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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC ONCOLOGY SUBCOMMITTEE OF THE
ONCOLOGIC DRUGS ADVISORY COMMITTEE

TUESDAY, NOVEMBER 1, 2011

8:00 a.m. to 4:00 p.m.

FDA White Oak Campus
White Oak Conference Center
Building 31, The Great Room
Silver Spring, Maryland

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1 P R O C E E D I N G S

2 (8:00 a.m.)

3 **Call to Order**

4 **Introduction of Subcommittee**

5 DR. BALIS: Good morning and welcome to the
6 pediatric oncology subcommittee of the ODAC. My
7 name is Frank Balis. I'm a pediatric oncologist
8 from the Children's Hospital of Philadelphia, and
9 I'll be chairing the meeting today. Let's start
10 off by introducing the panel members who are here,
11 and we'll catch up with the people as they arrive.

12 Greg, would you start please?

13 DR. CURT: Sure, thanks, Frank.

14 Greg Curt, medical oncologist and industry
15 representative to ODAC.

16 DR. ARNDT: Carola Arndt, pediatric
17 oncologist from Mayo Clinic, member of the
18 Pediatric Subcommittee, ODAC.

19 DR. MASCARENHAS: Leo Mascarenhas, pediatric
20 oncologist, Children's Hospital, Los Angeles.

21 DR. GORLICK: Richard Gorlick, pediatric
22 oncologist, the Children's Hospital at Montefiore.

1 DR. BRIGGS: Caleb Briggs, designated
2 federal officer, ODAC.

3 DR. FREEDMAN: Ralph Freedman, gynecological
4 oncologist, M.D. Anderson and also ODAC member.

5 DR. SHEARER: Patti Shearer, pediatric
6 oncologist, the University of Maryland Greenebaum
7 Cancer Center.

8 DR. SNYDER: Kristen Snyder, medical officer
9 at the FDA.

10 DR. REAMAN: Greg Reaman, FDA, Office of
11 Hematology and Oncology Products.

12 DR. TASSINARI: Melissa Tassinari, pediatric
13 and maternal health staff, Office of New Drugs,
14 CDER.

15 DR. PAZDUR: Richard Pazdur, director of
16 Office of Hematology Oncology Products.

17 DR. BALIS: Malcolm, do you want to
18 introduce yourself as well?

19 DR. SMITH: Malcolm Smith, National Cancer
20 Institute.

21 DR. BALIS: Thank you.

22 As a reminder, for topics such as those

1 being discussed at today's meeting, there are often
2 a variety of opinions, some of which are quite
3 strongly held. Our goal is that today's meeting
4 will be a fair and open forum for discussion of
5 these issues and that the individuals can express
6 their views without interruption. Thus, as a
7 general reminder to everybody, individuals will be
8 allowed to speak into the record only if recognized
9 by the chair. We look forward to a productive
10 meeting this morning.

11 In the spirit of the Federal Advisory
12 Committee Act and the Government in the Sunshine
13 Act, we'll ask that the advisory committee members
14 take care that their conversations about the topics
15 at hand take place in the open forum of the
16 meeting. We are aware that members of the media
17 are anxious to speak with the FDA about these
18 proceedings. However, FDA will refrain from
19 discussing the details of this meeting with the
20 media until its conclusion.

21 I'd also like to remind everyone present to
22 please silence your cell phones and other

1 electronic devices if you haven't already done so.
2 And again, the committee is reminded to please
3 refrain from discussing the meeting's topics during
4 breaks or lunch. Thank you.

5 We'll now proceed with the FDA's
6 presentation.

7 **FDA Presentation**

8 DR. TASSINARI: Good morning, everyone. I'd
9 like to set the stage for our discussions today
10 with a brief overview of the key elements in the
11 U.S. regulations. These regulations incorporate
12 the principles that are articulated in the National
13 Conference of Harmonization; namely that pediatric
14 patients should be given medicines that have been
15 properly evaluated for their use and that product
16 development should include pediatric studies when
17 pediatric use is anticipated. In addition to an
18 overview of the U.S. laws, I also want to focus a
19 little bit today on the impact this has for
20 oncology products.

21 Now, like all regulations, there are a lot
22 of acronyms, and these are the ones that you're

1 going to see through the presentation today.

2 The history of regulation of pediatric drug
3 development is fairly recent. The foundation of
4 our current legislation began in the 1990s with the
5 establishment of pediatric exclusivity as an
6 incentive for work done under a written request.
7 It also saw the issuance of the pediatric rule
8 which mandated attention to pediatric drug
9 development. These laws were replaced in 2002 and
10 2003 with the Best Pharmaceuticals for Children
11 Act, BPCA, and the Pediatric Research Equity Act or
12 PREA. These were subsequently renewed in 2007 as
13 parts of the Food and Drug Administration
14 Amendments Act or FDAAA.

15 An important new addition into the pediatric
16 legislation occurred in 2010 with the provisions in
17 the Biologics Price Competition and Innovation Act,
18 which is part of the Patient Protection and
19 Affordable Care Act that now allows biologics to be
20 studied under a written request.

21 To complete the picture here for the global
22 regulatory environment, the European pediatric

1 regulation came into force in January of 2007. The
2 regulation combines elements that are found both in
3 the BPCA and in PREA, so much of what of I'm going
4 to describe today for the U.S. legislation also
5 applies to this regulation.

6 The two pieces of the U.S. legislation
7 provide both mandatory and voluntary elements, and
8 as a result of the 2007 laws, results from studies
9 conducted under either PREA or BPCA must now be
10 included in labeling. And as noted earlier, recent
11 legislation now allows for the issuance of written
12 requests for a biologic product.

13 Under PREA, this is the obligatory portion,
14 pediatric studies are required for any NDA or BLA
15 or supplement with a new active ingredient, a new
16 dosage form, a new dosing regimen or new route of
17 administration. PREA applies only to indications
18 that are included in the submission, and drugs with
19 orphan designation are not studied under PREA.

20 There is a need for a submission of a
21 pediatric plan that must accompany any deferral
22 request that comes in with a NDA or BLA submission,

1 and this also includes nonclinical and formulation
2 plans in addition to the clinical trials proposed.
3 PREA requirements are a part of the approval for an
4 NDA or a BLA.

5 Now, PREA provides for waivers when studies
6 are not feasible or safe for a particular age
7 group. Waiver applications must be supported by
8 data indicating why the study cannot or should not
9 be conducted in that age group. Because pediatric
10 studies most often are conducted later in
11 development, deferral applications include a
12 proposal for the timing of the conduct of the
13 agreed-upon studies in the pediatric plan, and this
14 is a required element.

15 Now, if we turn to BPCA, remember this is a
16 voluntary program for which an incentive is
17 offered. A written request can be issued directly
18 by the review division, or most often it is
19 requested by the sponsor through the proposed
20 pediatric study request or the PPSR. The written
21 request may include pediatric indications that are
22 different from the adult indications. There are

1 several considerations that are reviewed, but
2 central to those considerations are the public
3 health need and the feasibility of the proposed
4 studies.

5 One of the elements of the FDAAA legislation
6 in 2007 was a mandated establishment of the
7 internal pediatric review committee. Expertise for
8 this committee comes from across the agency and
9 includes all disciplines that touch pediatric drug
10 development. The committee reviews, along with the
11 divisions, pediatric studies falling under either
12 PREA or BPCA.

13 Now, in Europe, the regulatory document is
14 called a pediatric investigative plan or PIP, and
15 it has elements that are found both through the
16 BPCA and PREA. All age groups must be addressed,
17 either by a waiver or a pediatric trial for the
18 conditions in which the product might be expected
19 to be used. There is a similar incentive, six-
20 month extension of the supplementary protection
21 certificate, and all products must have an approved
22 PIP in order to file a marketing authorization

1 application.

2 So what's now evolving here for the planning
3 of pediatric drug development programs is more
4 awareness of the need to integrate this thinking
5 earlier in the overall drug development. This is
6 being driven by these global pediatric regulations.
7 For the PIP, you can see this process starts at the
8 end of studies for adult pharmacokinetics, usually
9 at the end of phase 1, leading to an approved PIP
10 before the marketing authorization application.

11 In the United States, under PREA, if the
12 pediatric requirements have not yet been met, the
13 pediatric plans are required with deferral
14 applications. The deferred studies are then part
15 of the NDA or the BLA approval and are noted as
16 postmarketing requirements. Note, though, that the
17 discussion for a written request can begin anywhere
18 along the line, both prior to approval and
19 post-approval.

20 So what about drugs for pediatric cancers?
21 Well, they have the same regulatory expectations,
22 and then there are some added considerations.

1 Small numbers of patients demand thoughtful
2 approaches, and there must be the prospect of
3 direct benefit. Alternate therapeutic approaches
4 are needed to treat cancers in children, and this
5 leads to innovative trial designs. And protocols
6 are written in conjunction, usually with a CTEP and
7 other national cooperative research groups.
8 Conditions under study in adults do not normally
9 have a pediatric correlate, and, therefore, the
10 majority of products are going to be studied under
11 BPCA. There are going to be only a few that are
12 going to trigger PREA.

13 Now, the goal of an oncology written request
14 is to develop drugs that provide a meaningful
15 advancement in the treatment of children with
16 cancer. Now, ideally, these drugs would have
17 curative potential. But at the very least, they
18 should have the potential to prolong life, improve
19 the quality of life, reduce toxicity, or improve
20 efficacy.

21 Now, in general, the outline of a written
22 request contains the description of the indications

1 to be studied. A listing of the studies and the
2 key elements of the studies are included in this
3 written request, but note that the study protocols
4 are not a part of a written request. Nonclinical
5 studies and formulations are included when needed
6 to support the clinical trials that are proposed,
7 and when studies under a written request are
8 submitted, draft labeling is included in the
9 submission package.

10 For an oncology product to receive a written
11 request, there are several considerations, and
12 these can be the guide in determining whether or
13 not to submit a PPSR. Is there a mechanism of
14 action for the drug that suggests potential
15 activity? Is there a scientific rationale that
16 exists for the drug to be evaluated in those
17 pediatric cancers? Is there activity in
18 preclinical models? Has there been efficacy shown
19 in related adult cancer? Is there evidence that
20 the therapy will reduce toxicity with similar
21 efficacy to an existing therapy? And, finally, is
22 there potential to improve the quality of life for

1 that pediatric patient?

2 Consideration as well can come from the
3 discussions that we're going to have today from
4 this panel.

5 Typically, the written request for an
6 oncology product has included phase 1 studies to
7 establish the dosing range and phase 2 studies to
8 define the activity of the product. In both types
9 of studies, clear objectives in the targeted
10 population are defined as well as the statistical
11 plan to judge the success of the trial. When we
12 look at phase 2 studies, they can be designed, if
13 needed, to evaluate multiple cancer types.

14 There are other considerations based on
15 need, such as the pharmacogenetic/pharmacogenomic
16 studies that should be conducted if evidence from
17 other nonclinical or clinical data show that
18 genetic characteristics can influence drug
19 exposure, response or toxicity. And, importantly,
20 plans for validation of a companion diagnostic
21 device for the appropriate age groups should be
22 included if they're needed for the safe use of that

1 drug.

2 Work done under a written request for
3 oncology products rarely results in a labeled
4 pediatric indication. Phase 3 studies are
5 infrequent with a written request but can be
6 required as appropriate. And for non-oncology
7 products, these are a routine element of the
8 written request.

9 We currently lack a regulatory mechanism to
10 routinely receive data from pediatric oncology
11 studies performed post-approval outside of the
12 postmarketing requirements in the written request.
13 Consequently, the information from those studies is
14 not routinely reviewed by the FDA, nor are they
15 able to be included in the label. However, it is
16 expected and encouraged that any needed phase 3
17 trials would be completed as quickly as possible so
18 that we can consider the pediatric indication and
19 allow for the comprehensive labeling.

20 So, in summary, in oncology, we have small
21 and vulnerable populations that require thoughtful,
22 coordinated, well-designed clinical trials. And

1 it's also clear that looking at the current
2 environment, that the global regulations are
3 driving pediatric drug development. And, finally,
4 BPCA and its incentive have been successful to
5 provide a mechanism for data submitted to the FDA
6 for independent review, to expand the knowledge
7 that we have to improve pediatric care, and, most
8 importantly, to inform the product label.

9 Thank you.

10 **Clarifying Questions from Subcommittee**

11 DR. BALIS: Thank you, Dr. Tassinari.

12 Are there any questions from the panel?

13 [No response.]

14 DR. BALIS: I'd start with one. You
15 mentioned a couple times in your presentation the
16 limitations related to particularly small numbers
17 of patients and relatively few drugs that actually
18 make it to phase 3 study. When you consider
19 approving a drug for a pediatric indication, are
20 your criteria different for pediatric indications
21 than they are for adults, particularly in terms of
22 the statistical rigor that's required?

1 DR. TASSINARI: So the short answer is no.
2 We hold pediatric clinical studies and their
3 designs to the same standards as we do for any
4 adult study or indication. But we are aware of and
5 appreciative of the discussions we need to have for
6 the design of a pediatric trial, taking into
7 consideration such issues as the age and the
8 numbers of patients you might have within that
9 particular disease.

10 I don't know if anybody from the division
11 wants to elaborate any further on that for oncology
12 products.

13 DR. PAZDUR: I would just say that we would
14 consider pediatrics along with other rare diseases,
15 and I think we've demonstrated a great deal of
16 flexibility in looking at different types of
17 endpoints and different sizes of clinical trials,
18 basing approvals on established surrogates for
19 clinical benefit, response rates, time to
20 progression, biochemical markers of the disease,
21 et cetera.

22 So as was pointed out by Melissa, we're

1 aware of the small numbers of patients, and this is
2 part of not only in pediatrics but also an effort
3 in looking at rare diseases to look at a variety of
4 endpoints to be used.

