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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
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A P P E A R A N C E S

Workshop Co-Chairs

Amy E. McKee, M.D.

Deputy Director (Acting) Oncology Center of Excellence and
Supervisory Associate Director, Office of Hematology and
Oncology Products, FDA

Yaning Wang, Ph.D.

Director, Division of Pharmacometrics (DPM), Office of
Clinical Pharmacology (OCP), OTS, CDER, FDA

René Bruno, Ph.D.

Past-President, ISO P
Staff Scientist, Clinical Pharmacology, Roche/Genentech

Jin Y. Jin, Ph.D.

President, ISO P
Director and Principal Scientist, Global Head of M&S,
Clinical Pharmacology, Genentech

Workshop Speakers and Panelist

Issam Zineh, Pharm.D., MPH

Director, Office of Clinical Pharmacology (OCP), OTS, CDER,
FDA

Janet Woodcock, M.D.

Director, Center for Drug Evaluation and Research (CDER),
FDA

Sergey Aksenov, Ph.D.

Pharmacometrics Lead, Quantitative Clinical Pharmacology,
AstraZeneca

Armin Sepp, Ph.D.

Scientific Leader and GSK Associate Fellow, Systems
Modeling and Translational Biology, GlaxoSmithKline

1

2 Dean Bottino, Ph.D.
3 Senior Scientific Director, Quantitative Clinical
4 Pharmacology, Takeda

5

6 Haleh Saber, Ph.D.
7 Deputy Director, Division of Hematology Oncology Toxicology
8 (DHOT), OHOP, CDER, FDA

9

10 Sandeep Dutta, Ph.D.
11 Executive Director, Global Head, Clinical Pharmacology,
12 Modeling and Simulations, Amgen

13

14 Stuart Bailey, Ph.D.
15 VP, Biostatistics and Pharmacometrics, Novartis

16

17 Tito Fojo, M.D., Ph.D.
18 Professor of Medicine, Columbia University

19

20 Jérémie Guedj, Ph.D.
21 Research Scientist, French National Institute of Health and
22 Medical Research (INSERM)

23

24 Michael Maitland, M.D., Ph.D.
25 Director, Therapeutics, Inova Center for Personalized
26 Health

27

28 David Turner, Ph.D.
29 Associate Principal Scientist, Quantitative Pharmacology
30 and Pharmacometrics, Merck

31

32 Yanan Zheng, Ph.D.
33 Principal Scientist, Clinical Pharmacology & DMPK,
34 MedImmune

35

36 Amit Roy, Ph.D.
37 Group Director, Clinical Pharmacology & Pharmacometrics,
38 Bristol-Myers Squibb

39

40 Jingwen (Jenny) Zheng, Ph.D.
41 Director, Global Pharmacometric group, Pfizer

1
2 Nam Atiqur Rahman, Ph.D.
3 Director, Division of Clinical Pharmacology V, Office of
4 Clinical Pharmacology (OCP), OTS, CDER, FDA
5

6 Jerry Yu, Ph.D.
7 Team Leader, Division of Pharmacometrics (DPM), Office of
8 Clinical Pharmacology (OCP), OTS, CDER, FDA
9

10 Kellie Turner-Jones, Ph.D.
11 Senior Research Scientist, Global PK/PD & Pharmacometrics,
12 Eli Lilly and Company
13

14 Chao Liu, Ph.D.
15 Team Leader, Division of Pharmacometrics (DPM), Office of
16 Clinical Pharmacology (OCP), OTS, CDER, FDA
17

18 Daniele Ouellet, Ph.D.
19 Senior Director and TA-Group Leader, Global Clinical
20 Pharmacology, Janssen Research & Development
21

22 Lei Nie, Ph.D.
23 Team Leader, Division of Biometrics V, Office of
24 Biostatistics (OB), OTS, CDER, FDA
25

26 Patricia Keegan, M.D.
27 Division Director, Division of Oncology Products 2 (DOP2),
28 OHOP, CDER, FDA
29

30

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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

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

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

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

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

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

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

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

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

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

27 [APPLAUSE]

28 Challenge and Opportunity of MIDD in Oncology

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

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

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

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

25
26 So can we really optimize exposure response on both efficacy
27 and toxicity for cancer drugs? And can we figure out ways to
28 do that so that when we get the recommendation for dosing on
29 market it is backed up by quantitative information that we
30 understand. Can we achieve more integration of different
31 levels of knowledge? We have tremendous amount of basic
32 science knowledge right now about tumors based on the war on
33 cancer for the last 50 years, right? And so we have
34 tremendous amount of molecular information, target
35 information, all these sorts of things—tumor behavior and so
36 one—but we are still, I see some printout, we are still
37 using the RECIST criteria. [Laughs] We are still in the
38 translational space. In the clinical space, we are still
39 using the tools that we have used for a very long time. So
40 we may need to keep using these tools, but we can re-inform
41 them better with much more of the scientific information.
42 Can we construct models that bring this information together
43 and give us a more global understanding of both behavior of
44 the tumor and then the pharmacology of the drug overlaid on

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

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

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

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

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

3 Thank you.

4 [APPLAUSE]

5 Session I NON-CLINICAL MIDD IN ONCOLOGY

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

12
13 [APPLAUSE]

14
15 I am Jin Jin from Genentech. I also represent the
16 International Society of Pharmacometrics as the current
17 president. It is our great privilege to co-sponsor today's
18 workshop with FDA, and I will also act as a moderator for our
19 first scientific session.

20
21 Drug development starts in the nonclinical space and our
22 first session will showcase some modelling applications in
23 the preclinical space, and we will have three speakers
24 covering multiple aspects ranging from using assessment
25 pharmacology modelling approach, the informed immuno-oncology
26 therapy authorizations of _____, use of in-silico
27 modelling to help design up bispecific antibodies, and also
28 use of preclinical to clinical translation and modelling to
29 inform and further optimize the advocacy and the safety
30 balance for combination therapies. We will take a couple of
31 brief clarification questions at the end of each talk, and at
32 the very end, we invite all the speakers to come to the panel
33 joined by a couple of FDA colleagues with the general panel
34 discussion at the very end.

35
36 So now, I will introduce the first speaker for this session
37 Dr. Sergey Aksenov. Dr. Aksenov is a pharmacometrics lead in
38 Quantitative Clinical Pharmacology Division at AstraZeneca.
39 Given the interest of time, I will not read through the
40 detailed bios and this will be posted online afterwards.
41 Now, Sergey please come over.

42
43 Dr. Aksenov: Thank you, Jin. Good morning everyone. First of all,
44 I would like to thank the organizers for giving me this
45 opportunity to speak here today. I speak on behalf of my
46 many colleagues in office at AstraZeneca and all the
47 _____ partnership. The topic for my talk today is

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

3
4 Well, first of all, I would like you to _____ from
5 this, to walk you through the framework that we are using to
6 evaluate potential drug combinations. The approach that we
7 use integrates the PK/PD data, pathophysiology both animal
8 and human. Eventually we use this to make predictions for
9 _____ drugs in humans, and then I will talk about the
10 quantitative systems for oncology model for the immune cycle
11 in mouse, and you will see how we use that model to
12 understand the dynamics of the immune cycle and how it well
13 describes the type of radiation and anti-PDL1 antibodies
14 tumor cycle _____.

15
16 So this a general outline of the whole framework. So it
17 consists of two parts: the first part is the QSP -
18 quantitative systems pharmacology model. That is the one
19 from the left. The second part of it is what we call a *joint*
20 model. It is a model that links the output from the QSP
21 model to the _____. So what is a QSP model in this sort
22 of framework? It consists of three modules. The PK module
23 _____ that describe the pharmacokinetics of drugs,
24 concentration of drugs at the test site. The biology module
25 describes the drug targets and the signaling pathways where
26 this drug was designed, and it also describes the way drugs
27 do that biology of signalling there. And finally, the
28 physiology module describes the context for the drug, the
29 targets, the pathways _____. Eventually one of the
30 outputs from the variables from this physiological framework
31 links up to the clinical input and that is the joint model of
32 that. I will not spend too much time talking about it, but
33 that is where we — just to give you an idea of the thread
34 that pass through all of this clinical work to the post
35 clinical especially the _____ in patients.

36
37 Okay, so for the immune cycle, this is what that annual QSP
38 model looks like. This is again as an _____, the PK/PD
39 module here containing PK of the anti-PDL1 antibodies in
40 mouse, other compounds, and how the concentration of these
41 drugs and the effect of these treatments act on the
42 interaction between the immune components of the system. So
43 that is the PK/PD part of it. The biological part of it is
44 again the interactions between the immune components but also
45 the immune system itself and the whole body of the mouse.
46 And finally the physiological part is where the immune cycle,
47 the immune system links up to what we care about which is the
48 wall of every tumor, the tumor size of the mouse. That is
49 the readout for all of our prediction efforts given.

