the formulation that you have to take multiple capsules or tablets, so there is some work being done post approval to do that, and completing sometimes the clinical pharmacology package that there is a little bit of gap there, just given the speed of trying to get the drug to patients as quickly as we can. So again, that is really capitalizing on what we know _____ these other activities.

So I'll talk a little bit about ibrutinib. So ibrutinib is a BTK inhibitor. So BTK is part of the signaling pathway for the Bruton tyrosine kinase, a part of the B-cell receptor _____ here will stop somewhat the B-cell activation so any B-cell malignancies that _____ abnormal activation of the pathway, it has been found to be really useful and has shown efficacy in those type of malignancy. Ibrutinib is a covalent inhibitor so _____ IC50 less than 0.5 nM, and it binds to the cysteine residue of BTK. If we look at the indications so that in the US, the first time it was approved in late 2013 _____ approval there in MCL second line, and then it has received several _____ approval, as I said, in different B-cell malignancies, either _____ combination. The most recent approval is actually in chronic graft versus host disease, a little bit different patient type there.

So specifically for ibrutinib, if we talk about how to use model approach to support different indication, those of you who know a little bit ibrutinib know it is a very sensitive _____ substrate. So as part of the late-stage package, a lot of activities that we do are still under using a PBPK model _____ the drug interaction package. When we first submitted, we had a couple of drug interactions with _____ inhibitor, and then we worked closely with the FDA to really understand the different _____ of different _____ inhibitor, different types of inhibitor because we could not study all the different scenarios. With PBPK, it was really _____ ibrutinib to understand some of these effects and estimate those. So I think it is a really nice example _____ the example that I talked about. So we have had to fulfill a couple of PMR and post-approval measure, and we had to a study with omeprazole so that is the example also _____ it is a very specific sample of how we use

model-based _____ is also around the pediatric development using the PBPK model to help with estimating that starting dose versus _____ matrix scaling approach, and I think most people will have some model approach with that. So for those _____, bear with me while I explain the _____ study. So really this was a _____ study with PPIs or proton-pump inhibitor. Ibrutinib is wheat-based so it has a pH dependence _____ high pH. It is a BCS class 2 so high permeability and low solubility _____ with rapid absorption, Cmax within one to two hours. Ibrutinib _____ effect so it is sensitive to blood flow so if you take it with food, it is going to activate blood flow; therefore, you see an increase in exposure with food so Cmax two to fourfold increase and then you see about a twofold increase. It has nice safety so it is still a BTK that can be taken with or without food _____ even with food, it is within the range of what has been studied. So the study objective was really to evaluate the effect of omeprazole given for four days _____ single dose of ibrutinib _____ study design, we gave ibrutinib alone first and then a week later gave it after four days of omeprazole, so making sure that the pH was really elevated and we could see the effect of pH elevation. So these are the results. So the concentration, a very different kind of curve. So the open circle here will show the PK profile of ibrutinib alone so you could see how _____, and then the full circle will show the effect of ibrutinib with omeprazole. So lower Cmax but you could see the profile is a little different and some residual absorption there _____ that the AUC was actually maintained a little bit versus ibrutinib alone. If we look at what the PK parameter will look like, on the right _____ for Cmax of about 0.37 _____ AUC was pretty much similar between the two treatments_____ AUC 24, AUC 48, AUC _____ there is a little bump in the ibrutinib profile so _____ calculated in enough number of patients. You can see a little bit delay in absorption, two hours versus one hour; and in the half-life, a little longer here, I think just because of that residual absorption. _____ so on the top there so it is Cmax with ibrutinib alone and ibrutinib with omeprazole, and the cartoon below is the AUC. So again, AUC was fairly consistent _____ subject while Cmax, you could see a lot of subject _____. I think we felt fairly confident that _____ probably would not have an effect on efficacy and safety and we