5 DR. BALIS: Dr. Curt.

6 DR. CURT: Thank you, Dr. Balis.

7 One of the things we've discussed in this
8 subcommittee before is the discrepancy between the
9 U.S. and the European regulations, where the PIP,
10 to my knowledge, requires a phase 3 plan in a set
11 of diseases where phase 3 trials are rarely done.
12 So has that changed at all in terms of
13 harmonization between the U.S. and the EU in terms
14 of the PIP requiring a phase 3 plan?

15 DR. TASSINARI: I hesitate to speak directly
16 for the changes that the EMA may be undergoing or
17 the thought process that they have directly in
18 regards to that. But I will talk a little bit here
19 about one of the impacts of the timing differences
20 that we have.

21 The PIP, or the pediatric investigative
22 plan, as you've seen, the discussions for that and

1 the approvals for those original documents occur
2 much earlier than they tend to do here. One of the
3 caveats or the one of the problems with that is
4 that the discussions that are had at that point are
5 based on less data. And as a result, and this
6 being the only opportunity within the confines of
7 their regulation to develop this plan, anything
8 that is felt to be reasonable and possible based on
9 the evidence at the time is included in that PIP.
10 There are a whole series of modifications that
11 occur within that European document that allow for
12 changes in the program as more data is added.

13 As far as the United States is concerned, we
14 are hoping to actively engage a sponsor in
15 discussions of pediatric plans as early as
16 possible, and that generally is around the end of
17 phase 2 where we have a sufficient amount of data
18 to really understand where we might want to go.
19 And as a consequence, the results of those
20 conversations may look a lot different than the
21 original ones that were had for the PIP.

22 DR. CURT: Just to say, from the industry

1 point of view, the way the U.S. regulatory
2 officials handle this is eminently reasonable, and
3 it's sometimes difficult to put together a phase 3
4 plan for an agent as early as the European
5 requirements allow.

6 Malcolm, we've discussed this in the past, I
7 don't know if you might make a comment on that.

8 DR. SMITH: I would just second all that's
9 been said in terms of there's relatively little
10 known about an agent at the end of phase 1, and
11 it's very hard to make long-range plans at that
12 point. And so having a better sense of the agent
13 at the timing described is something that has made
14 sense to us. And in terms of thinking that you can
15 plan for phase 3 studies years in advance in the
16 pediatric setting, it's just not a reasonable thing
17 to do. It's hard to know what opportunities will
18 be available at that time, what commitments might
19 have been made to other agents in the interim, and
20 so I think that's an additional point that's really
21 important.

22 DR. PAZDUR: We will be asking members of

1 the EMA to come to either the next or subsequent
2 meetings to have a discussion because we have heard
3 obviously from many people concerns of
4 discrepancies between the U.S. approach and the
5 European approaches to pediatric disease. And,
6 obviously, we want to have a unified program here.
7 And we'll be talking about this perhaps even
8 tomorrow, but we would ask somebody, a
9 representative from the E.U. pediatric development
10 in oncology, particularly, to come to the next
11 meeting or a subsequent meeting, if that's not
12 possible for them.

13 DR. TASSINARI: And if I may add, this
14 awareness extends to the fact that both our agency
15 and the EMA have regular exchanges both at the
16 level of the oncology programs encompassing both
17 adult and children but also in the pediatric realm.
18 So we are making every efforts to understand the
19 limits of our own regulations to try and coordinate
20 as best we can, and particularly for populations
21 like these.

22 DR. BALIS: Dr. Reaman.

1 DR. REAMAN: I was just going to follow up
2 that there is regular communication between both
3 the FDA and the EMA as well as Health Canada. I
4 think there is an expanding appreciation on the
5 part of the EMA that we do need to work together in
6 coordination. As mentioned, not only do we not
7 have full understanding of the activity of an agent
8 at the end of phase 1 studies, but also there's
9 little appreciation as to how studies and where
10 studies are going to be performed.

11 So requiring the development of a phase 3
12 study to be performed only in Europe is really not
13 practical, not possible, not feasible. So there
14 really does need to be -- and there have been, I
15 think, evidence. So there has been evidence of
16 communication in advance of those decisions,
17 recognizing that this is really a global effort.

18 DR. CURT: Yes, that's good to hear because
19 it is a burden for the sponsor so early to do that,
20 so I'm glad you're talking about it.

21 DR. BALIS: Dr. Freedman.

22 DR. FREEDMAN: In the development of

1 pediatric plans for oncology products, does the
2 division have any view or feeling, or based on the
3 experience on the usefulness of the inclusion of
4 pediatric patients into phase 1 or phase 2 studies,
5 how useful has it been in contributing information
6 to the eventual usage of those drugs?

7 DR. REAMAN: Most of the information that we
8 have available to us that actually provides
9 information for the label has come from phase 1 and
10 phase 2 studies, so it's really a determination of
11 dose, maximally tolerated dose or recommended dose
12 for use, as well as toxicity profiles and specific
13 toxicities that are seen in the pediatric
14 population.

15 So most of the information has really come
16 from early phase rather than phase 3 studies, as
17 Dr. Tassinari mentioned. We don't generally
18 require phase 3 studies, or we don't generally have
19 data from phase 3 studies to make these decisions.

20 DR. FREEDMAN: I was more interested in the
21 inclusion of pediatric patients in adults --

22 DR. REAMAN: Oh, in adult phase. That's not

1 something that we've generally done, although there
2 have been discussions over time towards the later
3 portion of adult phase 1 studies, perhaps adding
4 pediatric patients of a specific age group, but
5 it's not something that has been really established
6 and practiced with any uniformity.

7 DR. FREEDMAN: Has it been useful?

8 DR. REAMAN: I'm not sure that we have any
9 evidence that it's been done, quite honestly, in
10 the past.

11 DR. BALIS: Thank you.

12 We can now proceed to topic 1, which is
13 discussion of sodium thiosulfate from Adherex
14 Technologies.

15 Caleb, do you want to read the conflict of
16 interest statement?

17 **Topic 1: Sodium Thiosulfate - Adherex Technologies**

18 **Conflict of Interest Statement**

19 DR. BRIGGS: The Food and Drug
20 Administration, FDA, is convening today's meeting
21 of the Pediatric Oncology Subcommittee of Oncologic
22 Drugs Advisory Committee under the authority of the

1 Federal Advisory Committee Act, FACA, of 1972.
2 With the exception of the industry representative,
3 all members and temporary members of the
4 subcommittee are special government employees,
5 SGEs, or regular federal employees from other
6 agencies and are subject to federal conflict of
7 interest laws and regulations.

8 The following information on the status of
9 this subcommittee's compliance with the federal
10 ethics and conflict of interest laws, covered by
11 but not limited to those found at 18 U.S.C.

12 Section 208 and Section 712 of the Federal Food,
13 Drug and Cosmetic Act, FD&C Act, is being provided
14 to participants in today's meeting and to the
15 public.

16 FDA has determined that members and
17 temporary members of this subcommittee are in
18 compliance with federal ethics and conflict of
19 interest laws. Under 18 U.S.C. Section 208,
20 Congress has authorized FDA to grant waivers to
21 special government employees and regular federal
22 employees who have potential financial conflicts

1 when it is determined that the agency's need for a
2 particular individual's services outweighs his or
3 her potential financial conflict of interest.

4 Under Section 712 of the FD&C Act, Congress
5 has authorized FDA to grant waivers to special
6 government employees and regular federal employees
7 with potential financial conflicts when necessary
8 to afford the subcommittee essential expertise.

9 Related to the discussion of today's
10 meeting, members and temporary members of this
11 committee have been screened for potential
12 financial conflicts of interests of their own as
13 well as those imputed to them, including those of
14 their spouses or minor children, and, for purposes
15 of 18 U.S.C. Section 208, their employers. These
16 interests may include investments, consulting,
17 expert witness testimony, contracts, grants,
18 CRADAs, teaching, speaking, writing, patents and
19 royalties and primary employment.

20 Today's agenda involves discussion related
21 to pediatric development plans for four products
22 that were either recently approved by FDA, are in

1 late-stage development for an adult oncology
2 indication, or in late-stage development in
3 pediatric patients with cancer. The subcommittee
4 will consider and discuss issues relating to the
5 development of each product for pediatric use and
6 provide guidance to facilitate the formulation of
7 written requests for pediatric studies, if
8 appropriate.

9 The product under consideration for this
10 session is sodium thiosulfate injection, sponsored
11 by Adherex Technologies. This is a particular
12 matters meeting during which specific matters
13 relating to sodium thiosulfate injection will be
14 discussed. The subcommittee will not be voting.

15 Based on the agenda and all financial
16 interests reported by the subcommittee members and
17 temporary members, no conflict of interest waivers
18 have been issued in connection with this session.
19 Related to the discussions of this session, Dr. Leo
20 Mascarenhas and Dr. Carola Arndt are recused from
21 participating in the discussions.

22 To ensure transparency, we encourage all

1 standing committee members and temporary members to
2 disclose any public statements that they may have
3 made concerning the product at issue. With respect
4 to FDA's invited acting industry representative, we
5 would like to disclose that Dr. Gregory Curt is
6 participating in this meeting as a nonvoting
7 industry representative acting on behalf of
8 regulated industry. Dr. Curt's role at this
9 meeting is to represent industry in general and not
10 any particular company. Dr. Curt is employed by
11 AstraZeneca.

12 We would like to remind members and
13 temporary members that if the discussions involve
14 any products or firms not already on the agenda for
15 which an FDA participant has a personal or imputed
16 financial interest, the participants need to
17 exclude themselves from such involvement, and their
18 exclusion will be noted for the record. FDA
19 encourages all other participants to advise the
20 subcommittee of any financial relationships that
21 they may have with the firm at issue. Thank you.

22 DR. BALIS: Thank you.

1 Drs. Arndt and Mascarenhas have left the
2 table, and before we move on to the presentation,
3 I'd like to have the panel members who joined us
4 after the initial introductions to introduce
5 themselves.

6 Nita, can we start with you, please?

7 DR. SEIBEL: Sure. Nita Seibel from the
8 clinical investigations branch of CTAP, pediatric
9 oncologist.

10 DR. SHURIN: Susan Shurin, the acting
11 director of the National Heart, Lung and Blood
12 Institute at NIH.

13 DR. SEKERES: Mikkael Sekeres, medical
14 oncologist, Cleveland Clinic.

15 DR. NEVILLE: Kathleen Neville, pediatric
16 oncologist and clinical pharmacologist, Children's
17 Mercy in Kansas City.

18 MR. LUSTIG: Craig Lustig, patient advocate,
19 18-year brain tumor survivor and independent
20 consultant.

21 **Introduction of New Participants**

22 DR. BALIS: Both the Food and Drug

1 Administration and the public believe in a
2 transparent process for information gathering and
3 decision-making. To ensure such transparency at
4 the advisory committee meeting, the FDA believes
5 that it's important to understand the context of an
6 individual's presentation. For this reason, FDA
7 encourages all participants, including the
8 sponsor's non-employee presenters, to advise the
9 committee of any financial relationships that they
10 may have with the firm at issue, such as consulting
11 fees, travel expenses, honoraria and interest in
12 the sponsor, including equity interest, and for
13 those based upon the outcome of the meeting.

14 Likewise, the FDA encourages you at the
15 beginning of your presentation to advise the
16 committee if you do not have any financial
17 relationships. If you choose not to address this
18 issue of financial relationships at the beginning
19 of your presentation, it will not preclude you from
20 speaking.

21 So we can now proceed with the sponsor's
22 presentation, and can you please introduce yourself

1 before you present.

2 **Industry Presentation - Franck Rousseau**

3 DR. ROUSSEAU: Good morning, my name is
4 Franck Rousseau. I represent medical affairs from
5 Adherex Technologies. I am a consultant for
6 Adherex. I don't hold any stock in Adherex.

7 First, I would like to thank the FDA for
8 inviting us to present to this advisory committee
9 and get your guidance on the STS program, which is
10 developed for pediatric use only. I will give a
11 brief introduction. It will be followed by Kristin
12 Knight, who is an expert audiologist who will
13 discuss pediatric hearing damage. Dr. Ed Neuwelt
14 will then go onto the preclinical and early
15 clinical data that supported the actual clinical
16 development of the drug. David Freyer will
17 describe for you briefly the overview of the two
18 phase 3 clinical trials ongoing in the world.
19 Dr. James Talcott will then review for you a big
20 part of our thinking since we met with the division
21 on how to assess otoprotection in adult and use
22 adult studies to do non-inferiority studies for

1 children. And I will come back to show you a slide
2 that is our proposal as a way forward.

3 In addition to the presenters, there are a
4 number of people that are collaborators from
5 academia, and in particular we have Lu Chen and
6 Mark Krailo, who both are statisticians associated
7 with the Children's Oncology Group, if there are
8 any specific questions regarding the study design,
9 et cetera.

10 So STS is a drug that has a regulatory
11 history. Orphan drug designation was given in
12 March 2004. The sole indication being developed is
13 a prevention of platinum-induced ototoxicity in
14 pediatric patients. So there is no adult drug
15 development program for this drug.

16 We had in March of this year a development
17 meeting with the oncology division, and among
18 several points of feedback, one that was a
19 particular challenge for us was the guidance to
20 demonstrate that STS do not reduce efficacy of
21 cisplatin; in other words, that the otoprotection
22 was not associated with the tumor protection.

1 The two phase 3 studies, the COG in the U.S.
2 and the SIOPEL, which is an international study,
3 have enrolled so far 156 children since October
4 2007. So I'll come back to that as my last slide,
5 but one of the big points in thinking and
6 discussion has been the guidance from the oncology
7 division to perform non-inferiority study in adults
8 for tumor protection in order to generate safety
9 data that would then allow a smaller study to just
10 demonstrate efficacy in children.