50

1 Again, just to show you how this would look like eventually
2 in this framework that we are using. The annual model that I
3 have talked about today is here on the left and the output as
4 well tumor size, tumor girth. So if you will click this, it
5 would re-circle here. So one thing that we are working is an
6 effort to translate this mouse tumor model to human. That is
7 necessary because what we will want to understand is how
8 combinations of drugs affect tumors in humans. In that what
9 we will do is we will develop a joint model of tumor cells
10 progression-free survival and overall survival. And the
11 joint model here—It is a technical term statistically. It
12 just means that we will be modeling multivariable divisions
13 for _____, variable tumor size and _____
14 progressions and deaths. And so the way we will do it is we
15 will link up predictions from the human #QSP model in which
16 _____ tumor cell response to this joint model that we
17 can build using all the information that is available to us
18 about the cancer—clinical information, clinical trial
19 data—and be able to predict the effect of the combinations
20 on progression free survival and overall survival, so in that
21 way we will be able to make the combinations.
22

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

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

14
15 So these six graphs show you the _____ that were used to
16 estimate the parameters in the model as well as model
17 predictions. So model predictions are the red lines. The
18 red lines are predicted _____. Individual mouse
19 profiles of tumor cell versus time are the gray lines, and
20 the median of those is that dash black line. So the vertical
21 axis is the tumor size. The horizontal axis is the time
22 since inoculation end-points with the tumor cell. So what
23 you see when you look in the control mice, the tumor growth
24 has been watched exponentially and once you apply anti-PDL1
25 antibodies to mice or radiation treatment with x-rays, you
26 see that the growth, the overall growth rate of the tumor
27 decreases but then it starts regrowing. The bottom row of
28 graphs show you the combination treatments, radiation plus
29 anti-PDL1 _____. And you see the dramatic effect on the
30 tumor size. On the average, the tumor size growth is
31 completely suppressed. Of course, there is some variability
32 between _____ here. What is interesting is that the
33 importance that this model was also validated using external
34 data. So these graphs show you predictions in data for a
35 different set of mice. Draw your attention to the rightmost
36 graph. So that is the graph where the combination of
37 radiation and anti-PDL1 was given together with anti-CD8
38 antibodies. So these antibodies deplete CD8+ effector cells
39 from the body, and so when mapped to a parameter in the
40 model, it is aligned with predictions with the data as well.

41
42 So given all these, we are confident that the models qualify
43 to spread the immune cycle directions in the mouse. That was
44 really the goal. And just to expand on this a little bit, we
45 can do two things with this model. We can address
46 mechanistic questions and try to understand exactly what
47 underpins the response of the tumors to these therapies as
48 well as to make predictions. So in terms of mechanistic
49 understanding, recall where the parameter of that image

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

36 And the real purpose of this model was to make predictions,
37 and so what you see here are heat maps of efficacy response
38 in mice treated with radiation plus anti-PDL1. The heat map
39 on the left corresponds to radiation treatment started on day
40 5 since inoculation of mice and the panel on the right is day
41 12. These are older which are more established tumors on the
42 right. The color corresponds to the degree of _____
43 response: The moss green is 100%. The red is 0, no
44 response. The rows in this graph correspond to the dose of
45 radiation from 0 _____ to 10 gray at the top, and the

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

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

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

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

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

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

35 Thank you.

36 [APPLAUSE]

37

1

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

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

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

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

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

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

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

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

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

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

5 [APPLAUSE]

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

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

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

31 Audience: _____.

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

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

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

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

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

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

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

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

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

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

22 [APPLAUSE]

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

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

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

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

7 [APPLAUSE]

8

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

12

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

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

1 _____ that, so that's the biological rationale for the
2 combination. _____ from magazines but it helps suppress
3 reactivation _____ last about two years. So the first
4 step in the technical part once we get the data is to start
5 with _____ the tumor growth inhibition data reverting
6 _____ exposures to free-fraction human exposures. So
7 basically what we do is we just _____. We get growth
8 rate for control, growth rate for treated mice and then we
9 use the transformation, we call growth rate inhibition or GRI
10 which is just the transformation over here and then basically
11 just to calibrate your intuition on what GRI means. GRI of 0
12 means you're doing no better than control. GRI above 200
13 means you're slowing down the tumor but not causing
14 regression. GRI of 100 corresponds to tumor spaces and
15 greater than 100% GRI is tumor regression. If you remember
16 from the Harvey Wong's slide before, it takes about 60% GRI
17 approximately to cause any kind of response rate _____.
18 The next step is we do this for every single dose combination
19 that we try in the mouse _____ free-fraction exposure in
20 the mouse and what we get is a grade of about 910 points in
21 the points for GRI as the function of 117 monotherapy, as a
22 function of 128 monotherapy, and then the combination space
23 _____. Once we have those points, we use a simple
24 _____. You can pick whatever models you want just fit
25 the monotherapy. So, GRI of drug A on 117 turns out to be
26 linear function and GRI of drug B which is 128 is a
27 saturating function of concentration. So the next step is to
28 use this equation here. Basically, the percent growth
29 _____ is taking to be the growth rate inhabitation due
30 to each of the two growths added together plus the _____
31 the two monotherapy, there's only one additional _____
32 that I need to estimate to get the surface which is this
33 _____ and basically what this shows is that there's a
34 slight synergy between 117 and type 228 which is one of the
35 _____ combination into the clinic and so the next step
36 will be to try to determine its maximum tolerated exposure
37 curve. The first step is to figure out what is the PK driver
38 of toxicity and so we considered maximum concentration
39 _____ and was a good predictor for 228 _____ TAK-
40 117 _____ better predicted for toxicity _____ as
41 the toxicity predictor. So these are _____ toxicity,
42 red or patients with those _____ progression. So we use
43 _____ concentration from this point forward. Then the
44 next step is to look at the combination. So this is once we
45 have the phase 1 data _____ represents the average
46 exposure for type 228 and type 117 for each patient in the

1 combination study. These ones along the axis are of course
2 all the monotherapy patients from the phase 1 studies in the
3 228 and 117 respectively and again green is the patients
4 _____ dose having toxicity _____ toxicity. Red are
5 patients who do. So then _____ two-dimensional logistic
6 regression on this data. So this is the equation here. It
7 basically just have _____ slow term for S, slow term for
8 Y and then an interaction _____ concentrations of S and
9 Y multiplied together and you get this brown surface where
10 lighter colors are higher probabilities of having _____
11 toxicity then the maximum tolerated dose is defined to be
12 just the lever curve of this probability surface where
13 probability _____ toxicities are 25% which is more or
14 less what a standard _____. When we _____ the MTE
15 of the maximum tolerated exposure and just for reference,
16 this is what _____ is the straight line here. So you
17 can see that the maximum tolerated exposure curve, like the
18 efficacy curve _____ synergy and both toxicity and
19 efficacy. So going back to this theoretical drawing first.
20 The question you can think of it is if you're _____ here
21 where an X is longitude and Y is latitude then as you walk
22 along this fence, the question is this fence was _____
23 on the map and latitude and longitude _____ where do you
24 reach your highest point and what latitude and longitude you
25 reach your highest point as _____ phase 2 dose
26 combination. So to animate this, you have—you're moving
27 along and what we do is we basically cut the surface along
28 this edge here, well we cut it vertically on this edge here
29 and you get a profile of efficacy as a function—as you
30 _____ basically and moving _____ you recommend
31 phase 2 dose rather than _____ doses that give you this
32 optimum efficacy value. So we tried this with our drugs, X
33 and Y, TAK-117 and TAK-228 and this is just a reminder the
34 _____ we used for this efficacy surface and then we had
35 to change the color coding to red for the _____ exposure
36 curve so that you could see them on the spot but the maximum
37 tolerated _____ exposure from mouse to humans and what
38 that means is when we slice the surface from the side, it
39 looks _____ this. Unfortunately, instead of going
40 upward, what if there were _____ combination, this curve
41 goes downward which means that once you take toxicity into
42 consideration, you are actually better off _____ with
43 all TAK-117 and no TAK-228 is you're better off with
44 monotherapy. We try this with all the different mouse models
45 that were tested and basically one product _____. So we
46 are going to revisit these predictions once we have—so this

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

7 [Laughs]

8 Bottino: This is like a memo where _____.

9 [Laughs]

10
11 Bottino: So in terms of the general methodology if we propose this
12 in the context of a simple problem _____ and phase 1
13 study with combination, we might want to take this
14 _____ efficacy surface and goes straight up _____
15 if we don't want to escalate over drugs at the same time or
16 some other sufficient conservative. The idea is to try to
17 get this to the _____ efficacy and _____ so you go
18 up and then actually _____ cohort you could try to
19 refund with uncertainty bands or _____ exposure curve
20 and then ultimately _____ recommended phase 2 dose or
21 expansion for phase 2 _____. To summarize, _____
22 to the point where you had been _____ in those aspects.
23 So recommended phase 2 dose finding _____ efficacy
24 optimization problem and we have successfully _____ and
25 the model in this case _____ PIKTOR combination would
26 not do as well as the monotherapy once you _____ dosing.
27 We recommend further validation on another combinations. We
28 try to _____. So we're trying to find other ways to
29 validate some of the other combinations. Finally, in
30 addition to all the authors, co-authors _____, thank
31 you. _____ and Brian Cooper for other contributions
32 that you made on these related projects. Thank you for your
33 time.

34 [Applause]

35 Bottino: Come in.

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

39 Bottino: Yes.

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

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

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

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

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

12 Audience: _____.

13 Bottino: Thanks.

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

15 Bottino: This one?

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

18

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

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

31 Bottino: _____.

32 Audience: _____.

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

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

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

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

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

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

38 PANEL DISCUSSION

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

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

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

4 Jin: Get closer to the microphone.

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

8 Aksenov: _____.

9 __: _____.

10 Aksenov: Use the microphone.

11 Jin: Closer to the microphone.

12 Audience: _____.

13 Jin: You just need to get closer.

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

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

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

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

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

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

3

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

10 Audience: Thanks.

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

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

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

31 ___: So for sure, there was _____ .

32 Bottino: _____ toxicity. Yeah.

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

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

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

7

8 __: Adam _____ .

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

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

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

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

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

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

5 __: Okay.

6 __: _____.

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

15 Jin: Maybe a last question from the audience?

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

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

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

6 __: _____ for visualization.

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

10 __: _____.

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

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

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

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

1 drug development better and if you _____ from 2016,
2 2017 _____ and based on that, there has been actually
3 some adjustment in phase 1 clinical trial design that is
4 _____ therapeutic doses _____ dose is so low.
5 Also in addressing the _____ representatives from
6 industry _____ from NCI _____ March 9th is an
7 attempt to address some of these gaps by bringing every one
8 together in _____ these models. It seems to me that
9 they were not talking to each other and certainly industry
10 was not aware of these models. NCI is funding these
11 programs but they do not know what their regulators need.
12 So _____ discussion to see how we can address some of
13 these gaps.

14

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

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

31

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

39 ____: _____.

40 ____: _____ comments.

41 ____: No. _____.

1 ___: Any audience would like to _____ comments?