could recommend to take it with PPI, but we really wanted to be able to support the clinical recommendation of what to do with this pH-altering agent. So we understood well the mechanism of action. Again, it is a covalent binding so what we decided to do was really to develop this mechanistic model based on the kinetic of binding and dissociation kinetics _____ and look at the effect on our target engagement, so taking target engagement as a surrogate for efficacy. Again, using this mechanistic model, I think somebody asked this morning on how you validate this. So what we did was to do some sensitivity analysis to look at _____ of the model given different assumptions into its parameters. We had some BTK _____ data so we kind of used that to make sure the model was doing, what it was predicting was appropriate. We also had done similar exposure response for efficacy based _____ Cmax and tried to use that also in supporting _____ recommendation. So this is the mechanistic model of BTK. So _____ represent the enzymes with BTK. I represented ibrutinib inhibitor and so you have formulation of the complex here, k_{on} _____. Again, it is a covalent binder; and then your inactivation _____ complex and into degradation that you could see from BTK _____ of the complex and also _____ itself. So what we did was that there was some published data that had been done on the association and dissociation _____ for ibrutinib on BTK, so we used these data. There was another publication that also had done some time-dependent studies _____ BTK half-life to inform that _____ degradation again from another publication that talked about the turnover of the BTK. So we plugged in these different assumptions there, the different _____ the different parameters to try to estimate what would be the _____ ibrutinib. Then here the concentration profile _____ what the I profile would look like, right? So what was the profile _____ omeprazole so we can look at what the effect was going to be with the _____ receptor _____. So this is the resulting simulation data. So we basically did the simulation up to steady state so the timescale was basically here _____ 24-hour profile at steady state, and here represent the receptor occupancy. So for ibrutinib alone, you could see there is still a little bit of variability _____ the day but all above 90%. With omeprazole, you can see that the effect, if anything, was just to _____ dose variability. So if we calculate the average receptor

occupancy, it was comparing 94% and 96% so very similar. So we felt fairly confident that this was really going to be helpful to make recommendation that _____ no difference. Let me skip to this one. So that is the data that we have following single dose, and single dose really kind of is an agreement with data. So on the open circle here, you got the PK profile _____ as you have seen with the omeprazole study _____ fairly rapidly from circulation; but you can see that the BTK here engagement, we have measured that at 4 and 24-hour that the enzyme, you see the complex formation. Because of the half-life of 24 hours for BTK turnover, it is maintained across that dosing. So the results of the simulation were consistent with what we had observed in that study. Again, as I have said, we did some sensitivity analysis for the different parameters, and we really stretched some of these _____. So threefold variation here for the BTK half-life so the _____ 24 and then we ranged between threefold higher and threefold lower to see the impact. So the impact was really actually not that much. It was about, at most, 10% on the affected cells; but if you look at the difference between the two treatments, that was also a very small kind of effect. The effect of _____ that was really nothing because the _____ is minus 1 to 1% so a very small effect even if you change the value a tenfold factor. Here a little bit more than it packed on k_{on} So if you _____ tenfold down, you can see _____ change, but if you increase that tenfold, then you will see a change in the BTK predicted value; but again, the difference between the two treatments was still very similar. So we felt that was really _____ assessment of our assumption there. We also had done some of the efficacy and exposure relationship so looking at just responder rate versus _____ quartile and exposure, on the left, there is Cmax; on the right is AUC. So there was really no relationship and you can see there is a fairly high life range and concentration, about a hundredfold there. Again, the drug _____ you are going to see some _____ variability; but the dose was selected to make sure that most of the patients would be above that 90% inhibition in 90% of your subjects so that kind of supported that as well.

So basically the conclusion were this mechanistic model was developed to really support the outcome of this drug interaction study with omeprazole and to be able to provide clinical recommendation _____ adjustment obstruction with the use of ibrutinib with PPI or other pH-altering

agent. The data supported the lack of clinical relevance or changes in Cmax which really _____ AUC that was similar between the two treatments. In terms of these examples, I think it is a nice small example that demonstrates the value of different modeling approaches. This one was a mechanistic model that really supports some of the conclusion that we want to make and some of the questions that we may have. I really want to acknowledge the people who helped and did some of this work, so _____ here is the _____ for ibrutinib worked closely with this _____ and, of course, the one who did most of the modeling here and these guys really helped with the omeprazole clinical study; and many more people that I am not mentioning here. That's it.

PANEL DISCUSSION

Moderator: Any questions? We can just invite all the speakers back if you have any questions and can ask them together, and we will also invite two additional panelists to join us to address any questions you have on this late phase _____ just use our own two additional FDA panelists, Dr. Pat Keegan on the far left and the community doctor of the division of oncology department too, and Dr. Lei Nie. She is one of the statistical team leaders covering oncology products. Again I will give them both an opportunity to give some comments, since they have not mentioned about this late phase.