11 There are a number of issues with conducting
12 such studies, and Dr. James Talcott will present
13 our thinking. And that's why we are proposing to
14 this committee a way forward that is slightly
15 different than the non-inferiority study in adults.
16 We are thinking that we would submit an NDA with
17 the COG study as a single phase 3 trial, assuming,
18 obviously, that the efficacy data would be
19 supportive. And that would constitute an
20 accelerated approval mechanism. It would
21 supplement in time the filing with the data from
22 the SIOPEL 6 as confirmation as well as a launch of

1 postmarketing cohort safety study to address
2 specifically the problem of -- the issue of tumor
3 protection in the pediatric population.

4 I will now leave the podium to Kristin
5 Knight, who will describe for you pediatric hearing
6 damage.

7 **Industry Presentation - Kristin Knight**

8 MS. KNIGHT: Good morning. My name is
9 Kristin Knight, and I'm a pediatric audiologist at
10 Doernbecher Children's Hospital in Portland,
11 Oregon, And I don't have any financial interests in
12 Adherex. I'm here to discuss the problem of
13 cisplatin-induced ototoxicity in children.

14 These are hearing results from a 4-year-old
15 with neuroblastoma before and after platinum
16 therapy. At the end of treatment, he acquired
17 moderately severe high frequency hearing loss and
18 along with that, the ability to hear the high
19 frequency sounds of speech that are critical for
20 the recognition of spoken language. Children
21 require more audibility for high frequency sounds,
22 those above 2,000 hertz, because their language and

1 processing abilities are not yet mature.

2 Please listen carefully. You're about to be
3 given a spelling test, and the words would sound as
4 they would if you had high frequency hearing loss.

5 [Audio played.]

6 MS. KNIGHT: And the answers to those words
7 are tree, map and desk, and if you missed some of
8 those words, the reason is due to the loss of high
9 frequency audibility and clarity for the sounds T,
10 TH, S and K.

11 Hearing loss from platinum therapy in
12 childhood is common. In a study of children
13 treated with platinum with various ages and
14 diagnoses, 61 percent acquired hearing loss in the
15 speech range; 41 percent of those required hearing
16 aids. And although hearing aids are very helpful
17 and necessary, they do not restore normal hearing.
18 Twenty-two percent of these children required dose
19 reductions or omissions of cisplatin because of
20 hearing loss.

21 The youngest children are at the greatest
22 risk. They acquire hearing loss more often and

1 experience more severe hearing loss at lower
2 cisplatin doses. Children under five years of age
3 at the time of treatment are at 21 times the risk
4 for acquiring moderate hearing loss compared to
5 adolescents.

6 Hearing damage in a developing child
7 negatively impacts several domains. The loss of
8 high frequency speech sounds impacts speech and
9 language development in young children and
10 literacy. High frequency hearing loss causes
11 disproportionate difficulty listening or
12 understanding speech and noise or across a room,
13 and both of those compound the hearing loss for a
14 child in a classroom setting. Even in older
15 children and adolescents, acquired hearing loss
16 negatively affects educational achievement, social,
17 emotional development, and quality of life.

18 In a study of school-age children with
19 minimal hearing loss, which was defined as slight
20 to mild or high frequency hearing loss, 37 percent
21 of those with minimal hearing loss repeated a grade
22 in school compared to a district normative rate of

1 3 percent. And finally, in a study of
2 neuroblastoma survivors, survivors with hearing
3 loss had twice the rate of reported problems with
4 reading, math, attention, and need for special
5 education services. And of the children
6 themselves, those with hearing loss reported poorer
7 quality of life and more difficulties at school
8 compared to survivors without hearing loss.

9 So I'd like to introduce Dr. Ed Neuwelt, who
10 will talk about the preclinical and clinical
11 studies of sodium thiosulfate.

12 **Industry Presentation - Edward Neuwelt**

13 DR. NEUWELT: Thank you. My name is Ed
14 Neuwelt. I'm a board certified neurosurgeon and
15 fellowship-trained neuro-oncologist at the Oregon
16 Health Sciences University. I have no financial
17 interest in this product or any product. However,
18 my university does have a license agreement with
19 Adherex for sodium thiosulfate. So I would like to
20 discuss the preclinical and clinical studies
21 dealing with primarily brain tumors that led to the
22 phase 3 COG trial.

1 The agent was brought to my attention when
2 we unexpectedly developed a significant amount of
3 high frequency hearing loss in patients receiving
4 carboplatin for brain tumors with intra-arterial
5 administration after blood-brain barrier
6 disruption. And one of the members of the NIH, who
7 was a family member, pointed out the sodium
8 thiosulfate may ameliorate certain aspects of drug-
9 induced ototoxicity.

10 So this is the drug sodium thiosulfate. Its
11 protective action can result in covalent thiol
12 binding of the electrophilic platinum, scavenging
13 of reactive oxygen species, and may, in particular,
14 be concentrated in the cochlea, perilymph and in
15 the kidney.

16 This graph in the guinea pig -- and guinea
17 pigs are used in hearing because they're much more
18 sensitive to ototoxicity than rats or mice -- were
19 done with or without sodium thiosulfate using very
20 sensitive electrophysiologic monitoring as measured
21 by sound intensity at different hertz levels on the
22 abscissa and sound intensity changes on the

1 ordinate.

2 The lower two lines show dramatic
3 otoprotection compared to the upper two lines when
4 cisplatin is given with or without sodium
5 thiosulfate. So sodium thiosulfate was
6 dramatically otoprotective in this guinea pig
7 model, which is one of the standards in the field.

8 In this series of three graphs, STS protects
9 against cisplatin ototoxicity in the rat, and we
10 are looking here at four hours and eight hours.
11 Because the cisplatin is rapidly cleared from the
12 circulation and the sodium thiosulfate has a plasma
13 half-life of about 9 minutes, and it requires a
14 400 to 1 ratio, molar ratio, to inactivate the
15 platinum, it was found that delaying the sodium
16 thiosulfate actually improves the ability to
17 protect against hearing and avoids the problem
18 of -- and achieves otoprotection without tumor
19 protection, as I will try to show you. Twelve
20 hours doesn't work.

21 Now, one of the standard cell models, in
22 vitro, in pediatric tumors -- and since I'm a

1 neuro-oncologist, we looked at the issue of the
2 DAOY, the DAOY medulloblastoma cell line. And as
3 you can see, at six hours after cisplatin
4 admission, sodium thiosulfate if then added has no
5 tumor protective effect that we could detect at
6 all.

7 Then we proceeded to in vivo studies in
8 collaboration with Pat Reynolds, and this is a
9 paper by Harned showing that if you give
10 simultaneous sodium thiosulfate in a neuroblastoma,
11 a non-CNS model, it's as if you didn't give the
12 cisplatin at all. But if you give it at six hours,
13 it's as if you gave the cisplatin alone without
14 sodium thiosulfate. There was no tumor protection
15 if the cisplatin and the sodium thiosulfate are
16 separated in time by six hours.

17 So, therefore, based upon these initial
18 clinical studies, both with carboplatin and with
19 cisplatin with very dramatic impact of sodium
20 thiosulfate reducing with carboplatin the incidence
21 of hearing aids from 52 percent to zero, COG became
22 interested in this, the possibility not only for

1 carboplatin but for cisplatin, which is a topic
2 that I will now turn over to Dr. David Freyer.

3 **Industry Presentation - David Freyer**

4 DR. FREYER: Good morning. My name is David
5 Freyer. I'm a pediatric oncologist at Children's
6 Hospital Los Angeles and the chair of the study
7 ACCL0431. I have no conflicts of interest or
8 financial interest in Adherex.

9 The primary aim of this study is to evaluate
10 the efficacy of sodium thiosulfate for the
11 prevention of hearing loss in children receiving
12 cisplatin chemotherapy. All of the power
13 calculations were made around that primary aim.
14 We're also pursuing several secondary aims and a
15 biology aim.

16 The key eligibility criteria for this study
17 are being diagnosed with any malignancy that is
18 typically treated with cisplatin, most commonly,
19 neuroblastoma, hepatoblastoma, medulloblastoma,
20 osteosarcoma, and germ cell tumor. All patients
21 must have a planned cumulative cisplatin dose of at
22 least 200 milligrams per meter squared to be

1 certain that they will be in the ototoxic range,
2 and the patients must demonstrate normal audiometry
3 at baseline.

4 The randomization is between receiving
5 sodium thiosulfate versus none, which is the
6 control arm, and the STS is administered
7 intravenously over 15 minutes, six hours after each
8 cisplatin dose.

9 This is the study schema. Enrolled patients
10 are randomized to either receive sodium thiosulfate
11 or not. On the control arm, all patients receive
12 the cisplatin according to their treatment protocol
13 that's appropriate for their specific cancer
14 diagnosis. Audiometry is performed at baseline and
15 within eight days prior to each cisplatin course,
16 and audiometry is performed at four weeks following
17 the completion of all cisplatin therapy and then at
18 one late time point 12 months later. The primary
19 endpoint for this study is the hearing status at
20 four weeks post-completion of all cisplatin
21 therapy.

22 This table demonstrates the current

1 enrollment by diagnosis along the left and by arm
2 of the study. As you can see, within the tumor
3 diagnoses categories, the randomization is fairly
4 balanced. Currently, we have 107 eligible patients
5 who have been randomized on this trial.

6 Within the past six months, two planned
7 interim analyses have been completed. The first
8 was a screen of early tumor responses. This was an
9 evaluation of best tumor response as reported by
10 the institution for each patient that were
11 summarized by tumor type and by study regimen. The
12 second planned interim analysis was a futility
13 analysis on the otoprotection question. This
14 involved central review of audiometry results by
15 the study regimen. The results of both of these
16 interim analyses were submitted to the Data Safety
17 and Monitoring Committee of Children's Oncology
18 Group, who met on August 10th, 2011 and made the
19 formal recommendation to continue the study as
20 planned.

21 As far as our plans for the study, with our
22 current enrollment of 107 eligible patients of a

1 planned 135, and with our current enrollment of
2 approximately one patient or more per week, we
3 anticipate completion of our accrual by
4 approximately mid-2012. And with completion of
5 their therapy and submission of data from the
6 institutions, we would anticipate that data should
7 be available for analysis by approximately
8 mid-2013.

9 SIOPEL 6 is an additional study that is
10 currently under way concurrently. This is a
11 multicenter, open label, phase 3 trial of the
12 efficacy of sodium thiosulfate. This is being led
13 by Dr. Peppy Brock in the United Kingdom, and this
14 study will be providing additional supportive data
15 for Adherex in addition to that coming from our COG
16 study.

17 The SIOPEL 6 study is focusing only on
18 hepatoblastoma patients, and the only
19 chemotherapeutic agent that they receive in that is
20 cisplatin. Their randomization is between sodium
21 thiosulfate and no sodium thiosulfate. This is
22 being conducted in the international setting

1 currently in nine different countries. Their
2 current enrollment is 46 of the planned 102.

3 So with that, I'll turn the podium over to
4 Dr. James Talcott, who will discuss some of the
5 challenges of doing otoprotection studies in non-
6 inferiority trials in adults.

7 **Industry Presentation - James Talcott**

8 DR. TALCOTT: Thank you. I am a medical
9 oncologist and the director of the Center for
10 Healthcare Quality and Outcomes Research at
11 Continuum Cancer Centers of New York, and I have no
12 conflicts.

13 In trying to consider the possibility of a
14 trial in adults, I felt it was important to address
15 the important clinical differences between adult
16 and pediatric cancers. In adult cancers, there are
17 lower response rates to platinum-containing
18 regimens in most cases, certainly for the most
19 frequent agents, primarily non-small cell lung
20 cancer, but other advanced epithelial malignancies.
21 Further, cisplatin is not a single agent but is
22 part of a complex regimen. It tends to reduce and

1 obscure the specific contribution of platinum in
2 combination chemotherapy regimens or the
3 chemoradiotherapy regimen that's common for the use
4 of head and neck cancer.

5 As a result of these two factors, the
6 cisplatin tumor response signal is harder to detect
7 in adults compared to children, where the response
8 rates are significantly greater. That leads to the
9 practical dilemmas of trying to carry out such a
10 disease. The low response rates in multiple agent
11 treatments therefore require very large studies
12 under reasonable assumptions for the impact of
13 cisplatin, given the efficacy of the regimen.

14 High response rates are necessary to
15 establish clinically meaningful non-inferiority
16 differences. Those occur only in uncommon tumors
17 compared to the bulk of adult oncology patients,
18 such as testes or placental choriocarcinoma, which
19 leads to the ethical dilemma faced by any IRB
20 attempting to try and approve such a study.

21 The high response rates required to detect
22 an adequate signal with a reasonably-sized study

1 increases the difficulty of the trials because it
2 raises the clinical stakes higher for curative
3 treatment, such as testes and head and neck cancer.
4 But the tradeoff in potential otoprotection that
5 would be offered to a patient enrolling in the
6 study is a much less serious consequence for
7 adults, even young adults, than for children.

8 It's difficult to conceive a study in which
9 one could obtain adequate informed consents for
10 patients to enter a study that risks reduced
11 survival in exchange for possibly reduced side
12 effects. Therefore, there's the paradox in adult
13 disease. The greater the assumed chemoprotective
14 risk, the greater the hurdle to approving a non-
15 inferiority trial. The lesser the assumed
16 chemoprotective risk, the weaker the rationale for
17 a non-inferiority trial. Now, these are not unique
18 to this study. It's simply that the features come
19 into high relief in a situation in which there is
20 an unmet need for chemoprotection in pediatric
21 children, the consequences of which are devastating
22 socially.

1 So on that point, I leave you to the summary
2 of the path forward we suggest.

3 DR. ROUSSEAU: So to go back, I'd like the
4 committee to keep this slide in mind to discuss our
5 proposal, which is, obviously, to not propose a
6 non-inferiority study in adults for the reasons
7 that were just presented by James Talcott. We feel
8 it's both impractical and probably marginally
9 irrelevant to the pediatric population.

10 Instead, we think that the best way forward
11 is to actually do a study in the pediatric
12 population. However, we've all seen the number of
13 patients that have been able to be accrued in
14 randomized-controlled trials since 2007 across the
15 United States and Europe and other countries, about
16 150 children. So we're not going to be able to
17 enroll 700 children in a reasonable time frame in
18 randomized-controlled trials.