2 ___: _____ with Dr. Saber. _____ that there are some
3 reviewers who _____?

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

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

20 Saber: I think _____.

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

33 Saber: _____.

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

38 SESSION II CLINICAL MIDD IN ONCOLOGY

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

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

13
14 Dr. Bailey: Thank you Sandeep. _____. This is a joint
15 presentation on our team. We are presenting _____
16 team statisticians _____. Dr. _____ mentioned
17 that _____ we need to _____ annual _____
18 transition _____ presentation _____ I began with
19 the presentation _____ presentation as well.
20 Certainly is that better? Fantastic. Okay. Please
21 _____ before _____ that again. I asked you about
22 these questions _____ just to let you know that some
23 of the details _____ will be _____ office and
24 _____ represent _____ specific _____ and
25 rather than _____ my presentation _____ red flag
26 _____. I think it is actually be _____ if we do
27 not forget the _____ studies of the first _____
28 drug for combinations into patients so what we think about
29 how we should optimize the endpoints we will use _____
30 translating activity into efficacy. _____ we must not
31 forget that _____ so they are still _____ safety
32 of the patients. However, we should think about designing
33 studies in a much more detailed way, learning from what we
34 see _____. To me, it is about, on the preclinical
35 side, understanding what we believe the drug do and then
36 generating data to try to validate what we have seen
37 _____ look for difference between _____ and
38 _____. Now, you could imagine _____ mentioned
39 having _____. I think we struggle with that. I would
40 like to see _____ just between what we have seen
41 _____ the ability to validate translation of that
42 information. _____ gained information and _____
43 which means having real time _____ use for decision-
44 making _____ and not specifically try to _____
45 design _____ retrospective use that data to answer
46 different questions. We should have _____ mind those

1 questions _____. There is a lot that should and could
2 be done to incorporate _____ data either from taking
3 preclinical _____ human but _____ human
4 _____ into combinations, translate data from the
5 _____ information with preclinical _____ synergy
6 _____ translate that into what we expect to see in
7 combinations. We also need to think a little bit better
8 how we translate data between patient populations
9 _____. Often we think of _____ studies only once
10 we determine that _____ activity of the drug in adults,
11 and I think that tends to _____ and we need to be a
12 little bit more considerate about how we can potentially
13 generate _____ activity generate data _____
14 populations and how to _____ translate that _____
15 to _____ across regions. There is a lot of discussion
16 between Western and Japanese _____ running _____
17 studies out there _____ go to specific region in
18 _____ diversity giving way between Western _____
19 Japanese _____ concept. We do not understand
20 diversity to predict the differences in how patients
21 differ _____. Additionally the use of
22 _____ volunteers, we are moving into area where
23 _____ drugs developing may not have the same level of
24 toxicity that _____ in the past and there are
25 questions as to how _____ use potentially healthy
26 volunteers _____ information _____ regions. I
27 think additional thinking is _____ as well as
28 _____ translation between _____ and this is just
29 _____ that increase interactions between statisticians
30 _____ and not just _____ the interaction of
31 oncologists _____. It is no longer _____ how the
32 statistician _____ forward. _____ that every
33 time _____ trials, we are using information _____
34 as well as _____ to understand the information
35 _____ make the best decisions _____ so
36 traditional challenges. This is why people elect to
37 _____ drug _____ determine _____. Hopefully
38 wise people _____ from that _____ safety has been
39 used. _____ some studies using _____, but it is
40 still important that we do consider safety as controlling
41 _____. I do not see the previous approaches were
42 _____ safety potential so you wanted to be able to
43 _____ avoid overdosing, but there are complications
44 _____. We need to be within a certain or very narrow
45 window where the MTD will be _____ activity or
46 efficacy, so therefore, _____ and _____ timely

1 fashion. _____ because it goes to why we want to
2 maximize the use of information _____. _____
3 that we should not be _____ introduce _____ with
4 the same number of patients. We should be looking at the
5 designs that we have put in place, understanding the value
6 that that would bring, the data that we will generate from,
7 so I think we need 50 or 100 patients within the study that
8 would _____ learnings that we understand the value of
9 the data it will bring back to us, so to me it is about
10 finding the best doses and not just necessarily _____
11 for _____ we talk about that _____, so we need to
12 have studies that allow flexibility in _____ patients
13 into _____, so again, just to look back, generally we
14 have to _____ toxicity data. We use that to establish
15 a starting dose. We have estimated exposure _____
16 that we expect to see _____. There is discussion
17 about _____ of the preclinical trials and negative
18 predictive value, positive predictive value and they tend
19 to be a little bit of negative _____ some toxicities
20 _____ everything, but we may _____ information
21 _____ dose toxicity relationship. Sometimes
22 _____ sometimes not, but _____ convert it into
23 _____ predefined dose range so you do not have
24 _____ sequence or organizations move to less
25 _____ 100% _____ steps _____ toxicity
26 _____. _____, so if _____ be able to use it
27 _____, then you can do much better than to simply say
28 _____, so _____ relationships, _____
29 commented on the fact that these were traditionally
30 introduced _____ you could still apply _____ and
31 the goal is to really try to target MTD _____
32 introduced is kind of _____ challenges _____
33 qualifications. _____ going back a little bit to this
34 discussion around the fact, for example, _____, it is
35 interesting to know that _____ approach introduces
36 _____, so it is not any _____. It actually is
37 _____. We do not _____ specific in making
38 decision _____ and I think that one of the big
39 differences is the fact how we integrate with clinical we
40 investigate _____ patients. _____ helps to
41 define this window potentially _____ doses that
42 minimize the risk of _____ to _____, so
43 _____, but we actually use _____ from within that
44 range _____, so I may have _____ 20. The ones in
45 the 20 _____ acceptable. I then used my assessment
46 _____ those levels from the _____ the view of the

1 PK related to _____ where the preclinical data was
2 indicating exposures to toxicity _____, so actually in
3 _____ as to whether we should make this _____
4 whether we should _____ investigate _____. I
5 _____ of that, but the nice thing around this is that
6 you can incorporate _____ if you have differences
7 between _____ species in terms of the projections for
8 MTD. We incorporate _____. You can allow for a
9 variety of _____ to allow you to slow down to approach
10 _____ as long as you have _____. _____ you
11 are not specifically defining upfront every single dose
12 that you will define maximum steps because we do not want
13 to encourage undue _____ so you would not be
14 _____ dose, but then you have this window _____
15 data. We have the flexibility to incorporate _____
16 between populations, so if I have some understanding from
17 the _____ differences between populations or if I want
18 to study _____ differences between the same trial, I
19 believe that maybe some differences _____ I can
20 incorporate _____ data _____ difference
21 _____ demonstrate _____ and this can also then
22 instead of being used as _____ study _____
23 optimize MTD _____ to integrate with the other data
24 that you have _____ make a decision which dose to use.
25 _____ drug _____ case of an antibody _____,
26 the weight of that other data will then transition as to
27 _____ about _____ if I reached an area of
28 _____. _____, so I would not make _____
29 steps _____ away _____ I expect to see _____
30 activity. There are additional approaches that integrate
31 _____ we can incorporate _____. We can do
32 _____ and then _____ approaches I have seen
33 _____ recently _____ extensions of that
34 _____ extensions again. The paper talked about the
35 ability to _____ MTD, so _____ with this is it is
36 a very nice approach to use, but to use it _____
37 increasing our _____ between _____ safety but
38 then not necessarily _____ a decision and then
39 _____ do this so _____ we have in our team who
40 _____ combination approach. _____ combination
41 _____ safety _____ with _____ exposure
42 relationships based on the _____ interaction between
43 the two and then counting for that within the _____
44 decision _____, so _____ have to augment
45 _____ left-hand side which is the case where we have
46 studied a few different _____ dose. We have not seen

1 any _____ and _____ potentially increase up to
2 _____ potentially _____ control to some level,
3 but when we actually _____ for _____ platelets
4 and we are _____ platelet counts over time, so you can
5 imagine we may have seen some _____ changes in
6 platelets. Actually _____ using _____ platelet.
7 We can actually now look at the risk of _____ within a
8 specific time _____. You can _____ potential
9 _____, so if we are to make this _____ slight
10 higher risk of _____ and we get this _____ risk
11 _____. At least, it will be incorporated in the
12 decision making. It may tell us overall _____, so
13 that is _____ safety assessment with other data.
14 _____ actually not expecting to see _____, so
15 _____ therapy, so examples _____ based on the
16 study _____ safety issues with this. _____
17 patient to 15 from _____. Really it is a question
18 here that it is not just _____, but we may see events
19 later and how to deal with this _____ when we are
20 making _____ decision from _____, but we are
21 _____, so there are a few different form of approaches
22 to do that. We could incorporate _____ data
23 _____ further and then we have an internal _____
24 reference _____ what we go by cycle the other end, so
25 _____ and it is still _____ introduces the
26 ability to look at those changes that occur within the
27 _____ as well, but it is very challenging when you are
28 in a situation _____ escalation is that _____
29 developing _____ to keep the patient long enough on
30 that treatment to be able to see _____ investigated in
31 terms of pushing to try to escalate _____ because they
32 do not see _____, and these patients _____ how to
33 be _____, so this formal approach is _____
34 changes that _____ still have information _____,
35 so another topic around this will be the studies when we
36 are designing a clinical trial, we should be designing it
37 in a framework that allows us to change into _____
38 reactions of information _____ trial without the need
39 for mention to _____ around the _____ estimate
40 _____, but to perform _____, the number of people
41 _____ the number of _____ so it is a custom to
42 _____ to _____ the time the patients have to wait
43 to get this, but the companies decide to do _____, so
44 that is the smart design to allow to make these changes and
45 this goes back again to the work that should be done
46 preclinical _____ cases _____ only _____,