Dr. Nie: I think in the opening remark is some talk about a Catch-22 dynamic. I think the speaker illustrated nice work that could be part of the solution, that is my first comment. My second comment is all the speakers are non-statisticians _____ I'm very impressed and I really hope a statistician can additionally more contribute to that aspect. A comment for this session is I would like to mention that the first speaker and second speaker also mentioned the difficulty of the exposure response, and the first speaker illustrated the dynamic nature, the low dose associated with _____, the high dose associated with _____, and the second speaker talked about you really need to see the dose all the time. That is a well-known concept in statistics because dosage is a cause of the efficacy, also in the constraints of the efficacy and safety, so we have to put these relations in the model. It is very complex and rarely in the past that has been considered. Thank you.

Dr. Keegan: Thank you. So I guess I'm going to start with comments that cover from the opening remarks as well, and I think that Dr. Woodcock is right. There are so many aspects of drug development that really incorporate a lot of knowledge in technology, and clinical trials is a little bit lagging behind here in oncology in terms of addressing new models and incorporating a lot of the really interesting science that we heard today. I would say that it took the rare and the phase 2 meeting where someone walks in with a fully developed pharmacokinetic analysis that says to us based on our review of everything that's happened thus far, we now know so much more about how to dose this drug. I would say I could probably count on one hand how often that happens, so I think that Dr. Woodcock is right that we really do need to use this new information to really inform phase 3 drug development, and so in that sense, I felt that the last topics in particular were really interesting and illustrated both how you can use that data to inform as well as what happens when you don't, and then you have an application sitting in front of you and realize that there's big trouble. I think the examples illustrated, you know, in one case, a drug that couldn't be approved because there was so much that really wasn't evaluated during the drug development process, critical aspects which may or may not have been addressable but certainly should have been discovered at the time of the marketing application. In other, and this is a situation we found ourselves in for many decades in oncology and should know what we're getting ourselves in, which is approving a dose that we don't feel comfortable with, that we feel that is unlikely to be marketed or accepted by the community, and we shouldn't be at that point anymore. We should actually know more. Another aspect that I think was touched on a little bit that in the morning, when we were having all this discussion about picking doses and looking at dose-limiting toxicity, I think one thing that I didn't hear as much of and I would have liked to was that when we talked about dose-limiting toxicity again, we are back at the cytotoxic base. People have grade 3 or 4 toxicity, and we're not…it does not fit the current paradigm for cancer development. You either have therapy and usable proteins with prolonged exposure for daily dosing of drugs and we no longer can just consider what's a grade 3 or 4 as we did when we gave cyclical chemotherapy every three or four weeks, and it was only alopecias, nausea, vomiting, and some cytopenia. We have very many different toxicities now, and many of the

grade 2 toxicities are equally intolerable or problematic, particularly in patient populations that are going to be taking the drugs for a long time. So as we get to more highly effective drugs and longer exposure and chronic dosing, I think we really need to rethink even the dose-limiting toxicity paradigm. To say that grade 2 fatigue is tolerable is kidding ourselves. To say that, you know, grade 2 hypertension over years is a good idea is not getting through. So I do think that we need to, as we look at some of the early models, we need to rethink how we approach dose-limiting toxicity. I think as we go into the phase 2, we need to look at a lot of these things like how tolerable were the drugs and what are the toxicities before we enter phase 3, because I think we're missing a lot of opportunities for successful drug development. While we'd all like to get to the end as quickly as possible, we'd also like to get there with a satisfactory end. We don't want to have a drug which, once it's out in the market, people are still trying to figure out how to use it or still concerned about the dose. I'm not _____ because the statistics are hard and beyond me, but this is a really fascinating presentation.

Moderator: Thank you. Any comments or questions from the audience?

Nie: _____ So it was a really great day when a lot of case studies _____ as well as the late phase and the post marketing area. I think we all agree that integrating all the data will help us to describe, explain and hopefully as well predict better and better what people are going to see. I think what we are today here is also trying to understand how can we move this field forward into good practice, so where…and I would also like to comment about how can we move this forward into good practice where there is methodologies or the different application areas where there is some points of considerations or guidance. How should we do in order to also from a small track perspective drive this forward.

Moderator: Good practice. Yes, that's in our objective.