19 So the mechanism that we think is both the
20 most practical is a postmarketing cohort study
21 where the case in the cohort would be traded
22 statistically to derive meaningful comparison of

1 exposure and non-exposure to STS.

2 With that, that concludes the presentation.

3 **Clarifying Questions from Subcommittee**

4 DR. BALIS: Thank you.

5 The floor is open for questions from the
6 panel. I might start while people are thinking.

7 You've shown, I think, both in the
8 documentation you provided and your presentations,
9 that the only selectivity of this rescue relates to
10 the timing of it relative to the dose of cisplatin.
11 And the study that you've conducted looks at to
12 giving it specifically at six hours after.

13 If you look through Children's Oncology
14 Group studies as a whole at cisplatin
15 administration, it varies from giving it over one
16 hour, one and a half hours, four hours, and six
17 hours as an infusion, and anywhere from one to four
18 days in a daily -- as a single dose over four days.

19 If you just give the thiosulfate as a rescue
20 agent six hours after the end of that infusion, the
21 exposure that occurs to cisplatin before that is
22 going to vary quite markedly based on the duration

1 of the infusion that the drug was given over.

2 How do you account for that with the way
3 that this drug works in terms of the critical
4 timing issue or the narrow window that you've got
5 to rescue?

6 DR. ROUSSEAU: I will ask Dr. Freyer to take
7 the question.

8 DR. FREYER: I may call on Dr. Neuwelt as
9 well to help with the answer to this question.

10 There is heterogeneity among the cisplatin
11 regimens, as you pointed out. The sodium
12 thiosulfate is given uniformly with respect to each
13 cisplatin dose. So while there are single-day
14 regimens and four-day regimens among the patients
15 who are being treated, for each dose of cisplatin,
16 it's administered in a uniform fashion over
17 15 minutes, beginning six hours after the
18 completion of the cisplatin.

19 We reasoned that the half-life of unbound
20 cisplatin is very short in the circulation, even
21 with longer infusions. So the six-hour time frame
22 should allow adequate drop of the concentration of

1 cisplatin in the serum to allow for the molar ratio
2 that's necessary to achieve the otoprotection.

3 Dr. Neuwelt, do you want to add anything to
4 that?

5 DR. BALIS: I think the question more
6 related to the -- not to the shortness of the
7 window but the length, because you showed in your
8 preclinical studies that 12 hours doesn't work.
9 And with a six-hour infusion and a six-hour delay
10 for giving the rescue, you're at 12 hours.

11 DR. FREYER: We were timing it from the
12 completion of the infusion as opposed to the
13 beginning of the cisplatin infusion.

14 DR. BALIS: Right. But I'm talking about
15 the cisplatin exposure starting with the beginning
16 of a six-hour infusion until six hours after that
17 infusion is a 12-hour exposure to the drug, is it
18 not? Before you give the rescue agent.

19 I guess I'm not making myself clear.

20 If you start your infusion at time zero and
21 you run the infusion for six hours, and then you
22 wait six hours to give the rescue, that's a total

1 of 12 hours of exposure to the drug before giving
2 the rescue agent. Based on the data that
3 Dr. Neuwelt showed, that 12-hour exposure, even
4 though it was 12 hours after a bolus dose, I think,
5 of cisplatin, had no effect on rescuing hearing.
6 And if you look at the protocols overall, the
7 predominant way it's given is a six-hour infusion.

8 DR. FREYER: Ed, do you want to comment at
9 all?

10 DR. NEUWELT: We were fully aware of this
11 range of different -- in the five major tumor
12 categories where the cisplatin is either given over
13 an hour or up to six hours, as you point out. We
14 picked the six-hour point because we felt there was
15 no evidence in our preclinical data or other data
16 that we were able to ascertain that there would be
17 any significant tumor protection at that time and
18 felt that the possible inclusion of patients
19 through getting the six-hour would still get a
20 significant otoprotection.

21 But your point is correct that six hours may
22 be too long for a six-hour infusion, but it's not

1 12 hours of drug exposure. It's six hours, and
2 then the STS is given, irregardless of however long
3 the cisplatin infusion is. And we feel this is
4 sort of analogous to leucovorin rescue for
5 methotrexate. You can vary the timing of the
6 rescue with very nice clinical impact and decreased
7 toxicity.

8 DR. TALCOTT: This is just a small point,
9 but the entire infusion does not occur -- in a six-
10 hour infusion, doesn't occur at the beginning. I'm
11 sort of breaking it down. For example, if you have
12 a six-hour infusion, five out of six of those
13 hours, presumably five-sixths of the dose, is being
14 delivered sometime less than six hours so that when
15 you are getting an STS infusion that takes place
16 over a relatively short period of time, yes, some
17 of it would approach the 12-hour maximum, but the
18 great majority would receive treatment in a period
19 less than that.

20 DR. BALIS: Thank you.

21 Dr. Sekeres.

22 DR. SEKERES: Thank you, Dr. Balis.

1 Part of what we're being asked to give an
2 opinion about is what trial would be a good way
3 forward towards some level of approval, and the
4 company has suggested the Children's Oncology Group
5 study might be a good one to support accelerated
6 approval. But I feel as if I don't know a lot of
7 details about the study to give an informed
8 opinion.

9 So, for example, when you're looking at
10 hearing loss in patients, you're stratifying your
11 analyses based on previous exposure to platinum
12 agents but not on the type of cancer that children
13 have. So how are you looking at these data to see
14 whether or not your drug actually could lead to
15 lower response rates when you're not comparing like
16 to like?

17 Another question I would have also is why
18 wasn't this a placebo-controlled study?

19 DR. ROUSSEAU: I will ask Mark Krailo, the
20 head of statistics to take the question.

21 Lu?

22 DR. CHEN: In terms of the hearing efficacy

1 comparison, the study is comparing the aggregate
2 population on the study. The study is not powered
3 to detect the separate treatment effect within each
4 subgroup. The study -- randomization is not
5 stratified by diagnosis, but as you can see from
6 the current enrollment table, so far the enrollment
7 on each arm is pretty balanced. And we will
8 perform some ad hoc analysis at the end of the day
9 to look for the effects or trends in the effect of
10 STS within different disease subpopulations.

11 The randomization is stratified by prior
12 radiation exposure and the duration of platinum age
13 by certain categories to control for the effect of
14 STS, vitals, risk factors.

15 DR. SEKERES: So I get that. I guess I buy
16 the primary endpoint of looking at ototoxicity in
17 this population. I'm still not sure why it wasn't
18 placebo controlled, but we can get to that in a
19 second.

20 What I'm concerned about and what's been
21 raised as an issue for us to consider is tumor
22 response and whether there will be enough data

1 generated from the Children's Oncology Group study
2 to assess whether this could actually have a
3 deleterious effect on response.

4 So how are you going to do that when your
5 study isn't stratified based on previous cancers?
6 Are you going to have enough power even to
7 determine whether or not there may be a deleterious
8 effect on response, on the arm that receives the
9 STS versus the arm that doesn't?

10 DR. CHEN: So the primary study question and
11 the way the study was structured is based on the
12 efficacy comparison on hearing loss. The study was
13 not designed nor powered to formally compare the
14 survival outcomes in terms of EFS and OS between
15 the groups -- between the two randomized arms.

16 So in the protocol, we discussed the
17 comparison in terms of survival outcome between the
18 two arms. The limitation in terms of power and the
19 exact analysis or I guess the exact design can
20 compare the two because we have such a
21 heterogeneous population. And, also, the
22 proportion of patients coming into the study from

1 each of the disease diagnosis, it's hard to predict
2 from the very beginning in terms of outcomes for
3 the subset by diagnosis. It also varies by the
4 treatment protocol that they were on.

5 So we actually talk about in the protocol an
6 approximate aggregated outcome as an educated
7 guess, and then we look at the power we have in
8 terms of comparing the survival endpoints, the EFS,
9 between the two arms. But since the primary study
10 question and then the study sample size is dictated
11 by the efficacy comparison, the power we have on
12 EFS/OS comparison is rather limited.

13 So in this protocol document, we provide an
14 example of the power we have between the two arms.
15 At the end of the day, if we have a roughly
16 59 percent EFS in the control arm, we will just
17 have about 80 percent power -- or slightly over
18 80 percent power to detect 25 percent difference in
19 EFS for the STS arm.

20 So, as you can see, we do not have adequate
21 power, but the study was not to detect the
22 difference in EFS and OS for the study using study

1 data alone. The study was not designed to detect
2 that EFS difference.

3 DR. SEKERES: Okay. So if you were on ODAC
4 and this study were presented to you, how would you
5 look at comparisons of response rates by disease,
6 given that the study isn't powered to examine that.
7 And I'm asking this not to be confrontational but
8 because this may come to us at some point, and I
9 completely understand these are rare diseases.
10 And, actually, I think this study design is really
11 clever for looking at your drug, but we're going to
12 be faced with the question about whether or not the
13 response rates are watered down by STS versus not.

14 So how would you approach it? Is it going
15 to be kind of eyeballing it? Is it going to be
16 looking at certain subgroups where you do have
17 adequate power to look at differences in response
18 rate?

19 DR. CHEN: You mean differences in response.
20 So first is the comparison I was talking about in
21 terms of the two are aggregate outcomes. So, yes,
22 we can do some stratifying analysis looking at a

1 disease specific subset or even some different
2 subgroup stain analysis.

3 But, as I said, I don't think the sample
4 size provide adequate power to definitely provide
5 an answer, even for the overall aggregate
6 comparison. But the data, once it comes to light,
7 will provide either some indication of whether or
8 not there is a dramatic difference or whether or
9 not there is any indication of a treatment
10 effect -- sorry; tumor protection effect.

11 But they only go as far as the data itself.
12 It's a limited study by its own, and you can make,
13 I guess, educated guess from those data. But you
14 probably would need other study data to support,
15 for example, the SIOPEL data or whether or not the
16 committee would consider a postmarketing trial to
17 be closely monitored during that interim to look
18 for any indication of a treatment tumor protection
19 effect.

20 DR. SEKERES: I'm sorry. I don't want to
21 take too much time. I just had that one other
22 question about just historically why wasn't this a

1 placebo-controlled study.

2 DR. CHEN: I think maybe David can answer
3 this question better.

4 DR. FREYER: We originally designed the
5 study -- or originally conceived the study actually
6 to be placebo controlled. But as we discussed the
7 feasibility of it within the Children's Oncology
8 Group, it would dramatically increase the
9 complexity and the cost of the study. And so we
10 decided to go with a non-placebo-controlled
11 designed.

12 DR. SEKERES: Thank you.

13 DR. BALIS: Dr. Smith.

14 DR. SMITH: So two questions, one related to
15 the COG study, and wasn't it the intent that this
16 was a proof of principle study for ototoxicity with
17 the plan that there would be subsequent definitive
18 randomized studies to look at the effect of STS on
19 EFS. And the second question relates to what the
20 intent of the -- what would be learned from the
21 postmarketing cohort safety surveillance study and
22 what the objective of that study would be.

1 DR. ROUSSEAU: I will answer the second
2 question, and I will let Dr. Freyer address the
3 first one.

4 The intent of the postmarketing surveillance
5 study is to both have a vehicle where you can
6 reasonably recruit a fairly significant number of
7 children in a reasonable time period and compare
8 exposure versus non-exposure by classical
9 epidemiological model of statistics. It's not as
10 strong as a randomized-controlled study, but I've
11 shown you the best effort of the SIOPEL and the COG
12 since 2007 is 156 children, where we feel that the
13 postmarketing study with the adequate collaboration
14 of the pediatric network could recruit probably
15 five to 800 children in three years.

16 So you do lose some inferential statistics
17 by not having a randomization, but, again,
18 tremendous power by having number. And since we're
19 talking about a fairly hard endpoint and homogenous
20 population, I think that we could have a meaningful
21 comparison of event-free survival in children
22 exposed or not exposed with the appropriate

1 statistical analysis.

2 DR. SMITH: So just a quick follow-up to
3 that while you're there, but it's nonrandomized.

4 DR. ROUSSEAU: Nonrandomized.

5 DR. SMITH: And so one could imagine that a
6 patient that I suspect may be at higher risk for
7 relapse, maybe that's not the patient I'm going to
8 give STS, whereas the patient who I think has a
9 better chance, I'm going to give STS for that.
10 There are all sorts of confounders that would
11 affect any estimate of EFS in that type of study.

12 DR. ROUSSEAU: You're correct, and that's
13 why the data collection and the study design would
14 have to be very careful in not just collecting the
15 children that enrolled but also the ones that do
16 not enroll, as well as the type of tumor and make
17 sure that there is not a systematic bias or a
18 channeling effect.

19 But the good side of pediatric oncology, at
20 least in the U.S., is that the vast majority of
21 patients are cared in a given network, and this
22 network, a very homogenous practice. So if we're

1 able to do analysis on an ongoing basis, we
2 probably would be able to detect a systematic
3 channeling bias in the conduct of the study.

4 DR. FREYER: Dr. Smith, could I ask you to
5 repeat your first question?

6 DR. SMITH: I guess, is it not the case that
7 this was intended to look at ototoxicity as a proof
8 of principle that the agent could indeed prevent
9 ototoxicity with a plan that there would be -- that
10 if it were able to do that, that there would be
11 subsequent definitive randomized studies to look at
12 the effect on EFS.

13 DR. FREYER: The discussions that we had
14 with the DCP when this was originally being
15 designed and submitted for approval was that it
16 indeed would be a primarily proof of principle
17 study, and it was acknowledged that we would not be
18 able to address with sufficient power the question
19 of tumor protection in this trial, that it would be
20 unfeasible to do that.

21 So, yes, the plan all along really was to
22 submit that question to a subsequent study. I

1 don't believe that we had settled on a specific
2 trial design at that point, but the question of
3 tumor protection, yes, did need to be addressed in
4 a larger subsequent study, provided this one showed
5 proof of principle, that it was efficacious for
6 preventing hearing loss.