1 but we already have studied _____. We should be able
2 to incorporate within _____ flexibility to switch to
3 _____ reaction and example _____ the compound
4 _____ thrombocytopenia and we are able because of the
5 way we approach _____ to introduce _____
6 treatments _____ because we have not _____ told
7 us _____ at the same time inform us that we should not
8 see any change at least in the activity _____ sense to
9 how about we translate _____, so we know _____ we
10 have _____ that we have exposures related to
11 _____. We know that we also have models that will
12 help us understand _____ changes, the dynamic changes
13 _____ or _____ that would be related to clinical
14 events, so _____ presentation _____. _____
15 presentation _____ talks about the assessment of
16 finding an optimal efficacy outcome when I am on my safety
17 boundary. We have to understand that safety boundary
18 changes over time, but the challenge can come if the safety
19 endpoint _____ is also related to the clinical outcome,
20 so _____ this case, the _____ also affected by
21 these treatments and we see changes in _____ we may
22 see the occurrence of _____ and there is _____ to
23 be able to look at the relationship between _____
24 potential _____ and there is also assessment of the
25 _____ that predict patients _____, so how do you
26 look at trying to optimize the outcome, whether going back
27 to investigate _____ treatment to mitigate some of the
28 _____ treatments if that is what is _____ because
29 we do not want patients having _____ but still
30 _____, so understanding _____ to go back to the
31 _____ trials _____ on how to change the frequency
32 of dose _____ and it should not be seen _____
33 event that we go through _____ should be able to
34 integrate to effort within a company or organization as we
35 are collecting data _____. _____. Just to
36 _____ if that is okay. This was an example for a
37 compound where we had multiple _____. We integrated
38 _____ three different _____ platelets. You can
39 see the reference _____, but this we used within the
40 study to help us understand how to _____ integrated by
41 _____ study design and this also goes how we could
42 consider to support those selections in safety efficacy
43 _____ on assessing the relationship between
44 circulating _____ necessity and ability to inhibit the
45 target with certain _____ within the _____ based
46 on what we can measure in the circulating _____, so

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

8 [APPLAUSE]

9
10 Moderator: So, we _____. If there is one more question? Or
11 questions? If not, thank you. We'll move on to the next
12 speaker. It is Dr. Tito Fojo. He is a professor of
13 medicine, Columbia University, and he will be presenting
14 on _____.

15
16 Dr. Fojo: Thank you. Thank you very much and thank you for the
17 invitation. So, basically what I'm going to describe to
18 you today is a novel method _____ analyzing tumor
19 kinetics and this is the summary of it. It actually rose
20 from a disagreement that Dr. Bates and I were having, and
21 we turned to _____ and we resolved it in her favor,
22 and basically what you see here is in blue, what we
23 generally measure in the clinically arena. The patient's
24 tumor regresses and they eventually _____ cannot be
25 achieved in the majority of patients with a solid tumor.
26 What is truly happening during that period of time is that
27 the fraction of tumor here shown by the red dotted line, it
28 is regressing in size here and it is gonna disappear
29 _____. The fraction of tumor which is shown by the
30 green dash line which is the persistent fraction of tumor
31 which is...

32
33 Audience: would you please speak into the mic...

34
35 Dr. Fojo: Okay?...and the green which is the green fraction of...it is
36 the resistant or relatively resistant fraction of tumor
37 which is gradually growing. At any point of time which you
38 see in the clinic, this is a combination of the sensitive
39 fraction, and this is gonna disappear, and the resistant
40 fraction that's gonna grow. This could all be described by
41 this equation down here at the bottom where the fraction of
42 tumor at the time it's seen, is the exponential of the
43 growth rate times the _____. The exponential result is
44 negative if _____. This is exponential. If you go on
45 Google, what you find is that exponential growth and this
46 is mostly _____ population kinetics. Exponential growth
47 is _____ by Ex and decay by E-x and that is exactly
48 what we are using in our analysis. And we know that tumors
49 grow exponentially and regress exponentially. We're doing

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

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

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

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

1 to about 150 patients and you've eliminated data from PFS
2 or OS, PFS and OS are the same. As you can see, this is
3 just a few hundred patients and the data that I have shown
4 you had over 500 patients in analysis. Is this something
5 that is unique to Volpak or unique to colorectal cancer?
6 No. We had shown this previously in prostate cancer and we
7 published it last year. If you go the Project Data Sphere
8 where a lot of data is housed, they have a warehouse, you
9 see the correlation in pancreatic cancer between the G and
10 the overall survival. The key here is that this is data
11 from three separate files and it has been blended
12 altogether. You get a G-value in pancreatic cancer. It
13 doesn't matter which trial you were on. It correlates with
14 overall survival. This transcends clinical trials. What
15 about breast cancer? _____. Not only does it
16 transcend clinical trials, here you have a combination of
17 both control and the experimental arm. _____
18 prediction of overall survival. This is renal cell cancer.
19 This is Sunitinib and interferon combined. You need to see
20 that it doesn't matter whether it is a targeted agent or
21 immunotherapy. It all combines to give you robust data.
22 Here's Sunitinib alone, and here as a surrogate for immuno-
23 oncology products. On Project Data Sphere and certainly
24 with the Volpak group especially, we'd be delighted to get
25 immuno-oncology data analyzed. You can see again a
26 remarkable correlation between G and overall survival. So
27 the one last point. We use it to decide which phase to
28 study to move forward. Could we benchmark other clinical
29 trials with the use of guide therapy? And the answer for
30 that is yes. What we have done here is we have taken the
31 data from the control arm as the reference or as the
32 benchmark. We have been taking the data from the
33 experimental arm and gradually pulled up one at a time, at
34 which point that commonly patients, the data from having
35 patients have been pulled, doing a thousand resamplings
36 with _____ and the number of patients with
37 unidimensional data is four. If you take the data from the
38 bidimensional measurements, you only need 33 patients. If
39 you take data from the volumetric analysis, you only need
40 27 patients. What I'm telling you here is active into this
41 clinical trial that had a 1.4-month survival advantage. We
42 used a benchmark, 27 patients, _____ this was the
43 superior treatment than the control arm. And then finally
44 this is the last _____. Does this apply in the real
45 world? Absolutely. So _____ also worked at the VA in
46 the Bronx in New York where we have our laboratories. And
47 actually you can go into the VA data which is called
48 _____. It's the largest free source of data in the
49 world. This is just a small portion of it. This is in
50 prostate cancer, and I will just tell that this is one

1 therapy and this is another, and what you can see here is
2 that by just looking at 36 patients who seek one therapy, I
3 can tell you that it is statistically inferior because it
4 has a faster growth rate than this patient over here. The
5 reason is because we have 928 patients in this patient
6 population in this comparison, and that becomes such a
7 large robust and reliable dataset that you can benchmark
8 against it, so soon, when we get around the publicists,
9 we'll be able to tell you an individual, for example, how
10 well the patients did. I could probably be able to tell
11 you how well patients that are 85 years old did compared to
12 the rest of the population because we are going to have a
13 dataset that is several thousand, actually over 5000, and
14 you can ask any question that you want for any small set of
15 patients. So you can see the benchmark, you don't need
16 _____. So finally what we plan to do in collaboration
17 with the Volpak group is to make this even better by
18 incorporating _____, and then here at the end, at the
19 top or five of us who have been fanatical about this for
20 the last decade and poured blood on it, and then at the
21 bottom highlighted in red, new colleagues in Volpak who are
22 incredible and whom I'm delighted to be working with, and
23 all the other people _____. I want to thank you for
24 your attention.
25

26 [APPLAUSE]

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

30 _____: _____ after some time in some patients.

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

40

41 _____: _____.

42

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

5

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

23

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

39

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

42

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

8

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

12

13 Fojo: Absolutely.

14

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

18

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

23

24 _____: Thanks.

25

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

29

30 Fojo: Thank you.

31

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

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

13

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

34

35 _____: Thank you.

36

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

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

6

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

25

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

31

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

36

37 Zheng: Thank you, thank you.

38

1 Turner: David from Merck _____. Quick question for you. Do
2 you use these G-values in care of an individual patient?
3 Would you ever tell a patient his or her G-value?
4

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

19

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

27

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

1 tool that we are using is the hazard function, okay, so
2 that the function $H(t)$ that defined the instantaneous rate
3 of experiencing even a time t , knowing that the patient has
4 not experienced yet even the x t . So from that function
5 $H(t)$, one can derive the survival mode _____ and one can
6 also adjust the variables to evaluate the effect of the
7 baseline covariant on the hazard function and basically how
8 covariant affects the hazard function and that's what it's
9 used in proportional hazards and Cox's function. So we
10 have typically in our framework longitudinal and survival
11 data. So we have time to event data and we have
12 longitudinal measurements. Typically the longitudinal
13 measurements that we have are PSA...excuse me, I'm sorry. So
14 we have longitudinal measurements. It's typically tumor
15 size or PSA. I'm sorry, I don't know where they have it.
16 Give me five minutes.

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

20

21 Moderator: _____ argue within the audience.

22 _____: _____.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

14 So in conclusion I hope — at least I have tried to convince
15 you that joint models are needed for two purposes: to
16 characterize the longitudinal process, increase
17 #22:32_____ informative dropout, to assess the
18 relationship between the longitudinal process and a time
19 treatment data. Okay? And it has long been limited to do
20 in our models, but we now have the tools to use it in
21 pharmacometrics even if there are still some technical
22 difficulties that you will face if you use it. There are
23 _____ you could see that there are still some
24 difficulties sometimes to calculate the likelihood when we
25 are working with models that are too much complicated or
26 defined by the length of time it is used. Also there is an
27 order — I mean joint model as I have presented here has
28 also the drawback of its virtues. It is a fully parametric
29 model and we need now to really evaluate different
30 parametrization, how the parametrization impacts on the
31 prediction that we make and so on. Okay?

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

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

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

23 Thank you very much.

24 [APPLAUSE]

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

36
37 Dr. Maitland: Thank you. So, to help ease you back from lunch, we're
38 going to give you a presentation that's a little less heavy
39 on the quantitative analysis and instead focus on clinical
40 perspective. The title of the talk is bringing the
41 community fair setting into the learning versus confirming
42 paradigm. I have to thank the meeting organizers, most
43 specifically Rene Bruno and Yanan Zheng. Arguably Dr.