[LAUGHTER]

Keegan: So I'll start with one that was started on a little bit. There was concern that, you know, we do these details up in phase 1 and then we don't look at it and we don't consider the phase 2, and some people brought it up that we don't do much dose ranging in phase 2. One of the reasons it was

mentioned was we do have to slow things down. I think we're going about as breakneck speed as we can with a lot of the seamless design trials and I think there's no reason not to take opportunity to continue to do a lot more evaluation in those phase 2 with those ranging in schedule assessment and then getting that data, particularly in those expansion where you remove the variability in patient population and usually focusing on one disease entity. It makes it less problematic and, you know, there's always some variability. I would suggest that I think a lot of my colleagues in pharmacology would suggest that dose ranging continues with the phase 2 portion. I don't think it has to slow it up that much if, you know, you build it into most of the trials. I would caution over interpreting that data, which I think was part of the strategy, but I think, because they only looked at one aspect and not the whole thing, but I do think that would be the best practice.

Nie: Okay. I can have statisticians talk about my idea and using that idea and talk about the life cycle approach. The ideal approach is early phase clinical use data and find a good study. Use a good methodology and find the phase 2 dose. In phase 2 dose, it depends. If it is really efficacious and no toxicity, then go ahead, just a single may be okay. But _____ the drug and find a good dose for phase 3. That is the ideal approach. But if this is not, all of them talk about the life cycle approach _____ You cannot do a profile in phase 1, you try phase 2. If you cannot do phase 2, phase 3. But if you're not happy with the dose, you can go to phase 4 and continue to optimize that. For many cases, going to phase 4, we can find the right dose by going the life cycle approach. Thank you.

_____: The only thing I was going to add in and I don't know if you have somewhere you wanted to go in terms of moving the field, right, so there has been a lot of these tumor modeling approach and obviously you develop this model once you get your late stage data and it's how you circle it back to the early data. I don't think we have that many example of applying it for. I think that something is a community that, you know, we can share some of these knowledge and there's always a question that if you go in a population that's a little different that has a different genetic mutation, how are the application of these models? Are they still valid? I think we still have some homework to do, especially in those cases. I think we did good in

sharing the…publishing these data, but I think to apply and treat it for, it's hard to do within, you know, a company that got to cycle all the time to be able to do that, so there's probably…there's something there that you can put in practice.

_____: Just some comments in terms of the tumor modeling efforts from the community. The things move forward rapidly, especially for the renal palliative therapy where for many cases the drug effect is starting directly on the tumor per se, but we have an immune system. So in terms of that, it a new concept in terms of how do we _____ or drug effect into this kind of a tumor suppression. For some drugs, this is always there and it could extend into effort with it before for _____ four doses, but the tumor suppression is sustainable, which means that the _____ activates some kind of a system, either through _____ or some other system which may not be fully described or based on clinical data, but each will be incorporated to _____ sustain the tumor suppression in immune drug use after some kind of period. So I think before we come up with a universal or good practice of this kind of effort, right now, still I think the community is trying their best to collect more data and especially in the combination therapy where it may have synergetic effect from both components in oncology which may even more complicate this kind of tumor model. So I would like to see more study results or data collected before we can come up with a good practice to address these clinical complicated issues.

Audience: I have one question. Is this on?

Moderator: Closer, closer to the mike.

Audience: One quick question.

Moderator: How we're all friends.

Audience: I did mean to ask a question for that.

[LAUGHTER]

Audience__: Alright, so I'll just speak loudly.

Moderator: Why don't you come up, there are people on line.

Audience___: I'm just wondering if anyone knows this. How do we go from model-based drug development about 10 or 15 years ago to modeling for drug development? Have we gone soft over age or is there some other reason for why

it's deformed? Alright, okay, so I'll go to the second question…

[LAUGHTER]

_____: Which is an interesting anecdote and I'm glad there's someone here from the FDA biostat department. So this is a…and I don't if this meeting between biostat and clinical pharmacology occurred on the FDA side or the sponsor side, but there was a situation where we had an active dose escalation algorithm in place and the operating characteristics showed to one of the reviewers on the _____, there was concern that there was too much probability of overdose. On the pharmacology side, there was a request to insert a new second dose, so instead of jumping from, I don't know, say 1 to 10 mg, 1, 5, 10, something like that, so what happened was that the operating characteristics did not get any better when we inserted that in intermediate dose because the scenario required that the second dose was toxic irrespective of the magnitude of the dose, so that means there was no inherent…there was no underlying pharmacology model for probability in toxicity and no concept in pharmacology, so it could have been 1 mg or 1.1 mg. The scenario seemed to require that 1.1 mg _____. I don't know if that's an FDA thing or is that just something that happened, I'm just curious, on its own.