7 DR. BALIS: Thank you.

8 Dr. Freedman.

9 DR. FREEDMAN: Thank you.

10 The sponsor had mentioned that the FDA had
11 suggested doing a non-inferiority study in adults.
12 And I was wondering, there does not seem to have
13 been much interest in using this drug in adults. I
14 know initially there were some studies on it, but
15 it doesn't seem to be of interest now. And I
16 wondered why this was. Is it because there are
17 alternative methods of dealing with the toxicity,
18 or is it because of the concern about a possible
19 tumor protective effect?

20 I think this is important if you get into
21 this issue of trying to do that type of study
22 because if a population is not going to get

1 benefit, either potential benefit from a drug, over
2 what is currently available, it is probably
3 unethical to do a study like this in that
4 population. And, of course, I agree that it would
5 be very difficult to consent subjects to that type
6 of study.

7 So if you could address my question.

8 DR. ROUSSEAU: You are absolutely right.
9 This is exactly the point Dr. Talcott was making.
10 The risk in adult is probably not different from
11 the risk in children, but the benefit is
12 significantly less. And that's why when Adherex
13 new management had to look at this program, it was
14 decided that the adult indication is probably not
15 worth it from a practical point of view, the
16 benefit doesn't outweigh the risk, where the
17 children's program, albeit, it's always difficult
18 to keep a program solely for a very small
19 indication, we felt that the benefit that the
20 children could derive from the drug would
21 potentially balance with the risk, if the risk is
22 not terribly bad.

1 And I think that so far, we can't rule that
2 it's bad, but we can rule out that it's terribly
3 bad. And that we think that with the mechanism
4 proposed, we can decrease this risk over time and
5 have an ongoing assessment that would reassure the
6 regulator, both here and elsewhere, that we're not
7 doing harm. But we will not be in a position to
8 have all the answers at the time of the submission.
9 That's very clear.

10 DR. BALIS: Thank you.

11 Dr. Shearer, then Dr. Curt, then we'll move
12 on to the open public hearing.

13 DR. SHEARER: Two comments, first of all, a
14 detail about the choice of platinum agent for STS
15 otoprotection. It's very important to understand
16 that this drug is geared toward protection from
17 cisplatin and not carboplatin. The auditory
18 physiology of both compounds are quite different.
19 When we look at the effects of carboplatin, they
20 are largely on the inner hair cell where as the
21 effects of cisplatin are largely on the outer hair
22 cell, which has been shown in a number of animal

1 models and postmortem studies to be affected after
2 cisplatin ototoxicity.

3 We have also looked in the auditory hearing
4 task force of Children's Oncology Group at clinical
5 studies on a 10-year period on a rolling cycle
6 every two years. Those are in the public domain.
7 Most studies show that carboplatin given at
8 nonmyeloablative doses, that is doses that are not
9 given for a bone marrow transplant, are not
10 ototoxic. So we have to be careful when we
11 interpret preclinical data that all platinum
12 compounds are not the same and that the real
13 culprit on the ear in children is cisplatin.

14 Secondly, I'd like to move forward and
15 address the question of Dr. Freedman about why
16 there's a difference in the need for studies in
17 children versus adults with cisplatin. And, again,
18 the answer is biphasic. First of all, a physiology
19 comment; and that is that when we look at the
20 developing ear, we know that cochlear efferents
21 coming down from the superior olivary complex to
22 the cochlea to the outer hair cell are not complete

1 at birth. Those cells continue to develop. So we
2 know that from a physiologic standpoint that the
3 immature ear is at tremendous risk.

4 Secondly, when we segue way into clinical
5 studies, we see that children under four years of
6 age are those who are most vulnerable to cisplatin
7 ototoxicity. So, again, I think when we look at
8 both carboplatin physiology in clinical studies and
9 when we look at cisplatin physiology in clinical
10 studies, we have a good understanding of why these
11 studies are important geared towards cisplatin in
12 young children.

13 DR. BALIS: Thank you, Dr. Shearer.

14 DR. ROUSSEAU: I will briefly answer to the
15 regulatory aspect of your question, and I will let
16 Dr. Neuwelt address the preclinical discussion.

17 The clinical trials are performed in
18 children receiving cisplatin, so the indication
19 that we would seek as a company would be prevention
20 of ototoxicity induced by cisplatin, not
21 carboplatin.

22 From a preclinical perspective, Dr. Neuwelt,

1 do you want to make a comment?

2 DR. NEUWELT: The issue of which hair cells
3 are affected depends on model, doses, and the
4 guinea pig is very different from the rat, is very
5 different to the mouse. But we did count the hair
6 cells after carboplatin, as you can see, on this
7 slide right here. And, as you can see, the
8 cochlear potential is on the left slide, and the
9 actual missing hair cells, which were virtually
10 all, in these carboplatin-treated guinea pigs,
11 outer hair cell loss. This was very carefully done

12 So what you say is true, depending on the
13 model, the chinchilla versus the guinea pig versus
14 the mouse versus the rat. But in these guinea pigs
15 with carboplatin getting doses that approached that
16 of myeloablative, it was the outer hair cells that
17 were lost, and we prevented that loss with delayed
18 sodium thiosulfate and the -- what was your other
19 point?

20 In the patients with carboplatin, because it
21 was given intra-arterially, particularly into the
22 vertebral artery, we approached the doses of

1 carboplatin, that the cochlea would see with
2 myeloablative doses of carboplatin. And by ASHA
3 criteria, which is the standard in America as
4 opposed to the Brock in Europe, we had an 89
5 percent incidence of ototoxicity by ASHA criteria,
6 which went down to I think, Kristin, 19 percent?
7 Nineteen percent with delayed sodium thiosulfate
8 administration. And we went, most impressively,
9 from a 50-some percent incidence of the need for
10 hearing aids in these brain tumor patients to
11 virtually zero.

12 We have not -- we have given maybe two
13 (thousand) or 3,000 does of sodium thiosulfate in
14 our brain tumors in the last 10 to 15 years, and we
15 haven't had, since the introduction of -- this is
16 industrial dose sodium thiosulfate, 16 to 20 grams
17 per meters squared. Lesser doses don't work. We
18 have not had a single patient that -- maybe
19 one -- that's required a hearing aid.

20 These results were so stark that in my
21 resubmission of my Javits award, which initially
22 funded this, and that's a seven-year award from the

1 NIH, we did -- one of the questions of the study
2 section was whether we should do a randomized
3 phase 3 trial. And I have the letter, and I'm
4 happy to provide it to the committee, that our IRB
5 very carefully assessed both the tremendous loss,
6 decrease in ototoxicity as evidenced by hearing
7 aids and by ASHA criteria. And they said that they
8 would not feel that there would be equipoise in our
9 population of brain tumor patients to justify a
10 phase 3 trial. So we have not been allowed, and
11 the study section accepted that letter as -- and
12 I'm happy to provide it, if you like.

13 DR. BALIS: Thank you.

14 DR. NEUWELT: Does that answer your
15 question?

16 DR. BALIS: Dr. Curt, do you have a short
17 question?

18 DR. CURT: Yes. I was just wondering if
19 there's anything known about the risk of
20 ototoxicity from platinum by exposure, either from
21 Cmax or from AUC, just to determine which children
22 would be at the highest risk of hearing loss?

1 DR. NEUWELT: The children, quite honestly,
2 that are the highest risk depends on their
3 genetics. About 80 percent of the children get
4 substantial hearing loss. Twenty percent -- and
5 the multiple genome models that were recently
6 published in Nature Genetics clearly indicate the
7 culprits. And I have a copy of a paper which I've
8 provided -- am I allowed to -- if it's not fully
9 published, we could at least give a table
10 where -- identifying those genes which account for
11 the 20 percent of the children who don't get
12 ototoxicity.

13 Interestingly, there's an occasional where
14 it's one ear and not the other, which is -- and
15 dramatic differences between the ears. So the
16 exact reason for that is not clear. But the
17 difference in ototoxicity is clearly a genetic
18 base, and we're hoping in future studies, as in
19 both of the COG study, which David is the head of,
20 and in the SIOPEL, which Peppy Brock is running,
21 we're sending all the tissues to Canada for this
22 polygenomic analysis of -- what's it called? Well,

1 genetic susceptibility. But the effects are
2 dramatic. You can identify, with a power of three
3 or four zeros, the at-risk population.

4 Does that answer the question?

5 **Open Public Hearing**

6 DR. BALIS: Thanks.

7 We have to move on to the open public
8 hearing. We'll have more time for discussion when
9 we get to the questions. Thanks.

10 I have to read this disclaimer again. I
11 apologize. But both the Food and Drug
12 Administration and the public believe in a
13 transparent process for information gathering and
14 decision-making. To ensure such transparency at
15 the open public hearing session of the advisory
16 committee meeting, FDA believes that it's important
17 to understand the context of an individual's
18 presentation.

19 For this reason, FDA encourages you, the
20 open public hearing speaker, at the beginning of
21 your written or oral statement to advise the
22 committee of any financial relationships that you

1 may have with the sponsor, its product, and, if
2 known, its direct competitors. For example, this
3 financial information may include the sponsor's
4 payment of your travel, lodging, or other expenses
5 in connection with your attendance at this meeting.

6 Likewise, the FDA encourages you at the
7 beginning of your statement to advise the committee
8 if you do not have any financial relationships. If
9 you choose not to address this issue of financial
10 relationships at the beginning of your statement,
11 it will not preclude you from speaking.

12 The FDA and this committee place great
13 importance in the open public hearing process. The
14 insights and comments provided can help the agency
15 and this committee in their consideration of the
16 issues before them. That said, in many instances
17 and for many topics, there will be a variety of
18 opinions.

19 One of our goals today is for this open
20 public hearing is to be conducted in a fair and
21 open way where every participant is listened to
22 carefully and treated with dignity, courtesy, and

1 respect. Therefore, please speak only when
2 recognized by the chair. Thank you for your
3 cooperation.

4 Can we have speaker number 1, please?

5 MR. HOFMEISTER: Hi. My name is Joshua
6 Hofmeister. I would like to thank you for this
7 opportunity to speak to you guys at this meeting
8 today. There's a little bit of information you
9 should know about me. I'm 14 years old, and I was
10 diagnosed with neuroblastoma cancer when I was one.
11 I had to take chemotherapy, tumor removal surgery,
12 and I had to get a bone marrow transplant. I
13 suffer from hearing loss, and I wear hearing aids.

14 Sure. I wish I didn't have hearing aids.
15 Everybody tries to be completely normal because
16 some people can be mean even if there is something
17 wrong with them. On plenty of occasions, I have
18 been picked on because of my hearing. Kids I don't
19 know come up to me and start talking to me. They
20 get quieter and quieter until I can't hear them,
21 and they just laugh at me and call me deaf boy.
22 All we do is try the best we can. I mean, if we

1 have to live with it, we might as well make the
2 best of it, which is what I aim to do and
3 accomplish here today.

4 I want to be a part of the solution so that
5 kids when they have to get chemotherapy for cancer,
6 they don't have to lose their hearing. My hearing
7 has affected me in many ways. Some ways are good,
8 and some ways are bad. My friends have to repeat
9 to me what I say or what others say so that I can
10 stay active in a conversation. I don't think my
11 friends mind doing that for me, but I can see it
12 being annoying for them.

13 Also, I miss assignments in high school.
14 Some teachers don't put dates of assignments on the
15 chalkboard. They just say it once, and they don't
16 mention it again, so I get confused. I also have
17 to get tutored in English and math. I don't
18 understand text or algebraic equations like other
19 students, and I can't remember definitions by
20 myself. I've had tutors before, and they help me
21 improve my grade because they go through thoroughly
22 the material with me.

1 Some of the good ways hearing aids have
2 affected me are that I can decide if I want to
3 listen to somebody. If my mom is telling me I
4 forgot to do my homework assignment, I can just
5 turn off my hearing aid. Then I don't have to
6 listen to her complain.

7 I also had to get my right kidney taken out
8 of my body during the tumor removal surgery.
9 Because my kidney got taken out, there are sports I
10 physically can't play because if I get hit hard
11 enough in my left kidney, I could die from kidney
12 failure. Also, there are other surgeries that I
13 have gotten. The tumor removal surgery that I have
14 gotten goes a quarter to one-half the way around my
15 body. I also have many smaller scars that put
16 tubes through my body.

17 So you can see chemotherapy has left me with
18 many problems. If you take away the -- if you keep
19 the hearing, it will be one less problem to deal
20 with. I want this drug to help tomorrow's kids who
21 get diagnosed with cancer. This drug is supposed
22 to protect patients' hearing so they don't have to

1 lose it during chemotherapy. It sounds too good to
2 be true, especially to me. I know that this won't
3 help me with my hearing, but if I can help
4 tomorrow's children, I want to help as much as I
5 possibly can.

6 I understand that there are people here
7 today that may not want to test the drug. I also
8 understand the reason that you are concerned to
9 test it is because you don't want innocent people
10 to die. You are thinking very negatively about
11 this drug. I want you here today to open up your
12 mind and think about what I have to say.

13 What if the drug does exactly what it is
14 meant to do? Then cancer patients can return to
15 their life just how they left it. Patients can
16 still hear the same as they do after cancer as they
17 heard things before they had cancer.

18 I realize I am more fortunate than others.
19 Some patients die, and I am still living. I also
20 want you to think about this. Every doctor's
21 biggest dream is to cure cancer. This is one step
22 closer to helping kids with cancer. Also, what

1 happens if we don't test the drug now? In 10 or
2 15 years, what if they bring it up again and it
3 does actually work? Later in life, we would test
4 the drug, and we wish we would have done this
5 sooner. I just want you to consider what you would
6 be doing by letting doctors test the drug. Think
7 of all the good it could do.