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

1 trying to improve the care of patients in our system. Not
2 coincidentally, this great opportunity arose in 2014 when
3 an Exxon Mobile, which had been directly across the street
4 from Inova Fairfax Hospital, decided they were moving back
5 to Houston and left this 120-acre campus and about 2
6 million square feet of office space available for some
7 buyer. The Commonwealth of Virginia along with Inova
8 Health System purchased the property and has begun to fill
9 it with plans that included our having an ambulatory cancer
10 care center, a laboratory building directly adjacent that
11 is now committed to being cohosted by Inova and the
12 University of Virginia, and then to have next door to that
13 this facility for biotech and health IT. In the meantime,
14 since that's due to open in 2019, I moved my practice to
15 this rather humble-looking community medical office
16 building across the street from the hospital. It's here
17 over the past year and a half that I've had the opportunity
18 to practice in a less academic, more community-oriented
19 environment. Related to the request of the meeting hosts
20 today, I now will just address for you some real-world
21 examples of a couple of patients who I actually interacted
22 with in clinic this week. So patient 1 is an approximately
23 30-year-old woman who presented in 2014 with prolonged
24 menses. She underwent an endometrial biopsy which
25 unfortunately revealed endometrioid adenocarcinoma.
26 Patient 2 is a woman in her 30s who also presented with
27 similar symptoms after she initially had an abnormal
28 screening cytology. She underwent her D&C in January 2014,
29 also with a diagnosis of endometrioid adenocarcinoma. They
30 both sought gynecologic oncology surgeons to have
31 unfortunately at such a young age hysterectomy. Patient 1
32 proved to have stage IIIC2 disease. Patient 2 had stage
33 IIIC1 disease. Given the high likelihood that those
34 diseases would recur, both patients underwent standard of
35 care adjuvant therapy, patient 1 with cisplatin and
36 doxorubicin followed by radiation therapy with progesterone,
37 patient 2 with adjuvant carboplatin and paclitaxel followed
38 by radiation. Both had no evidence of disease for more
39 than a year during routine surveillance. Patient 1 in
40 March 2016 had recurrent disease and received carboplatin
41 and paclitaxel, patient 2 in October 2015 with carboplatin,
42 letrozole and doxorubicin, etc. Both patients again had
43 some evidence of disease control. Patient 1 in August 2017
44 was found on CT surveillance imaging to have recurrence in
45 the retroperitoneal lymph nodes. Patient 2 had been
46 chronically on bevacizumab through September 2017 and now

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

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

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

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

43 [APPLAUSE]

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

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

1 threshold on an SLD basis for progression, so this suggests
2 that they either have growth of a non-targeted lesion or
3 formation of a new lesion, yet still you can see a lot of
4 these patients have shrinkage in their target lesions, so
5 these patients are actually benefiting, and so this really
6 begs the question of how do we treat these patients and
7 should they be labeled the same as the other patients on
8 drug? Now to sort of further complicate matters, if you
9 look at individual lesions, so here, each vertical column
10 represents a single patient, you will see that some
11 patients have a combination of growing and shrinking
12 lesions such that you have patients who actually progress
13 when you have a shrinking lesion and you have some patients
14 who are responding to growing lesions, so there's a lot of
15 gray area here. Obviously we sort of reassess them to make
16 sense of all this information. Just to start out, the
17 purpose of this presentation, we came up with a
18 stratification system. I will show you here. So on the
19 far right, we have our typical aggregate growth and these
20 are patients who have SLD growth greater than 20%. Next,
21 the mixed growth are our patients who have single lesion
22 progression, so they have progression of one lesion but not
23 enough to meet the threshold for SLD progression. Then we
24 have patients who regressed with no growth in the target
25 lesions either with or without a mass, so plus and minus.
26 Of course, we have our disease control group on the left.
27 We will come to this schematic after a while to look at
28 some of these results. So again we started with
29 KEYNOTE-001. This is our random dataset. We have a fairly
30 large dataset here, and when you go through all the filters,
31 you see that approximately 60% of our patients have
32 progressed prior to treatment discontinuation. When you
33 look at the general breakdown here, you see that we have a
34 fairly good representation across these different subgroups
35 that we define. So after analyzing KEYNOTE-001 would be a
36 fairly perspective analysis to apply the rules to KEYNOTE-
37 052, again bladder cancer population. When you look at
38 that data, you see generally the same proportion of
39 patients belonging to individual subgroups. So I think, in
40 it of itself, that's an important finding because it is a
41 very different complex and you see that patients are
42 progressing for different reasons and have underlying
43 differences in their disease status, but it really begs the
44 question, what is the outcome of these different subgroups?
45 So here we start with a Kaplan-Meier plot of KEYNOTE-001
46 again and this is our disease control group. You can see

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

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

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

11 [APPLAUSE]

12
13 Our next speaker is Dr. Yanan Zheng from MedImmune.

14
15 Dr. Zheng: Thank you for the introduction and it is really an honor to
16 be invited to the _____ workshop and I hope to take
17 this opportunity to talk about our _____ MedImmune in
18 modeling of the tumor kinetics and overall survival but
19 verify prognosis including durvalumab's efficacy for
20 _____. So as many of you know, durvalumab is an anti-
21 PD-L1 monoclonal antibody that has been developed for
22 cancer immunotherapy. Its mechanism of action is to block
23 the interaction between the PD-L1, its effects on both
24 tumor cells as well as immune cells can lead to these
25 factors as described on T-cells. Blocking the interaction
26 between PD-L1 and its receptor will result in enhanced T-
27 cell activity as well as T-cell mediated tumor cell killing.
28 Therefore, leading to tumor shrinkage. Just earlier last
29 year, durvalumab has been approved for patients with
30 locally-advanced or metastatic urothelial carcinoma that
31 have progressed following not even maintaining chemotherapy.
32 The approval of durvalumab _____ using the patient, as
33 many as supportive data from the study 1108, which is at
34 phase 1/2 dose escalation expansion study in solid tumor
35 which includes using expansion for _____ 10 mg per
36 kilogram Q2W. So in that study, durvalumab has
37 demonstrated favorable efficacy with concurrent objective
38 results with a 17.8 in a total population in 27.6 in the
39 PD-L1 type sub population where the _____ high was
40 defined as greater than 35% of PD-L1 expressions in the
41 tumor biopsy. At this time, it corresponded to a median
42 survival of about 18.2 in the overall population and 20
43 months in the PD-L1 type population. Now, the question
44 about we would like to address is how can we further
45 improve the efficacy, how we will benefit and impact
46 patients who are likely to respond to durvalumab treatment

1 so that we can use that to greater _____ and also to
2 guide the physicians' decision to identify who are the best
3 patients to treat. So to answer this question a
4 pharmacologic modeling approach is _____ because
5 better than the traditional approach which looks at
6 dichotomized response to date, the pharmacologic modeling
7 focused on the entire longitudinal tumor responses to each
8 individual patient which contains a lot more to each
9 information and also it allows us to evaluate the
10 biomarkers in a continuous fashion rather than looking
11 _____ receptors. Further it is a powerful tool to
12 have a systematic way to evaluate the multi-
13 variant/covariant analysis. So, using the pharmacologic
14 modeling approach, we developed a tumor kinetic and overall
15 survival modeling framework for immuno-oncologic therapy.
16 So first, we developed a tumor kinetic model to describe
17 the longitudinal tumor response over time which enhances
18 the tumor growth as _____ K_g as well as the tumor
19 killing in response to immunotherapy which is _____
20 K_{kill} and then we then developed an overall survival model
21 which uses the predictive tumor dynamics from the tumor
22 kinetic model as the input function and predicts the
23 survival from _____ over time. In addition, we also
24 developed a dropout model to describe the relationship
25 between the tumor response and the likelihood of patient
26 dropout from the study. Lastly, we performed a multi-
27 variant/covariant analysis on all of these models to
28 identify significant factors not only for tumor growth but
29 also for tumor killing, the dropout as well as survival.
30 So, using this modeling framework we have analyzed data
31 from using patient in the study in _____. So, here on
32 the left-hand side you can see only a third of individual
33 tumor kinetic _____ from the study. Here, the tumor
34 size is defined as the sum of the longest parameter. So
35 you can see that there is a modeling agent _____
36 individual responses and when you look at each individual
37 responses closely, that is the _____ essentially three
38 different type of tumor dynamic profiles. So the first
39 type is one that has continued tumor progression whereas
40 the second one shows that the last tumor shrinkage rather
41 than _____ and then reaches a steady state over time
42 as opposed to _____ and the third type is
43 characterized by initial increase in tumor size. So,
44 _____ has little progression and then followed by
45 tumor shrinkage which suggests a delay in the tumor
46 response in these patients. So in order to describe these

1 different types of tumor kinetic responses, we developed a
2 model that describes the tumor growth as first _____
3 models and K_g here and then the tumor killing in response to
4 anti PD-L1 treatment and the scores as added killing rate
5 constant K_{kill} and here the growth rate is modeled as first
6 order kinetics as done in the standard models and the
7 killing rate is modeled as the same order kinetics to
8 represent _____ reaction which will be the immune
9 cells and the tumor cells and also allows the system to
10 reach input again over time as consistent with _____
11 data. Also, in order to describe the delay in tumor
12 response in some of the patients, we also incorporated a
13 delay in the immune response which is modeled using a
14 transit compartment model, a model rate with K_{kill} so that in
15 some patients the killing rate increases from zero is
16 maximum value over time and allows to delay tumor response.
17 So with these structural model with each individual the
18 ability in incorporating the population to the tumor
19 kinetic model, we are then able to describe all the
20 different types of tumor kinetic _____ in the study.
21 And another important aspect in the tumor response is that
22 there is a strong relationship between the tumor response
23 and the dropout. As you can see from the individual
24 profiles, the patients who do not respond and progress with
25 the study tend to drop out of the study early. So very
26 limited data from these subjects, whereas the patient who
27 responded to the drug tend to stay in the study for a
28 longer period of time. Therefore, we needed to develop a
29 dropout model to track the range _____. So here, it
30 shows the different tumor kinetics in the study using the
31 final tumor kinetic model coupled with the dropout model.
32 Again we can see that the model is finally _____
33 fairly well, both in terms of mean response as well as the
34 durability among individual patients. So with the model,
35 we can then perform model-based covariant analysis to
36 identify significant covariates for a tumor kinetic
37 _____. Specifically, with both the tumor growth rate
38 constant K_g as well as the tumor killing rate constant K_{kill} .
39 So data in gathering _____ action of anti-PD-L1
40 therapy is to induce the T-cell mediated tumor killing.
41 Therefore, the factors that impact the tumor growth rate
42 are considered as prognostic factors as those who even have
43 another treatment whereas the factors that affect tumor
44 killing are computed as related factors because those
45 should be related to the treatment effect. So for the K_g ,
46 the growth rate we evaluated around the potential

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

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

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

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

8
9 Thank you.