Nie: We will first try to answer your question. Is that model based that you're modeling from. You know, _____ what we do, we actually do not like model based _____or have a single-arm trial that's not modeling based. So that's why we promoted to MCT mode approach in phase 2 including many doses _____ instead of just a single dose. That's why we right now still promote more model based _____. Maybe right now, _____ and establish biomarker to simulate the model-based simulator complex design. All of these concepts were not emphasized before. With the second question, it's a little bit difficult to answer because I do not know the context, so a statistician may consider some potential risk. Doctor, do you have any comments?

_____: Yeah, I'm also from the Office of Biostatistics. I would say two _____. You got to go back to the FDA and say _____.

Keegan: Yeah, actually they may also be looking at these different aspects of what happened, right, so the statisticians are saying, just basing on the amount of work, you know, did it all basically, does it look like it's balanced statistics? You know, the clinical pharmacology people may actually have been informing and usually in a phase 1 are also preferably drawing on toxicology data to maybe suggest an intermediate dose. And then I think the third, which is, you know, the clinical people have taken a look at it to say, well, what exactly are we doing when we're exposing the people, you know, and what are the thresholds that are being used, because neither the clinical pharmacologist or the toxicologist or the statisticians are going to be able to interpret some of the rules. And I think the last is if this happened a couple of years ago, then you should just let it go, okay?

[LAUGHTER]

Keegan: We now see on a regular basis at least half of the applications coming in with some _____ dose-finding approach. And we've learned, okay, so, you know, if you get a straight answer, yes, ask, but I mean, in general, I think we were just probably gaining familiarity with the approaches.

_____: I was mostly just wanting to highlight an opportunity for the statistical side to have more pharmacological concepts for what worst case scenario is, where there might be a certain shape of the dose toxicity is the worst case scenario, not just a particular numbered dose, that's all.

Keegan: Oh, okay.

Moderator: Thank you. I hear you.

[LAUGHTER]

_____: I just wanted to follow up _____ the basic approaches that are commonly used _____. One thing I really advise is that a lot of the discussion around questions occurs in question, do I understand the question right and send it back to the FDA and understand the response. They sent back a response. It's just as easy for a call to occur to be able to clarify some of the situations. Some of the challenges around some scenarios that are presented in operating characteristics are often scenarios chosen as absolute worst case scenarios that easily could have really possibly occurred. It is also important for those

scenarios _____ the likelihood of that scenario even occurring. So I definitely encourage through a positive experience the potential for _____.

Moderator: If I may, I can add a little bit on the first question, model-based versus model-informed. To me, it really doesn't matter. In fact, if you look at the history when we were one of the few who were mainly using the model-based analysis, I can tell you, we were trying to get some resource from a group of five. We did not get it. Somehow during the PDUFA VI, there was a change in model informed. All of a sudden, industries supported PDUFA VI, and now you look at how much support you get from commissioner from PDUFA VI, I don't care what you call it.

[LAUGHTER]

Moderator: If I get support, whatever you call it.

_____: Thanks again. I was going to comment that MIDD _____ comment. And I think, you know, with immunotherapies, what we realize quite early on from the experience was that the conventional PBPK models don't really hold, because the conventional PBPK model has either a direct effect or an indirect effect. Ultimately even if there's a lag in the effect, the drug _____ you effect is gone. _____ many of these immunotherapies, they are wrapping up the system and just self-perpetuating essentially, so I think the…so what do we do? I mean, you know, rather than leave it at that, I think the answer to me is coming back full circle in the beginning of today's session where we're talking about, you know, pharmacology markers. I think those are the kinds of models that may be described in situations and eventually may have a perpetuating effect. You know, many companies have now reactive efforts in this area. I have to say, so do we. We have a very compelling example, not in oncology, but a different therapeutic area, just to give an outline where we use the system pharmacology model to select a dose for a phase 2 study for a combination therapy, so I think this is very effective for combination therapy where you have different sort of targets and then is there a synergistic effect and the model predicted the synergy very nicely and the trial was read out and the model-based was spot on, so I think, you know, bringing it back full circle I think will have a lot of potential with pharmacology models _____.