8 Thank you for your time.

9 DR. BALIS: Thank you very much for your
10 insight.

11 Can we have speaker number 2, please?

12 MS. COLLINS: Good morning, ladies and
13 gentlemen. I do not have any financial relations
14 with this study at all.

15 Well, that's my son. That's my cancer
16 survivor. He's my living example of all the good
17 being done here at the FDA. The fact that he's
18 alive proves that what happens here does, in fact,
19 work. If he had been diagnosed 25 years ago, he
20 might have died before we even realized that he had
21 cancer. But he was diagnosed in 1999 with a
22 15 percent chance to survive. After chemo,

1 surgery, and a bone marrow transplant, he was lucky
2 enough to take part in what is now considered the
3 two proven therapies to improve the odds of
4 survival for neuroblastoma.

5 This process to explore and approve these
6 treatments are working to increase the odds of
7 survival for our children. And for that, I am
8 honored to be here to witness it in action, let
9 alone speak before you. I am so proud to be here
10 today, not just as a mother of a survivor of
11 neuroblastoma but because of why we are gathered,
12 to focus on the quality of life for these children,
13 these kids who are blessed enough to actually beat
14 the cancer and live the life that we are so
15 gallantly fighting for.

16 This is not an area that is discussed often
17 with your child while they're in treatment. In
18 fact, I only did it really once. It was done right
19 after his diagnosis when I had to sit down and
20 discuss his protocol. Josh was to receive both
21 cisplatin and carboplatin, plus a handful of other
22 drugs. He was to receive vincristine,

1 cyclophosphamide, ifosfamide, etoposide,
2 doxorubicin, and topotecan. The side effects that
3 we discussed included a multitude of possible
4 effects, such as issues affecting his heart, his
5 kidneys, his thyroid, his gait, his GI tract, the
6 real possibility that he would be sterile, the
7 possible development of learning disabilities and
8 then, of course, specifically his hearing loss.

9 All of this was prefaced by one ultimate
10 statement, which I'll never forget. He has to be
11 alive first before you can even consider the side
12 effects. It's a very God forsaken place for a
13 parent to hear a statement like that, and, yes, at
14 that point I broke down and cried and then took a
15 deep breath and accepted the challenge at hand. I
16 prayed for survivorship, and I left the worry about
17 the side effects to another point in time. And we
18 got lucky. He didn't die.

19 He is a survivor, and like I also like to
20 say, a thriver. But that is no simple statement
21 because the fight for us isn't over just because
22 Josh got classified with no evidence of disease.

1 Cancer, as bad as it was, is not all that he
2 suffers with. He hasn't had it easy. He suffers
3 moderate to severe hearing loss in both ears, and
4 that is not all. He also has suffered significant
5 GI issues over the years, and the severe migraine
6 clusters can leave him vomiting and in significant
7 pain for days at a time. He also has a number of
8 neurological effects that can make learning a bit
9 of a challenge, including an auditory processing
10 delay.

11 About two months ago, I read the abstract
12 from Pediatrics, originally dated March 2010
13 entitled, The Auditory Late Effects of Childhood
14 Cancer Therapy, a Report from the Children's
15 Oncology Group. It's really not a bad report, but
16 it's a very clinical report. It's filled with
17 stats and doesn't adequately reflect people's
18 lives.

19 The report doesn't talk about all the tears
20 my son has shed. It doesn't talk about when he
21 gets made fun of wearing his hearing aids, or when
22 his hearing loss made playing on the travel soccer

1 team impossible because they blamed him for
2 mistakes simply because he couldn't hear them talk
3 on the field. It doesn't touch on Josh's
4 sensitiveness of being different when all he wants
5 to do is just be like every other kid.

6 There are times today that the hearing loss
7 really isn't that big of a deal. We just go
8 through one day joking and having a good time, and
9 I don't even think about it. And then something
10 small will happen, and I look over, and I realize
11 he missed the joke entirely.

12 A few weeks ago, we were in the car when he
13 made a comment, "Boy, my life sucks." He was
14 sitting in the back seat of the car, and he just
15 couldn't hear the conversation I was having with
16 his brother, who had just started to sit up front
17 because of the airbag issues. He had finally
18 gotten big enough to sit up front. It didn't occur
19 to me that Josh was sitting in the back and missing
20 our entire conversation. And after two days, he
21 just got fed up and broke down in tears.

22 I feel horrible when things like that

1 happen, when I, just like every other teacher,
2 every coach, every person on the street -- I will
3 at times overlook the multitude of little things
4 that he has to do each and every day to overcome
5 his hearing loss because it's an invisible
6 challenge. He doesn't have purple stripes. He
7 doesn't have hives. He just can't hear, but he
8 does an awful lot. He doesn't complain, and he
9 doesn't give up. He reads lips. He reads
10 nonverbal cues, and he constantly evaluates
11 everything around him, attempting to piece together
12 things the best that he can. And he misses stuff
13 anyway. And to put it simply, he just doesn't know
14 what he can't hear.

15 There's a lot that Josh and I do together to
16 overcome his hearing challenges. Hearing loss
17 affects the cycle of learning, so his reading and
18 writing skills are affected, and we've had to work
19 hard over the years to try to make up the
20 difference. Not everyone realizes that hearing
21 affects your access to vocabulary and your
22 understanding of the world around you. I've had to

1 talk more to Josh to give him language that most
2 kids get just playing trucks in a room where the
3 grownups are sitting there talking. He didn't hear
4 the grownups talk, so he didn't learn from those
5 conversations, and so I've had to give him that
6 language separately.

7 So together, Josh and I, we talk about
8 everything. And when school becomes challenging,
9 we work through the challenges together, and this
10 is a lot of extra work. And that's on the good
11 days. But on a day that Josh is tired, or he's
12 sick, or he's anxious, or he's dealing with his GI
13 issues, or struggling through his migraine
14 clusters, his ability to work with those hearing
15 aids is significantly more difficult.

16 It's like a prosthetic that everybody
17 forgets is fake. Everyone forgets that he has to
18 work a lot harder than everybody else in order to
19 be able to hear. So on the days he's not feeling
20 well, the hearing aids are the first things he
21 takes out, sometimes even before kicking off his
22 shoes and taking off his jacket and collapsing on

1 the couch. Imagine how tired he must feel to
2 purposefully isolate yourself from everybody around
3 you.

4 We have more neuroblastoma survivors alive
5 today than the world has ever seen. We now have
6 the possibility of rewarding these survivors with a
7 life that can be easier to live, easier to enjoy
8 than my Josh. These kids endure the cancer fight
9 better than most adults. Some of them would curl
10 up in the corner and cry, but Josh did it playing
11 with Barney, playing with Teletubbies and watching
12 Winnie the Pooh.

13 He endured the side effects of the treatment
14 without much complaint simply because he didn't
15 have anything else to compare it to. He didn't
16 know how much better things could be. But we
17 adults, we know better. We are the adults that are
18 fighting for them. We're fighting for them to stay
19 alive and hopefully fighting for them to have a
20 really great life to stay alive for.

21 A mother at the time of cancer treatment
22 doesn't have the luxury to think about the side

1 effects that result if her child survives. But
2 that's the luxury that each one of you have the
3 wonderful opportunity to face right now. That's
4 the luxury that I beg you to consider this
5 challenge that is facing you, and I recognize that
6 it has a whole bunch of unique issues with it. But
7 I do ask that you struggle to continue to find a
8 solution to allow the study to continue.

9 An announcement that tomorrow's survivors will have
10 one less thing to struggle with, that they won't
11 have to suffer from the hearing loss because of
12 platinum-based chemotherapy would really be
13 incredible for all of us to hear. Thank you very
14 much.

15 **Questions to the Subcommittee and Discussion**

16 DR. BALIS: Thank you.

17 The open public hearing portion of this
18 meeting is now concluded, and we will no longer
19 take comments from the audience. The committee
20 will now turn its attention to address the task at
21 hand, the careful consideration of data before the
22 committee as well as the public comments.

1 We'll now proceed with the questions to the
2 subcommittee.

3 Dr. Snyder.

4 DR. SNYDER: What study design will be
5 required to definitively demonstrate the efficacy
6 of sodium thiosulfate in preventing cisplatin-
7 induced ototoxicity?

8 DR. BALIS: The floor is open for
9 discussion.

10 Dr. Smith.

11 DR. SMITH: I think the COG study that was
12 described is a good start in terms of preventing
13 cisplatin-induced ototoxicity. Dr. Balis mentioned
14 some important points about the different infusion
15 durations and the different ways that cisplatin is
16 administered. And so in analyzing the COG trial
17 and any other data that are developed, it will be
18 important to look at those additional variables,
19 such as how the cisplatin is administered, what
20 other drugs its administered with, all the
21 covariates like that. But the randomized trial
22 should allow the demonstration of protection from

1 ototoxicity.

2 DR. BALIS: Other comments?

3 [No response.]

4 DR. BALIS: I think this gets to the
5 question, in part, that was discussed at the very
6 beginning of the FDA presentation, that relates to
7 the numbers of patients we have to do these
8 studies. And I think the question we're really
9 asking, that we need to get on to probably, is more
10 the issue of the rescue than it is -- this
11 discussion has been kind of based on the
12 presumption that the current studies will show a
13 therapeutic effect. Obviously, if that's not the
14 case, I think we don't go any further from here.
15 And part of this is really a planning issue. I
16 think the studies that will demonstrate whether
17 this can prevent ototoxicity we'll hopefully get
18 from the studies that are ongoing, which have a
19 fairly high bar.

20 I think the COG study is powered to detect a
21 50 percent improvement in hearing, and I think if
22 it can do that, I'm not sure that we need more

1 definitive evidence that it's otoprotective than
2 that.

3 Dr. Sekeres.

4 DR. SEKERES: Thank you, Dr. Balis.

5 So at face value, the Children Oncology
6 Group study seems to be a good one looking purely
7 at efficacy, and we'll deal with the other issue, I
8 guess, next.

9 One question I have in defining
10 efficacy -- and this may be a naive question; I
11 apologize for this -- does all ototoxicity occur
12 immediately or within the 12 months during which
13 the study is looking at ototoxicity, and what are
14 the criteria for demonstrating that the 50 percent
15 decrease is clinically meaningful?

16 DR. BALIS: Anybody from the sponsor want to
17 field -- sorry. Dr. Shearer.

18 DR. SHEARER: All ototoxicity does not occur
19 within the first year. We know that in patients
20 who have received cranial irradiation, that
21 ototoxicity may be delayed for years, five years,
22 six years, seven years, eight years, nine years,

1 ten years. There are also studies coming out now,
2 and the sentinel paper is by Bertolini, et al.,
3 showing that there can be delayed hearing loss
4 after cisplatin regimens for children who do not
5 have brain tumors. So the jury is out in terms of
6 how long is long enough to follow children. But we
7 know that most of the damage in most patients
8 without brain tumors treated with cisplatin does
9 occur early. It is probably irreversible.

10 So I don't know of any data that would
11 direct us right now toward a longer monitoring
12 period. That is under consideration, but the data
13 are not firm in terms of directing us to go longer,
14 especially in non-irradiated patients.

15 DR. SEKERES: That's reasonable. I mean, we
16 can't expect somebody to conduct a study for a
17 decade to capture all of this hearing loss, but if
18 we're getting 90 percent of it, for example, within
19 a year, then that's a reasonable time to study it.

20 So what dictates that the amount of
21 decrement in hearing loss that the study's powered
22 on is clinically relevant? And, actually, how is

1 the -- the difference in hearing loss upon which
2 the study is powered, how is that being measured?

3 DR. BALIS: I think the question is if you
4 just describe the endpoint for the randomized study
5 and how you determine that the difference that
6 you're looking for is clinically significant.

7 DR. FREYER: Right. I'll ask Kristi to
8 comment on that. We decided to use the ASHA
9 criteria. There are three different major grading
10 systems that are currently in use in the world. In
11 the United States, it tends to be the CTCAE. We
12 decided to go with the ASHA criteria because
13 they're more sensitive. One of the chief
14 criticisms about CTCAE is that it's not sensitive
15 enough to detect clinically meaningful hearing
16 loss, but I'll let Kristi speak to the issue of the
17 ASHA criteria and whether the differences we're
18 looking for are clinically meaningful.

19 MS. KNIGHT: They are going to present a
20 slide that just lists the ASHA criteria, and it's a
21 binary criteria; you meet criteria or not. And it
22 is very strict and very sensitive. Most children,

1 at least that I see in my clinic, meet criteria by
2 the first guideline, a decrease in hearing
3 sensitivity of 20 dB or greater at one test
4 frequency compared to baseline. So all the
5 children on this COG study get a baseline
6 evaluation, get regular monitoring, and we're
7 looking at change compared to that initial
8 assessment.

9 Changing by ASHA criteria does not
10 necessarily indicate communicatively significant
11 hearing loss. It does definitely mean change in
12 hearing related to treatment. There are other data
13 that's being collected that will look at -- answer
14 that clinically meaningful question.

15 DR. SEKERES: So the study is powered on a
16 50 percent fewer patients meeting one of these
17 criteria?

18 MS. KNIGHT: Meeting the ASHA criteria.

19 DR. FREYER: The data are -- actually, all
20 of the raw audiometry data are being submitted to a
21 central review process in COG where two blinded
22 reviewers are reviewing all of the audiograms, the

1 actual audiograms that are sent in. And they're
2 all being graded according to the three systems
3 that I mentioned, the ASHA, CTCAE and Brock. So
4 we'll actually have the ability to report our data
5 according to all of those systems which each have
6 their advantages and disadvantages.

7 DR. SEKERES: Thank you for explaining that.
8 It seems like a reasonable endpoint to me.

9 DR. BALIS: Dr. Reaman.

10 DR. REAMAN: Can I just get some
11 clarification? Was it well understood when this
12 study was developed that there would be a diversity
13 of patients with various diagnosis and different
14 platinum-containing regimens? How important -- and
15 given the fact that there is a high bar -- but if
16 another study were deemed necessary to definitively
17 demonstrate efficacy, how important does this
18 committee feel that the patient population studied
19 should be as well defined as possible from the
20 standpoint of diagnosis and treatment and other
21 confounding treatments vis-a-vis radiation therapy?