10 [APPLAUSE]

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

12
13 Dr. Roy: Let me start by thanking the organizers for inviting me and
14 let me say some of the role that we have been doing at BMS
15 along the lines of _____. I would like to start by
16 stating somewhat more explicitly the _____ role in dose
17 selection that had been alluded to in some previous talks
18 where we had been talking about using tumor response in
19 making decision on dose selection and why that is really, so
20 unlike any other therapeutic area, the oncology endpoint in
21 the early phase of a trial is different from the phase III
22 ipilimumab trial anywhere in most cases where the endpoint is
23 somewhat single-based, either it is tumor response rate or
24 its PFS at baseline research whereas its is based oftentimes
25 on survival. It has also been alluded to you like the
26 necessity being pointed out by Dr. Woodcock the assessed
27 number of ORR. Our research actually does not use all
28 available data. Usually, it requires a minimum new recent
29 followup, let us say, for six months, let us say, and they
30 have before that ipilimumab use and this is _____, so
31 you have duration of followup with every situation response
32 _____. More of our... And there is also exponential
33 study in a limited number of subjects that we have, so the
34 point being that what we want to do is... This is actually
35 what is reasonably well despite all the talks starting, you
36 know, this morning, but I think there is a lot more that we
37 can do due to university setting of necessity and data are so
38 precious and only fragment use of all the available data. We
39 will disclose selection becomes more complicated overall
40 honestly.

41
42 So the proposed approach that we have been following is very
43 much along the lines from the other speakers here. We got
44 across the tumor growth dynamics and overall survival for
45 tumor genotype. Maybe the assumption that these tumor growth
46 dynamics and overall survival is more agnostic with
47 nivolumab. That is to say, the more you characterize the

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

17
18 So that I can motivate these concepts with every case done
19 and effectively with this, quite recently, it was published
20 with _____ utilizing a few number of TGD-OS model
21 _____ on nivolumab applied to break overall survival
22 with ipilimumab. So the advantage, these are both immune-
23 checkpoint inhibitors, but actually, the mechanism of action
24 is actually complementary. Ipilimumab stimulates the
25 activation of and proliferation of T-cells whereas nivolumab
26 primarily reactivates quiescent T-cells in the tumor
27 microenvironment, and there is evidence that these mechanisms
28 of action are complementary comes from a peripheral file we
29 have regarding advanced metastatic melanoma which shown that
30 complementing the two is better than having it alone,
31 so somewhat they are adding something to each other.
32 We actually have a very interesting set of data set within
33 inhouse to evaluate this because what happened was that
34 ipilimumab was approved for 3 mg/kg once every two weeks for
35 four doses, and other than from the basis of a phase III
36 study that was initiated prior to BMS becoming involved in
37 the development of the drug and then in the end we got
38 involved in the development of the drug, there were several
39 phase II studies that were conducted, one of which was of
40 two-ranging phases. In these two-ranging phases of the study,
41 we found that the 10-mg/kg dose given once every two weeks
42 had better tumor response, RECIST response, than the 3-mg/kg
43 dose. Soon after that, the phase III study led up. It was
44 positive for ipilimumab solely received _____, but we
45 also have a postmarketing commitment to the phase III study
46 to evaluate free-growth system, free-growth study _____.
47 Subsequently in the meantime, nivolumab came along and it has
48 a short benefit in overall survival for metastatic melanoma
49 as well as other genotypes. This is an aside to those that
50 were initiated for three weeks of the nivolumab versus the

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

5
6 We now address to the approach to tumor growth dynamic
7 modeling. We have decided to sort of move to an initial
8 model for describing profile, and it was shown over here
9 significant loss from ipilimumab and what you can see usually
10 are three distinct profiles, types of packet of response, and
11 these had been classified based upon initial model approach
12 that had been given nivolumab. And what you can see clearly
13 is that... Okay. I think I said that. Just to make sure, the
14 tumor growth dynamic model was based upon a model that was
15 published by Young some years ago. We did some modification
16 to actually make sure the model had one component that has no
17 growth at all because otherwise everyone has growth with this
18 that has been present over time. And that was not the fact
19 that we had seen. We had enough stable tumor growth that we
20 had seen. And also as an aside, we make a point that in this
21 case tumor shrinkage model was exponentially decreased. The
22 tumor growth is of linear increase. We also think
23 exponential increase to growth rate models that we have taken
24 very comparable. And as you can see given the limited amount
25 of data that we have for patients who are progressing, a
26 linear growth model recently discussed that recently at least
27 after that.

28
29 Into the view of looking at this, maybe you can say, "Okay.
30 The subjects in this no-growth group of subjects are lacking
31 growth better in terms of overall survival" whereas the
32 progression-free overall survival _____ we have linear
33 growth survival. So a few points to make over here, we
34 decided to use that data profile because again _____
35 even though we may not get a deep response we have a long
36 durable response and this is a thing. A single fine-point
37 example, we can get tumor shrinkage and maximum tumor
38 shrinkage. You might get some subjects who have high
39 shrinkage that involve generally overall survival. So that
40 is the reason why we chose the shrinkage model.

41
42 So here are some key results from this long study.
43 Interestingly, the progression-free survival was very similar
44 for the three _____. I am showing the reference that
45 whereas there was a highly significant difference in overall
46 survival. So there was about 6% to 7% difference in maximum
47 survival at one year. So the approach that we have taken
48 actually is to accumulate a setback. So the approach that we
49 have taken in terms of overall survival modeling is to
50 include all the baseline prognostic factors that can include

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

9
10 So here are the results of the study, a complete list of
11 study, a completely different drug. We did _____ in
12 describing the 3-mg/kg dose and the 10-mg/kg dose.
13 The effectiveness had turned out very good. Despite this,
14 the model has captured some of the benefit, additional
15 benefit, with the 10-mg/kg dose. So what we are showing here
16 is how can we actually use this model to limit the data and
17 how can we actually do. So if you take a limited data from
18 this phase III study with ipilimumab, 35 subjects turnout
19 with six months' followup and you use the model for free-
20 tumor growth survival, can you relate the better overall
21 survival with 10-mg/kg as better treatment for the patient?
22 This shows exhaustive direct horizontal line that is showing
23 the observed differential in survival percentage at one year
24 and in two years, and the _____ show the distribution of
25 clinical trials that show an advantage. So approximately
26 between, you know, 70% and 75% _____ would show that the
27 10-mg/kg dose has been shown better even though PFS was
28 essentially identical in percentage.

29
30 So in summary, the TGD-OS model developed with one drug,
31 nivolumab, _____ rate of survival for a different drug,
32 ipilimumab, providing proof principle that this set of
33 approach could be agnostic to the drug in terms of tumor
34 shrinkage and the tumor response profile may be sufficient to
35 break the overall survival on the drug. This set of model
36 can be used to leverage data from all new clinical data from
37 _____ receptors to form a program of _____
38 modification and several set of improvements to the TGD-OS
39 model can be made and maybe discussed at the _____.

40
41 Moderator: Alright _____. Our next speaker is Dr. Rene Bruno
42 _____.

43
44 Dr. Bruno: Thank you, and welcome to the FDA _____ ISoP
45 _____ find interesting _____. So _____
46 breakthrough _____ is a drug _____. In fact,
47 there is a link between _____ treatment _____.

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

21
22 Okay so then we developed a model based on those data
23 _____ model _____. The tumor growth inhibition
24 _____ using is _____ that is being presented by
25 _____ except that instead of _____ patients
26 depending what you see, we used a population approach with
27 that. Patients _____ we could estimate _____ for
28 each of the patients. We then _____ population
29 approach _____. The only thing _____ at least
30 _____ baseline, you can _____ that in the POPLAR
31 study, we had 277 patients; and 91% of the 277 patients
32 _____. What I am showing here is the typical profiles
33 of the _____. What you see _____ is docetaxel,
34 and you see that docetaxel _____ initially _____
35 than we would expect; and then there is _____ compared
36 with atezolizumab _____. So if you got any of the
37 matrix _____ overall survival, you will see at least
38 that _____ as we are using earlier is not going to
39 predict the benefit from atezolizumab. Same when we have
40 the _____ using in the past. Of course _____ and
41 we want to predict the _____. So you will see that
42 those things _____. Now let's see what's happening in
43 those patients that we defined as _____ those patient
44 who are _____ right? _____ and here you see that
45 there is _____ between docetaxel and atezolizumab

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

4
5 Now we are going to _____ of the patients, and we
6 developed _____ models _____ two baseline
7 characteristics _____ met sites _____ so it is
8 not a good assessment _____ patients _____ number
9 of sites that are _____. When we use _____
10 treatment effects _____ but when you _____
11 explain the _____.