_____: I have a question for FDA in the _____. I think the publication of some basis of approvals online including the detailed report summarizing both the sponsor analysis and also the regulator analysis has been tremendously insightful and helped really to advance MIDD drug development. As we can see also from different discussions today, there are a lot of application of MIDD _____ addressing PMC/PMR questions or supplementary findings for SND and SPOA. Is there any potential…I know you're already keeping our FDA colleagues there busy, but is there any potential for them to publish basis for approvals for the supplementary findings _____? We don't need to have an absolute answer.

Keegan: First, let me clarify that when you say summary basis for approval, what you're really talking about are the original NDA and DLA review documents that are around the FDA website. We also publish manuscript primarily for clinicians usually the oncologists or cancer research, and generally those don't have a lot of information. The pharmacokinetics, I mean, it describes it but it doesn't go into as greater detail as looking at the review. The reviews can be all posted for anything that ends up, you know, with a labeling change, but it requires that we receive requests for that, so we would have to have freedom of information and request that those be published. _____ although perhaps Dr. McKee can tell us if there is. I think we internally process it. We're frustrated with that too. We would like them to put everything on, and so I'm not sure if that will be happening in the future, but if there is a particular application where you have an interest, I think the rule of thumb is like we get three requests, that's enough for them to trigger. We should put this on the website. So, you know, that's what you should _____.

[LAUGHTER]

Keegan: Also you should make your concerns known to the agency that you would like to see more of that because I think, you know, we're comfortable with doing that, but it's just not our current policy. It might be a manpower issue, but if they heard there was enough demand for it, that might facilitate faster action in that regard.

Dr. McKee: I'm Amy McKee. And just to clarify on what Pat said, it is a staffing issue within our division that redacts information that's publicly put on our website. So if you

put in enough information requests, eventually it gets put up on the list of things that will be put on the website, so any supplements you're interested, you and all your colleagues keep sending a request for it.

_____: Thank you.

Moderator: Doctor, I've heard similar feedback during the reco session. Multiple people ask me, why don't you put the reviews for the supplement online just like the original one? My answer was, I don't know. I should. As long as you request, the FDA will, you know, through the Freedom of Information, will give it to you, but I guess now you heard it. You have to request multiple times, then it can potentially be on the website for everyone to review. But I guess it's a staff issue. But in theory, they are all public information once the drug _____. I think we're…I have to thank my speakers and panelists. We went by 15 minutes because we started late, so I would like to keep this on time. We're exactly on time. I know some of you will catch the airplane, so we will move to the next one. Once again, I thank our speakers and panelists. Thank you very much.

[APPLAUSE]

Dr. Jin: I think we have had a very busy day. Thanks for still staying here until the end of the day. I will just give a very brief summary and also share some of the three key points that's touched me during today's workshop. I will try to keep it very brief.

I think one thing that's very clearly seen is MIDD oncology is a very fast-evolving area on multiple fronts, including many of the novel immunotherapies, combinations, including many development of…I don't have any slides, by the way, just in case you're looking…and also a lot of novel evolvement of experimental approaches and also end points, whether it is about a novel annual model to address immunology-related unique questions or autometric measurement for tumor size and novel biomarkers. A lot of these are evolving fast because techniques also offer us novel data versus to gain more scientific insight by analysis. We also have seen throughout today's presentation many novel quantitative approaches, whether it is more _____ modeling with a different type of modifications, whether it is more of a system modeling

approach on the PBPK front or the QSP front. Yeah, they should do that. On the more practical side, it is very exciting to see from Dr. Michael Maitland's presentation that we are also developing novel ways in electronic systems to collect more real-time patient data, whether at that side or even from patients at home, so that will give us also a unique source to understand what's happening both about the disease and also about the therapies in the real-world setting.