22 DR. SEKERES: Well, it's unusual that as a

1 committee we're asked to debate efficacy separate
2 from what I would look at as a safety issue of the
3 tumor protectant effect. So I think if you -- I
4 mean, my opinion, if you put those two together,
5 looking at both efficacy and the tumor protectant
6 effect, I think it's pretty critical to define the
7 underlying disease clearly and have it powered to
8 compare like to like because I think it's going to
9 be pretty challenging to see if there's a tumor
10 protectant effect when you're looking at five
11 different diseases, all of whom were exposed to
12 different types of platinum, potentially, and
13 radiation therapy as well.

14 DR. BALIS: Dr. Shurin.

15 DR. SHURIN: I certainly would agree with
16 that. I'm very concerned about the issue of the
17 variability in the way that the platinum is given
18 in terms of our ability to really sort out both of
19 these issues, both the efficacy issue and the
20 safety issue, because the pharmacokinetics makes it
21 really very complicated because it's all an issue
22 of when are you giving over what period of time,

1 whether or not you're either protecting hearing or
2 addressing -- or protecting the tumor.

3 The issue of the other therapies really does
4 become a major complication, and I think
5 Dr. Shearer mentioned this. One of the key things
6 to keep in mind is that this drug may not protect
7 against the kind of toxicity that appears years
8 later, particularly in central nervous system
9 tumors when there's inflammation, there's
10 radiation, there's surgery. There are other
11 factors which may actually affect both hearing and
12 communication, and you can't actually expect this
13 drug to protect against damage that isn't related
14 to the specific therapy.

15 So I think how this is designed, I actually
16 support the idea that you look at a year because my
17 guess is that this drug may not protect against
18 some of the hearing loss that comes later, but it
19 may not actually be related to exactly the same
20 mechanism.

21 DR. BALIS: Dr. Gorlick.

22 DR. GORLICK: This is beginning to touch on

1 the second question, but cisplatin is used in a
2 range of malignancies, some of which are more
3 unfavorable prognosis where it tends to be used in
4 combination, some where it can be even used as
5 single agent that are relatively favorable
6 prognosis.

7 The issue that this sort of brings up is
8 that the ethical consideration of reducing therapy
9 varies depending upon the disease that's treated,
10 meaning many of the favorable prognosis
11 malignancies are very salvageable with alternative
12 therapies or can be treated with combination
13 therapies that will ameliorate that effect.

14 Your primary endpoint is likely to be
15 addressed in the context of the trial, but is it
16 the scale that can address the second question?
17 And that's going to be the driver of the study.

18 DR. BALIS: I think from my perspective, if
19 we're going to look towards doing a second round of
20 studies to look specifically at efficacy from the
21 perspective of its otoprotective effect, that we
22 can't delay addressing the question about whether

1 it is potentially protecting tumors as well.

2 I don't think we -- as Dr. Sekeres said, we
3 can't really split those two out. We can't put
4 patients at risk without looking to see if we
5 actually are placing them at risk.

6 Dr. Smith.

7 DR. SMITH: I think, if I understand what
8 you're asking, that it would be important to define
9 as best you can the intended use and what is the
10 population, how much cisplatin are they getting,
11 how is it administered, what is their risk of
12 ototoxicity. That would be the information. The
13 label would describe an intended use, and you want
14 to be as clear as you can about what the population
15 is, what the benefits are when the product is used
16 as intended. And so defining as best you can the
17 population I think would be important.

18 DR. REAMAN: That's exactly what I was
19 trying to get to. And to address Dr. Gorlick's
20 point and Dr. Balis', clearly separating the issue
21 of efficacy and potential toxicity herein limited
22 to tumor protection is a real issue, and I agree

1 they can't be separated.

2 I think the problem is looking at the sort
3 of prognostic characteristics of the specific
4 populations based on diagnosis would be difficult
5 because I think the better prognostic group of
6 patients may well be older and to some extent less
7 at risk for platinum-related ototoxicity. And I
8 think the issue of additional therapies certainly
9 confounds the issue considerably.

10 Obviously, we've known all along that there
11 were difficulties with numbers, and doing a classic
12 non-inferiority study, which would be required to
13 demonstrate lack of tumor protection, would be
14 difficult, to say the least, and possibly not
15 really feasible without an international trial,
16 which also might raise some additional issues.

17 DR. BALIS: Thanks. Perhaps we should move
18 on to the second question since I think we're
19 starting to address that in the discussion anyway.

20 DR. SNYDER: Okay. The second question that
21 we'd like you to address is what type of trial
22 design would be required to confidently demonstrate

1 that sodium thiosulfate does not provide tumor
2 protection? Please also comment on the appropriate
3 patient population or populations for study.

4 DR. BALIS: In the paperwork provided, the
5 sponsor had proposed seeking accelerated approval
6 if the current studies showed an otoprotective
7 effect and then addressing, as I interpret it, the
8 issue of tumor protection in a postmarketing study.
9 And you just briefly touched on that at the end of
10 your discussion.

11 Could you provide us a little bit more
12 information on exactly what your proposed
13 postmarketing study would look like?

14 DR. ROUSSEAU: As I briefly discussed at the
15 end of the presentation, we are thinking that the
16 realistic way to go forward in a timely fashion
17 would be to collect prospective information,
18 preferably in the COG network, either as an
19 industry-sponsored study or co-sponsor study, the
20 detail would have to be worked out, where every
21 child who was treated for a tumor that receives
22 cisplatin would be captured in terms of tumor

1 characteristic at baseline, treatment actually
2 received and outcome.

3 STS would be used or not depending on the
4 current local protocol, the physician's desire and
5 the family's wish obviously to receive or not the
6 molecule. And at the end with appropriate
7 statistical measure to do stratification on the
8 baseline disease as well as the dose of cisplatin
9 received, the age of the children and all variable
10 known to be predictive, we would look at endpoints
11 like event-free survival at one year and at three
12 years and overall survival to reassure ourselves
13 that STS does not reduce significantly the tumor
14 response as compared to no STS.

15 DR. BALIS: Thank you.

16 Any other questions or comments?

17 DR. NEVILLE: So did you say the use of STS
18 would be based on physician or parent choice?

19 DR. ROUSSEAU: Well, I assume that following
20 an accelerated approval, there would be some
21 warning, probably a black box on the label, that
22 this drug may confer some level of tumor protection

1 or tumor protection has not been demonstrated,
2 something to that extent. And I would think that
3 as a parent, I would want to know the benefit and
4 the risk of the drug being offered to my child. So
5 I assume that some parents may opt in and some may
6 opt out.

7 DR. NEVILLE: So then I guess my question is
8 how do you prevent confounding from more severe
9 tumors, parents declining, STS?

10 DR. ROUSSEAU: I think there is always an
11 element of risk of that, but you stratify by the
12 baseline characteristic of the tumor. So the
13 analysis would be adjusted for that very factor.
14 If we end up in a situation where none of the
15 severe children receive STS or do receive STS and
16 the benign do not, then we have a problem that we
17 cannot surmount by statistical analysis.

18 However, if you go into a sample size of 8
19 to 900 children in a network where you capture
20 about 90 percent of the pediatric tumor in the
21 United States, I think it would be highly unlikely
22 that such situation would occur. I would think

1 that there would be enough cases, treated and
2 untreated, to have a meaningful comparison of the
3 effect on the survival.

4 DR. BALIS: Dr. Shurin.

5 DR. SHURIN: This sounds as though it might
6 have some impact on the ability to actually conduct
7 trials within the Children's Oncology Group.
8 Dr. Krailo is here. I was wondering if he would be
9 able to comment.

10 No? Okay.

11 I'm just concerned that if you have that as
12 an added variable in the studies that are going on,
13 and it does actually offer some degree of tumor
14 protection. It may make it very difficult to get
15 meaningful endpoints on the other therapeutic
16 studies that are being conducted.

17 DR. BALIS: I think most people here in
18 pediatric oncology know this, but we recently
19 surveyed the solid tumor studies that were open in
20 that group. And just to give people an idea of
21 what tumors we're talking about here, if we talk
22 about just basically taking any patient going on to

1 cisplatin, there are a number of brain tumor
2 studies in those patients getting radiated. It may
3 actually, based on what we heard, be excluded from
4 this.

5 Germ cell tumors, hepatoblastoma,
6 neuroblastoma, osteosarcoma, a couple of rare tumor
7 protocols, one retinoblastoma protocol; so there
8 are a total of 12 different studies that included
9 cisplatin as part of the primary therapy. Now, not
10 all of those patients may -- depending on how the
11 eligibility criteria are set in terms of cumulative
12 dose and other issues may be eligible for those.
13 But that's the population that we'd be pulling
14 from.

15 The other difficulty, I think, with that
16 approach is that if it's not balanced, survival
17 rates obviously differ by diagnosis. The other
18 issue is that the contribution of cisplatin to any
19 particular treatment regimen with a given disease
20 or even within a patient is not going to be uniform
21 across all of these studies.

22 Dr. Shurin.

1 DR. SHURIN: You also have significant age
2 variability because you've got hepatoblastoma and
3 neuroblastoma, which is predominantly in very young
4 children, which really ought to be the target group
5 for this for the reasons that the company's already
6 mentioned. And then you have osteosarcoma, which
7 is predominantly adolescents and older people,
8 which, again, may make it difficult to get real
9 answers to the questions, way beyond just the
10 variability in terms of the underlying disease and
11 therapies.

12 DR. BALIS: Dr. Freedman.

13 DR. FREEDMAN: This may be heretical, but
14 you've got a situation where you can't do a
15 randomized control study for this type of issue.
16 But what about the possibility of doing the type of
17 study that you presented and in a preplanned
18 fashion, comparing it with a historical database
19 from prior randomized? It's not a -- it's not
20 through choice, but the question is if you can't do
21 a randomized control study to look at tumor
22 protective effect, what other options have you got

1 and would it be worthwhile to consider as long as
2 it was preplanned? COG has a phenomenal database
3 of patients.

4 Just throw it out as a suggestion.

5 DR. BALIS: Dr. Smith.

6 DR. SMITH: I think the idea that we can't
7 do a randomized study should be addressed. And to
8 directly answer the question about what kind of
9 trial design, I think the randomized trial design
10 would be the appropriate design for addressing the
11 tumor protection issue and should be one in which
12 cisplatin is playing a prominent role. Ototoxicity
13 is a prominent adverse event so that the risk of
14 potential tumor protection are addressed.

15 I think this would be a case where a
16 factorial design would be appropriate, that you
17 could be randomizing to sodium thiosulfate and
18 there may be other things that are happening to
19 those patients in the context of clinical trials,
20 but there is a randomization to -- and that would
21 make it more -- one of the issues addressed was, is
22 a pediatric community going to want to spend five

1 or six or seven years, however many years it is, to
2 do a randomized study that's only addressing
3 otoprotection. And I think using the factorial
4 design would allow additional questions to be
5 answered at the time.

6 Another issue that has just been briefly
7 alluded to is that because there is a potential for
8 otoprotection, more cisplatin may be able to be
9 administered. So, in fact, if there is no tumor
10 protection, more cisplatin can be administered.
11 There's the potential that EFS may
12 actually -- could be improved. And that would
13 actually make the kind of equivalence design a bit
14 easier to reach, in the sense that looking at
15 90 percent confidence intervals, you would have a
16 better chance if, in fact, you could give more
17 cisplatin to the patients receiving sodium
18 thiosulfate because of lack of ototoxicity.

19 So I think we shouldn't just assume that a
20 randomized study couldn't be done, and that in one
21 or more of the populations that a randomized study
22 potentially could be done. Potentially several

1 populations could be studied with a planned kind of
2 meta-analysis of the randomized of the different
3 patient populations that were randomized.

4 DR. PAZDUR: I guess I have a question that
5 I'd like the committee to comment on, and that's
6 with regard either to a randomized study or the
7 cohort study; and that is it being initiated and
8 done in a post-approval setting and the
9 practicality of that.

10 Here again, if the drug does receive
11 accelerated approval, the FDA, in the minds of many
12 people, are saying that this drug is safe and
13 effective for the intended use. And many people
14 forget the caveat that this is kind of a
15 conditional approval here, but it's on the market.
16 And we found a great deal of problems with
17 accelerated approval once the drug is approved,
18 okay, and then going back in the same disease
19 setting, so to speak.

20 That's why with other accelerated approvals,
21 what we've allowed sponsors to do was to explore
22 this in a different setting. And usually we're

1 talking about antineoplastic drugs here in an
2 earlier stage of the disease. But to try to do it
3 in the same disease setting after the FDA has said
4 this is safe and effective is somewhat problematic,
5 and that's why I really do have concerns. And I'd
6 like some discussion on this; is this even
7 practical to do.

8 Remember, there are alternative mechanisms
9 other than accelerated approval for the
10 availability of drugs that are unapproved, and
11 these are expanded access programs, intermediate
12 size protocols that even allow sponsors to charge
13 recovery cost for therapy before this is approved.
14 And given the very niche nature of this population
15 here, would those options probably be better served
16 here?

17 And I'd like some discussions on this
18 because I would not want to get into a situation
19 where we rush to approve this drug and we can't
20 simply do a randomized trial, and then we're in a
21 quagmire of 10, 15 years later, what's this drug
22 really doing to overall survival and we discover,

1 God fear, that we're really doing more harm than
2 good.

3 So could people comment on this?

4 DR. BALIS: Dr. Shurin.

5 DR. SHURIN: I think that's a really
6 important point because the in vitro data suggests
7 that there is tumor protection. What we don't know
8 is whether there's tumor protection in vivo, and we
9 don't know how much that may vary by tumor type,
10 and perhaps most importantly, how much it varies by
11 the timing of the administration. So that we're
12 taking a drug which is not particularly toxic in
13 itself, but if you give it at the wrong point in
14 time, may actually rescue the tumor.