12
13 Now we are _____ model in simulating the POPLAR study,
14 and this _____ here. We are simulating _____
15 study _____ distribution for each of the _____
16 and what you see here is a prediction of _____ we
17 predict the _____ we did that for all of the patients
18 and we did that by baseline biomarker expression. So
19 patients that expressed _____ PD-L1 at baseline
20 _____ tumor cells or immune cells _____. Those
21 patients are benefitting a bit more _____ when the
22 patient not expressing PD-L1 _____. In addition to
23 that, we have a marker or a gene expression of the T-
24 effector and interferon _____ genes _____, and we
25 could show _____ predict the model _____
26 benefitting the patient with high _____ gene
27 expression _____. Now we can _____ further and
28 we predict that in phase 3 studies _____. This study
29 _____ docetaxel _____ but still we can predict
30 the phase 3 study based on the tumor dynamic data
31 _____ in patient by data of the biomarkers. Here you
32 will _____ the patient with no expression of PD-L1
33 benefitted. Patient with _____ gene expression
34 benefitted _____. Here we have the _____ here we
35 got the phase 2 study _____ when the _____ phase
36 3 _____ comparing atezolizumab to _____ but still
37 we see the same thing in the _____. Here we have the
38 _____. Here it is a qualification of the model
39 _____ but we have the two groups of the patients.
40 First group were first-line patients, cisplatin _____
41 group were second-line patients who _____ and you see
42 that _____ patients _____ first line versus
43 second line= _____. Now we go to that model and we
44 predict the _____ that is comparing _____

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

21

22 [APPLAUSE]

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

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

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

10
11 So I want to talk about _____ tumor size data. Tumor
12 size data actually is _____ trials. Tumor size
13 actually _____ so those information can help us to
14 bring the _____ tumor size _____ contains a lot
15 of information _____ the drug effect difference caused
16 by _____ or caused by _____ tumor size _____
17 information. _____ it has been diagnostic _____
18 tumor size _____. So that relationship can be
19 quantitative _____ relationship actually _____ to
20 project long-term clinical outcome using the _____
21 tumor size _____ information. So in this aspect, FDA
22 made a huge contribution to _____ this exercise
23 _____ from the FDA _____. So the objective of
24 _____ presentation is to present two cases to
25 demonstrate the value of using _____ data and prior
26 knowledge for decision making, and specifically _____
27 first-line treatment for metastatic renal cell carcinoma.
28 This presentation _____ the impact of the proposal so
29 I am not going to go _____. So the new treatment
30 assessed here is axitinib plus avelumab. Another
31 _____ combination X+Y which is masked treatment
32 _____ as a first-line treatment of sunitinib. So the
33 first step is to pull _____ data from the new
34 treatment sunitinib and then _____ dynamic model.
35 Data from axitinib plus avelumab come from _____
36 patients. This actually is _____ considering this is
37 a phase 1b study. Data from combination of X+Y come from
38 _____ data only from 10 patients. For standard of
39 care data, _____ information. So the drug effect, as
40 I said, can be estimated using _____ study; and the
41 drug effect _____ from the model _____ and
42 compare the two new treatments versus sunitinib. This
43 comparison _____ focus on two parameters. One is the
44 tumor size _____ which is _____ this presentation.
45 Another is drug effect on tumor shrinkage rate. The reason

1 to _____ tumor size _____ of the treatment so
2 that parameter _____ can be estimated _____ much
3 information about the tumor growth. So this is the tumor
4 dynamic model we use in _____ proposing _____.
5 This model basically has _____ assumptions. The first
6 assumption is that tumor growth _____ growth rate of
7 KL indicated in this equation. The second assumption is
8 that tumor shrinkage _____ in this equation. The
9 third parameter is about described resistance. Eventually
10 it is assumed that the tumor _____ meaning the tumor
11 will regrow _____ actually describes how _____.
12 This slide shows the tumor reduction after treatment of
13 axitinib plus avelumab _____ patients. As you can see,
14 tumor size shrinkage is quite a lot, and this reduction is
15 good. However, we don't know how good is good enough for
16 _____ combination model. So this slide shows the
17 comparison between two treatments off axitinib plus
18 avelumab versus sunitinib. So all the _____ represent
19 tumor size reduction from sunitinib, and the right line
20 represents tumor size reduction from combination. So as
21 you can see, combination did cause greater tumor size
22 reduction as compared with sunitinib. However, I think
23 _____ so the tumor size reduction rate is actually
24 more _____ compared between the combination versus
25 standard of care sunitinib. So as you can see, the
26 combination did _____ greater tumor size reduction
27 rate as compared with the sunitinib. The difference
28 actually is statistically significant. This slide shows
29 the tumor size reduction _____. So as you can see,
30 the combination caused more tumor size reduction and the
31 difference is statistically significant. So the same
32 _____ we will actually apply to treatment X+Y, and
33 this I would say _____ data for the second combination
34 _____ tumor size reduction. When compared with
35 sunitinib, the reduction does not _____ better than
36 the standard of care. For the tumor size reduction rate,
37 this is actually really _____ so no surprise. For the
38 tumor size reduction _____, the second combination is
39 _____ sunitinib. So based on that, actually the
40 second combination _____ move forward not only based
41 on this exercise but _____ to this agent. So this
42 _____ support _____ of the combination of
43 axitinib plus avelumab _____ for the second
44 combination, and I hope the case convinced that a modeling
45 approach can be informative _____ knowledge for that.

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

3

4 PANEL DISCUSSION

5 [APPLAUSE]

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

10

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

17

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

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

7 Moderator: Thank you. Dr. Yu?

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

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

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

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

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

32 Roy: Overall survival.

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

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

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

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

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

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

1

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

15 Moderator: We'll have the next question.

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

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

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

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

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

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

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

42 Audience: Thank you.

43

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

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

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

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

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

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

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

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

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

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

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

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

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

35

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

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

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

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

33 [APPLAUSE]

34 SESSION III MIDD BEFORE AND AFTER APPROVAL

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

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

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

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

1 from baseline versus the total daily dose and so I told you
2 we have a data at 150 twice daily and 200 twice daily so this
3 300 mg represents the 150 twice daily and then 400 this is
4 the 200 mg twice daily, and so based on this analysis of
5 biomarker data from patients with cancer, we are seeing
6 target inhibition, it is maximized at those levels of 150 or
7 200 mg twice daily and ultimately in this study, the maximum
8 tolerated dose was identified as 200 mg twice daily and that
9 is one of the dose levels that was carried for into the
10 registration study but we also used the dose of 150 mg twice
11 daily and so the modeling and simulation work that we did in
12 the study helped to support carrying those doses forward into
13 registration studies. So now we fast forward to the time
14 when we were preparing to see the data from registration
15 studies MONARCH 1 and MONARCH 2 and we need to develop a
16 population pharmacokinetic model because we need to do
17 covariant screening to determine if there are any patient
18 level cofactors that would require dose adjustments but we
19 knew that we are going to have a lot of data from a lot of
20 patients because we are incorporating data from that first
21 study I just showed through JPDA. The data from MONARCH 1
22 and an extensive clinical pharmacology package when we have
23 data from our C14 study and _____ study, a
24 clarithromycin interaction and rifampicin interaction study
25 so it is a lot of data and knew it would be a computational
26 intensive exercise so we developed an intermediate model and
27 that is the structure of the model I am showing you here. It
28 is a two-compartment model and this is full of _____
29 only and we used this as a tool to screen the covariants that
30 we were just to see things impact dosing and with this small
31 _____ we screen for those covariants, those that came
32 out of it or if we tested in our ultimate model population
33 pharmacogenetics so _____ where we incorporated that in
34 the metabolites as well and here is the structure of that
35 model. It is a mechanistic model and we wanted to be able to
36 describe the exposures not only of the parent but the active
37 metabolites and to _____ and that is important because
38 given their activity, they could be contributing to both
39 advocacy and safety, only needed a way to output exposures to
40 determine if anyone _____ was driving either efficacy or
41 safety and we used all of the data and fit this model to it
42 and this is what we used as input for other exposure response
43 analysis and modeling. So the impact of this model, we were
44 able to describe the disposition of the parent and to active
45 metabolites highlights and it was useful for exposure
46 response analysis and it helps to understand the relative

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

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

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

45 [Applause]

1 Moderator: I think we have time for two questions.

2 Audience: Yeah. I wonder _____.

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

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

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

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

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

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

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

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

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

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

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

36

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

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

3
4 Dr. Liu: Thank you. Good afternoon. My name is Chao Liu and I'm
5 from _____ at FDA. It is my great honor to do this
6 presentation at this session. Today I would like to talk
7 about models _____ NDA/BLA review for presenting two
8 review cases. Before starting my presentation, I'd like to
9 make a disclaimer that the views in this presentation
10 represent my personal opinion. We are presenting these two
11 review cases. I will show that _____ the analysis of
12 _____ response relationship may _____ assessment
13 of efficacy, safety as well as dose. In addition,
14 modeling-based analysis _____ can be used to
15 _____ two cases can provide some insight to _____
16 in terms of the relevance of the modeling _____
17 analysis for NDA/BLA review.