Last but not least, hopefully all the totality of information will give us a filter for individualizing therapy oncology as mentioned by both Dr. Jenny Woodcock and also Dr. Michael Maitland. I see practical provision in the field is really the individual patients we are talking about. So with a few of these so fast evolving, I think it's overwhelming for anyone of us to really catch up. I think we are always stronger and smarter together, so we really need to work together and also have this real-time merging of the frontier sides. Whether we are talking about the real-time merging of experimental sides and also the quantitative sides, we learn as the model learns from us where all these novel quantitative approaches real time and also for the experimentalists learning from us. What are some of these quantitative approaches? Can we use at fingertip to gain more scientific insights from their new systems? Or it's also a call for merging of even within the quantitative sides. We heard in the last session even talking between an aesthetician and also a pharmaconutritionist, not even to add additional informatics scientists, engineer system pharmacology modelers. So merging of these scientific disciplines, I think, this real-time merging will be very critical. Today we are at FDA, so it's very exciting to see this merging of the scientific approach and also record of the patients because no matter how the size we are doing, we are trying to get approved to help patients. So how to make these new size impact the record of the patient's decision making? We require this real-time dialogue among all of us so that we keep each other informed about these new evolving techniques rather than each one of us struggling by ourselves. I think this is really a common _____ that's also in the spirit of _____, but I just want to re-highlight that today.

The second thing, I think, one thing Dr. Jenny Woodcock mentioned really resonated with me. She mentioned

sometimes perception of new approaches sometimes will actually add risk, especially add risk for drug interactions. However, she is pointing out that we have to try these things in spite of the risk. We can take small incremental steps in reality, but we have to make changes. So how to make that concrete step? Hopefully in today's workshop is a starting point, but I think we really need to have a very concrete path and action pass moving forward, whether under the _____ umbrella, it means some additional followup, probably a workshop on more focused areas or the pilot ideas. I know the pilot is another workscreen for _____, maybe calling out some specific pilot ideas for areas of interest or it can maybe in the non-competitive space as mentioned by Dr. Rene Bruno for CIC or Cancer Immunotherapy Consortium or by Dr. _____ regarding writing some maybe integrating information and knowledge _____ we do that collective intelligence and help each other move forward. I think they are representing the International Society of Pharmacometrics. I think ISOP is a scientific society for including scientists like us really devoting our career for MIDD, so ISOP I think will love to be at least one of the venues to help advance these areas and we would love to hear from all of you guys whether you are online about additional ideas and see what are some of the concrete things we can link forward. Our annual conference will be happening in October in San Diego of this year and the conference theme is modeling without boundary, so it's also focused on promoting the idea of collaboration, especially international collaboration, and also fusion and integration of different approaches. So many of these are overlapping or do they seem, so hopefully we can have multiple fronts and other conferences to help to proceed the field moving forward.

Last thing I want to share one observation is today we have speakers from industries from academia and also from FDA, but there's one voice that we are missing. We are missing the voice from patients. Although patients are touched upon by multiple speakers in questions by Dr. Michael Maitland and Dr. _____, but patients are really what we are all working for. We are working for the patients. For oncology patients, this means survival. And this is about people's lives. So the last thing I would like to call for _____, so I think we're talking about people's lives here. We really need to work together. They are moving in the field at a very fast speed. Some of us have friends

and families who either battled or is battling with cancer right now. As Dr. Rene Bruno mentioned, Dr. _____ who is a dear friend for some of us and have worked almost exclusively in tumor dynamics modeling for many, many years, he is unfortunately currently battling this basal cell carcinoma and that is the reason he has to cancel his trip to this specific workshop at the very last minute. The options are running out for him and he is in very desperate need of immuno-oncology therapy. We are struggling with finding him drug access in France for immuno-oncology therapy, so for anyone who is listening in the room or online, please help if anyone of you can provide even remote help because you will be not only helping one real patient, but more importantly, you will be helping someone who is devoting his career and now his life for MIDD oncology. I think this also will be tremendously help to advance our field forward. That's all, thank you.

[APPLAUSE]

Jin: So now I would like to invite my fellow co-chair, Dr. Amy McKee from FDA to come over to give the final round of remark.

Dr. McKee: I don't…I don't think I can end with anything better than what's said other than to say thank you for everyone who came and participated. I think this is one of the most lively discussions I've ever seen in this room, and I think the one point that I would take away from this is it is clear that all of us need to have more cross-discipline talk both within our own organizations and between our organizations to use modeling to more prospectively drive drug development, so thank you all for sharing your views and your data and everything that you brought to the table today. Thank you.

[APPLAUSE]