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

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

1 patient. The _____ analysis on the left was based on
2 the _____ data collected from a subset of the subject
3 _____ AUC of day 15 of cycle 1 is flat, suggesting
4 _____ over the dose range of 500 to 1000 mg b.i.d.
5 The plot on the right shows the dose exposure relationship
6 based on _____ analysis of over 300 patients. The
7 _____ plot represents the distribution of the
8 individual exposures. _____ results from the
9 _____ data. Subjects with 500, 625, 750 and 1000 mg
10 b.i.d. doses showed _____. Thus, based on the
11 _____ analysis, we concluded that dose exposure
12 relationship as flat from 500 to 1000 mg b.i.d. We also
13 evaluated the exposure response relationships for efficacy
14 and safety of this drug. Exposure-efficacy relationship
15 between rociletinib _____ response rate was explored
16 using data from patients who were treated _____. The
17 relationship was _____. In the plot, the mean
18 _____ 95% _____ of the observed response rate of
19 _____ rociletinib exposure _____. The actual
20 plotline _____ represented _____ is 95%.
21 _____ represent the distribution of rociletinib
22 steady-state AUC at each dose group. The plot shows that
23 within the smaller range between 500 and 750-mg b.i.d.
24 doses, the effect of the drug exposure to efficacy
25 _____. Using this model, the predicted ORR for the
26 500, 625 and 750-mg b.i.d. dose _____ risk factors
27 were identified. Based on the exposure-efficacy analysis,
28 the results _____ efficacy across different dose
29 levels. No meaningful different in efficacy would be
30 expected by increasing the dose level about 500 mg b.i.d.
31 _____ M502 is primarily responsible for hyperglycemia.
32 The plot on the left represents the exposure-safety
33 relationship between M502 steady-state AUC and the instance
34 of grade 3 or 4 hyperglycemia as evaluated by the FDA.
35 _____ 95% _____ of grade 3 or 4 hyperglycemia
36 _____ M502 exposure are represented by the _____
37 represent the _____ incidence of grade 3 or 4
38 hyperglycemia _____ represent the distribution of M502
39 steady-state AUC at each dose group. For exposure-safety
40 analysis, there appeared to be a correlation between
41 increasing M502 exposure and the incidence of grade 3 or 4
42 hyperglycemia, suggesting that a patient with high M502
43 exposure has a greater risk of grade 3 or 4 hyperglycemia.
44 _____ M460 is responsible for QTc prolongation. As
45 shown on the right, a model predicted correlation between
46 M460 exposure and QTc prolongation but the _____

1 concentration of M460 and _____ from baseline. The
2 solid _____ represents the predicted change from
3 baseline _____ QTc _____ correlation between
4 prolongation of the QTc interval and the increasing M460
5 concentration. Finally _____ similar exposure from
6 500 to 1000 mg b.i.d. _____ from different dose levels
7 will provide _____. In addition, based on the
8 identified exposure response relationship from 500 to 750
9 mg b.i.d., patients with higher rociletinib exposure are
10 unlikely to have further benefit. However, subjects with
11 higher metabolite exposure are at greater risk for QTc
12 elongation and hyperglycemia. Thus we _____ proposed
13 625-mg dose was not adequately supported based on available
14 data. FDA's analysis was _____. Along with other
15 issues _____ approval based on available data. A
16 complete response _____.

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

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

12 To address these challenges _____ model strategy was
13 adapted. The standard of using a constant exposure matrix
14 subject level _____ exposure matrix was used
15 _____ tumor size was used to assess the drug efficacy.
16 In terms of _____ safety _____ AE was associated
17 with _____ exposure. Finally in the simulation
18 _____ to address the _____ dose adjustment
19 _____ trial _____ to incorporate the dose
20 exposure-safety interaction. The exposure-safety and
21 efficacy relationship between lenvatinib and everolimus
22 _____ tumor size was explored _____ trial.
23 _____ tumor growth rate _____ to the natural
24 growth rate minus the suppression effect from lenvatinib
25 plus everolimus. _____ from the three arms of the
26 previous study _____ to estimate model parameters.
27 Tumor _____ growth rate was referred _____ study
28 where a placebo arm _____ renal cell carcinoma
29 _____. Meanwhile through communication with FDA, a
30 longitudinal _____ AE _____. AE is _____
31 dose adjustment were treated _____ and this model will
32 be used to predict the dose _____ regimens to form the
33 dose adjustment cost by _____. So in terms of
34 selecting the alternative dosing regimen _____ dosing
35 regimen were simulated to predict the efficacy and safety
36 profile. At each dosing regimen _____ dose adjustment
37 _____ adverse events was _____ overtime based on
38 the _____ E-R _____ of a single-agent dosing
39 history overtime where each dose level is represented by
40 different _____. Finally based on the generated
41 dosing history, the tumor dynamics was simulated _____
42 efficacy at each dosing regimen. This slide shows the
43 simulated tumor dynamics. At each graph, the X axis is the
44 time of the treatment up to one year, and the Y axis is the
45 relative tumor size compared with baseline. _____ is
46 a single agent _____ values of the tumor dynamics.

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

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

29 [APPLAUSE]

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

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

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

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

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

27
28 So specifically for ibrutinib, if we talk about how to use
29 model approach to support different indication, those of
30 you who know a little bit ibrutinib know it is a very
31 sensitive _____ substrate. So as part of the late-
32 stage package, a lot of activities that we do are still
33 under using a PBPK model _____ the drug interaction
34 package. When we first submitted, we had a couple of drug
35 interactions with _____ inhibitor, and then we worked
36 closely with the FDA to really understand the different
37 _____ of different _____ inhibitor, different
38 types of inhibitor because we could not study all the
39 different scenarios. With PBPK, it was really _____
40 ibrutinib to understand some of these effects and estimate
41 those. So I think it is a really nice example _____
42 the example that I talked about. So we have had to fulfill
43 a couple of PMR and post-approval measure, and we had to a
44 study with omeprazole so that is the example also
45 _____ it is a very specific sample of how we use

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

1 could recommend to take it with PPI, but we really wanted
2 to be able to support the clinical recommendation of what
3 to do with this pH-altering agent. So we understood well
4 the mechanism of action. Again, it is a covalent binding
5 so what we decided to do was really to develop this
6 mechanistic model based on the kinetic of binding and
7 dissociation kinetics _____ and look at the effect on
8 our target engagement, so taking target engagement as a
9 surrogate for efficacy. Again, using this mechanistic
10 model, I think somebody asked this morning on how you
11 validate this. So what we did was to do some sensitivity
12 analysis to look at _____ of the model given different
13 assumptions into its parameters. We had some BTK
14 _____ data so we kind of used that to make sure the
15 model was doing, what it was predicting was appropriate.
16 We also had done similar exposure response for efficacy
17 based _____ Cmax and tried to use that also in
18 supporting _____ recommendation. So this is the
19 mechanistic model of BTK. So _____ represent the
20 enzymes with BTK. I represented ibrutinib inhibitor and so
21 you have formulation of the complex here, k_{on} _____.
22 Again, it is a covalent binder; and then your inactivation
23 _____ complex and into degradation that you could see
24 from BTK _____ of the complex and also _____
25 itself. So what we did was that there was some published
26 data that had been done on the association and dissociation
27 _____ for ibrutinib on BTK, so we used these data.
28 There was another publication that also had done some time-
29 dependent studies _____ BTK half-life to inform that
30 _____ degradation again from another publication that
31 talked about the turnover of the BTK. So we plugged in
32 these different assumptions there, the different _____
33 the different parameters to try to estimate what would be
34 the _____ ibrutinib. Then here the concentration
35 profile _____ what the I profile would look like,
36 right? So what was the profile _____ omeprazole so we
37 can look at what the effect was going to be with the
38 _____ receptor _____. So this is the resulting
39 simulation data. So we basically did the simulation up to
40 steady state so the timescale was basically here _____
41 24-hour profile at steady state, and here represent the
42 receptor occupancy. So for ibrutinib alone, you could see
43 there is still a little bit of variability _____ the
44 day but all above 90%. With omeprazole, you can see that
45 the effect, if anything, was just to _____ dose
46 variability. So if we calculate the average receptor

1 occupancy, it was comparing 94% and 96% so very similar.
2 So we felt fairly confident that this was really going to
3 be helpful to make recommendation that _____ no
4 difference. Let me skip to this one. So that is the data
5 that we have following single dose, and single dose really
6 kind of is an agreement with data. So on the open circle
7 here, you got the PK profile _____ as you have seen
8 with the omeprazole study _____ fairly rapidly from
9 circulation; but you can see that the BTK here engagement,
10 we have measured that at 4 and 24-hour that the enzyme, you
11 see the complex formation. Because of the half-life of 24
12 hours for BTK turnover, it is maintained across that dosing.
13 So the results of the simulation were consistent with what
14 we had observed in that study. Again, as I have said, we
15 did some sensitivity analysis for the different parameters,
16 and we really stretched some of these _____. So
17 threefold variation here for the BTK half-life so the
18 _____ 24 and then we ranged between threefold higher
19 and threefold lower to see the impact. So the impact was
20 really actually not that much. It was about, at most, 10%
21 on the affected cells; but if you look at the difference
22 between the two treatments, that was also a very small kind
23 of effect. The effect of _____ that was really
24 nothing because the _____ is minus 1 to 1% so a very
25 small effect even if you change the value a tenfold factor.
26 Here a little bit more than it packed on k_{on} So if you
27 _____ tenfold down, you can see _____ change, but
28 if you increase that tenfold, then you will see a change in
29 the BTK predicted value; but again, the difference between
30 the two treatments was still very similar. So we felt that
31 was really _____ assessment of our assumption there.
32 We also had done some of the efficacy and exposure
33 relationship so looking at just responder rate versus
34 _____ quartile and exposure, on the left, there is
35 C_{max} ; on the right is AUC. So there was really no
36 relationship and you can see there is a fairly high life
37 range and concentration, about a hundredfold there. Again,
38 the drug _____ you are going to see some _____
39 variability; but the dose was selected to make sure that
40 most of the patients would be above that 90% inhibition in
41 90% of your subjects so that kind of supported that as well.

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

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

15 PANEL DISCUSSION

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

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

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

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

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

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

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

38 [LAUGHTER]

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

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

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

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

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

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

29 Audience: I have one question. Is this on?

30 Moderator: Closer, closer to the mike.

31 Audience: One quick question.

32 Moderator: How we're all friends.

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

34 [LAUGHTER]

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

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

37 Audience__: I'm just wondering if anyone knows this.
38 How do we go from model-based drug development about 10 or
39 15 years ago to modeling for drug development? Have we
40 gone soft over age or is there some other reason for why

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

3 [LAUGHTER]

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

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

40

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

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

17 [LAUGHTER]

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

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

29 Keegan: Oh, okay.

30 Moderator: Thank you. I hear you.

31 [LAUGHTER]

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

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

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

14 [LAUGHTER]

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

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

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

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

35 [LAUGHTER]

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

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

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

5 _____: Thank you.

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

22 [APPLAUSE]

23

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

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

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

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

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

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

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

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

18 [APPLAUSE]

19

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

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

34 [APPLAUSE]