15 We've dealt with this in methotrexate and
16 various other drugs. This is not a new concept for
17 us. But it does seem that some real control over
18 how this drug is used -- I mean, the potential
19 benefit is huge, and the potential downside in
20 terms of protection against effective therapy is
21 not something that we should ignore. The big issue
22 is that it seems at this point in time, it doesn't

1 seem as though we have sufficient data to be able
2 to, with great confidence, sort of put this out in
3 an uncontrolled setting. So I would think that it
4 would be worth really designing some approaches to
5 both answer the question and ensure availability.

6 DR. BALIS: Dr. Smith.

7 DR. SMITH: Let me clarify, my comments were
8 predicated on the idea that this would be a
9 requirement for approval, not that there would be
10 an accelerated approval that would require a
11 randomized study. I think there would be a very
12 real risk if there were accelerated approval that
13 we would be in the setting 10 or 20 years up the
14 road finding that we had made the wrong decision,
15 that tumor protection was a greater problem than we
16 had anticipated, and more harm would have been done
17 than not.

18 We have the chance now to address the
19 question that the physicians and families want to
20 know, is there tumor protection or not, and that
21 should be addressed before approval.

22 DR. BALIS: Dr. Sekeres.

1 DR. SEKERES: Thank you, Dr. Balis.

2 So I agree with Dr. Smith, and I've also
3 been reflecting on some of the things that
4 Dr. Talcott has said. And, Jim, you always have a
5 gift for being very patient, focused, and thinking
6 about when you're on the front lines how you're
7 actually going to present a study to somebody.

8 And I just have a devil of a time trying to
9 figure out if this did receive accelerated
10 approval, how you would then present this drug,
11 which may have something prominent on the label
12 saying we don't know about the tumor protectant
13 effect, to a family. I mean, if this were -- let's
14 really bring it to the front lines -- if this were,
15 God forbid, my child who had cancer, and I was
16 offered with saving his or her hearing versus
17 getting rid of his or her cancer, the hearing
18 wouldn't even be a focus upfront at that initial
19 decision.

20 So I think this would be a real difficult
21 drug to have accelerated approval and have any type
22 of assuredness that a well-conducted study could be

1 finished in a timely manner afterwards.

2 DR. BALIS: Mr. Lustig.

3 MR. LUSTIG: I think sort of on the same
4 note, I would have real concerns about the
5 feasibility of the study given the consent process.
6 I think that this would have to be a very nuanced
7 discussion, and I think consent is often not a
8 nuanced discussion. So putting in front of the
9 family the decision of curative therapy and the
10 potential for something that would have very, very
11 significant long-term benefit but could potentially
12 impact the value of the curative therapy, I think
13 is not a decision I think we should be asking
14 people to make.

15 I think either there -- if this study as
16 proposed move forward, I think there would just
17 have to be something around the consent process to
18 ensure that there would be, again, some more nuance
19 about whether it relates to the specific disease
20 and whatever data we have related to the potential
21 impact, the potential negative impact, of giving
22 this additional protective drug for the

1 ototoxicity.

2 But I think, in my experience, these
3 informed consent discussions are very difficult.
4 They're often at a time when the family is in
5 great, obviously, crisis and emotional distress,
6 and I think that this is the kind of issue that has
7 to be done in a very, very, much more detailed
8 discussion perhaps. And so how that proceeds would
9 be of concern to me.

10 DR. BALIS: Thank you.

11 Rick, I think to answer your question from
12 my perspective, in looking at it two ways, one is
13 there are certain precedence for cancer control
14 studies to be done across protocols in the
15 Children's Oncology Group successfully. Secondly,
16 almost all of the randomized trials we do are with
17 agents that are on the market. We rarely do
18 phase 3 studies with an investigational drug. And
19 it's just been the tradition that if -- that the
20 first thing that's offered to patients is
21 participation in a clinical trial, even if it's
22 with agents that are already approved.

1 The other thing I'd say is that the issue
2 that you're bringing up, Mr. Lustig, is correct,
3 but that discussion, if this drug does receive
4 accelerated approval, will be no different. The
5 same discussion will be had, whether it's in the
6 context of a clinical trial or somebody just
7 getting treated. The issue is no different.
8 You're in this situation of balancing or
9 considering whether you want to risk hearing loss
10 versus risk a potentially higher risk of your
11 cancer recurring.

12 The only difference will be that by the time
13 we get to that setting, we'll hopefully at least
14 know about the otoprotective effects. We won't
15 know the other. It will be an unknown. And I
16 think the decision is going to be difficult for
17 families, whether they're participating in a
18 clinical trial or not.

19 Now, obviously, the discussion about
20 accelerated approval is very hypothetical at this
21 point because we don't have the data, and that will
22 I think be a discussion, as Dr. Sekeres says,

1 probably for a separate ODAC meeting as to whether
2 that is warranted or not.

3 Dr. Neville.

4 DR. NEVILLE: Just to echo Dr. Shurin's
5 comments, perhaps, too, there's such a wide disease
6 spectrum being considered, that the potential
7 benefit is not the same for all patients. So when
8 you are considering accelerated approval, I think
9 you need to very carefully consider which patient
10 population you would grant that to.

11 DR. BALIS: Any other questions or
12 discussion?

13 Dr. Gorlick.

14 DR. GORLICK: The effects of cisplatin on
15 hearing loss are cumulative with increasing dose.
16 Do you actually need to give the STS with all of
17 the doses? It's more of a question, obviously.

18 DR. BALIS: Dr. Shearer, do you want to
19 address that?

20 DR. SHEARER: Complex question, complex
21 answer. If you look at a paper by Mike Schell,
22 published a number of years ago, there are two

1 curves in that paper, and they're actually
2 represented in the manuscript from the Auditory
3 Hearing Task Force of Children's Oncology Group.
4 There are effects of radiation on hearing loss,
5 depending on the dose of cisplatin that's given.

6 So the first thing we know is that radiation
7 exaggerates or accentuates platinum dose for dose.
8 Secondly, we know that the type of tumor that a
9 child has makes a difference, and children with
10 brain tumors are at higher risk. Children with
11 brain tumors with shunts are at even higher risk.
12 We also know that the age of the patient with
13 little children under four exaggerates or
14 accentuates the risk dose for dose.

15 So it is dose dependent, but there are a lot
16 of confounding variables that go into the answer to
17 that question. Generally speaking, doses of
18 greater than 360 milligrams per meter squared are
19 the ones that cause the most problems, but that is
20 not to say that a dose under 360 or 450 per meter
21 squared -- and 450 per meter squared is what we
22 give in an osteosarcoma protocol. That's where we

1 start to see problems, but in certain populations,
2 you might see problems at doses less than that.
3 And that is why serial audiograms are done in
4 patients on protocols receiving cisplatin.

5 DR. BALIS: Dr. Smith, do you have another
6 question?

7 DR. SMITH: I was just going to comment that
8 I think with this type of agent, this protective
9 agent, there are two aspects of its benefit. One
10 is that it protects against the toxicity, the
11 other, that it doesn't decrease or diminish the
12 effectiveness of the cancer treatment. And so it
13 is hard for me to think about an accelerated
14 approval that addresses one by not the other. And
15 so I would need better explanation for why one
16 would give approval for something as safe for its
17 intended use when you've only addressed only half
18 of the issue regarding its overall effect on the
19 patient.

20 DR. BALIS: Dr. Pazdur, any other issues you
21 want us to address before we close this session?

22 DR. PAZDUR: No. I think this was great.

1 Good discussion. Thank you.

2 DR. BALIS: Thank you.

3 This session is now adjourned. We'll take a
4 brief 10-minute break so we'll be back at, let's
5 say, 10:30. Panel members, please remember that
6 there should be no discussion of the issue at hand
7 during the break amongst yourselves or with any
8 member of the audience. Thank you.

9 (Whereupon, a recess was taken.)

10 DR. BALIS: We'll now proceed with topic 2,
11 which is a discussion of vismodegib from Genentech.

12 Caleb, can you read the conflict of interest
13 statement?

14 **Topic 2: Vismodegib - Genentech**

15 **Conflict of Interest Statement**

16 DR. BRIGGS: The Food and Drug
17 Administration, FDA, is convening today's meeting
18 of the Pediatric Oncology Subcommittee of Oncologic
19 Drugs Advisory Committee under the authority of the
20 Federal Advisory Committee Act, FACA, of 1972.
21 With the exception of the industry representative,
22 all members and temporary members of the

1 subcommittee are special government employees,
2 SGEs, or regular federal employees from other
3 agencies and are subject to federal conflict of
4 interest laws and regulations.

5 The following information on the status of
6 this subcommittee's compliance with the federal
7 ethics and conflict of interest laws, covered by
8 but not limited to those found at 18 U.S.C. Section
9 208 and Section 712 of the Federal Food, Drug and
10 Cosmetic Act, FD&C Act, is being provided to
11 participants in today's meeting and to the public.

12 FDA has determined that members and
13 temporary members of this subcommittee are in
14 compliance with federal ethics and conflict of
15 interest laws. Under 18 U.S.C. Section 208,
16 Congress has authorized FDA to grant waivers to
17 special government employees and regular federal
18 employees who have potential financial conflicts
19 when it is determined that the agency's need for a
20 particular individual's services outweighs his or
21 her potential financial conflict of interest.

22 Under Section 712 of the FD&C Act, Congress

1 has authorized FDA to grant waivers to special
2 government employees and regular federal employees
3 with potential financial conflicts when necessary
4 to afford the subcommittee essential expertise.

5 Related to the discussions of today's
6 meeting, members and temporary members of the
7 subcommittee have been screened for potential
8 financial conflicts of interests of their own as
9 well as those imputed to them, including those of
10 spouses or minor children, and for purposes of
11 18 U.S.C. Section 208, their employers. These
12 interests may include investments, consulting,
13 expert witness testimony, contracts, grants,
14 CRADAs, teaching, speaking, writing, patents and
15 royalties, and primary employment.

16 Today's agenda involves discussion related
17 to pediatric development plans for four products
18 that were either recently approved by FDA, are in
19 late-stage development for an adult oncology
20 indication, or in late-stage development in
21 pediatric patients with cancer. The subcommittee
22 will consider and discuss issues relating to the

1 development of each product for pediatric use and
2 provide guidance to facilitate the formulation of
3 written requests for pediatric studies, if
4 appropriate.

5 The product under consideration for this
6 session is vismodegib sponsored by Genentech, a
7 subsidiary of Roche. This is a particular matters
8 meeting during which specific matters related to
9 vismodegib will be discussed. The subcommittee
10 will not be voting.

11 Based on the agenda and all financial
12 interests reported by the subcommittee members and
13 temporary members, no conflict of interest waivers
14 have been issued in connection with this session.

15 To ensure transparency, we encourage all
16 standing subcommittee members and temporary members
17 to disclose any public statements that they may
18 have made concerning the product at issue.

19 With respect to FDA's invited acting
20 industry representative, we would like to disclose
21 that Dr. Gregory Curt is participating in this
22 meeting as a nonvoting industry representative,

1 acting on behalf of regulated industry. Dr. Curt's
2 role at this meeting is to represent industry in
3 general and not any particular company. Dr. Curt
4 is employed by AstraZeneca.

5 We would like to remind members and
6 temporary members that if the discussions involve
7 any other products or firms not already on the
8 agenda for which an FDA participant has a personal
9 or imputed financial interest, the participants
10 need to exclude themselves from such involvement,
11 and their exclusion will be noted for the record.

12 FDA encourages all other participants to
13 advise the subcommittee of any financial
14 relationships that they may have with the firm at
15 issue. Thank you.

16 **Introduction of New Participants**

17 DR. BALIS: Thank you. And we'll welcome
18 back Drs. Arndt and Mascarenhas from their COI
19 exile. Back to the table.

20 For the record, both the Food and Drug
21 Administration and the public believe in a
22 transparent process for information gathering and

1 decision-making. To ensure such transparency at
2 the advisory committee meeting, FDA believes that
3 it's important to understand the context of an
4 individual's presentation.

5 For this reason, FDA encourages all
6 participants, including the sponsor's non-employee
7 presenters, to advise the committee of any
8 financial relationships that they may have with the
9 firm at issue, such as consulting fees, travel
10 expenses, honoraria and interest in the sponsor,
11 including equity interest and those based upon the
12 outcome of the meeting.

13 Likewise, the FDA encourages you at the
14 beginning of your presentation to advise the
15 committee if you do not have any financial
16 relationships. If you choose not to address this
17 issue of financial relationships at the beginning
18 of your presentation, it will not preclude you from
19 speaking.

20 We'll now proceed with the sponsor's
21 presentation. And, Dr. Low, can you introduce
22 yourself, too? Thank you.

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Industry Presentation - Jennifer Low

DR. LOW: I will. On behalf of Genentech, I'd like to thank the FDA and the pediatric subcommittee of the ODAC for inviting us to discuss the pediatric development plan for vismodegib, a hedgehog pathway inhibitor. My name is Jennifer Low, and I'm the global development leader for vismodegib.

In our presentation today, I will be describing the mechanism of action of vismodegib and our key clinical findings in adult patients. I will then discuss pediatric development of vismodegib in medulloblastoma, including why we believe a diagnostic test is necessary and the potential safety concerns unique to children. I will conclude by outlining the key opportunities and challenges we anticipate in developing vismodegib for children.

The hedgehog signaling pathway is critical for embryonic development. Intact signaling is required for migration and differentiation of midline structures, such as the developing neural

1 tube, the brain, and the face. In the figure on
2 the left, in the absence of hedgehog ligand, the
3 patched receptor suppresses signaling of
4 Smoothened. However, when the hedgehog ligand is
5 present, such as in the figure on the right, it
6 binds to patch, and this relieves the suppression.
7 Smoothened is allowed to signal, leading to
8 downstream activation of transcription factors,
9 such as GLI1.

10 For hedgehog pathway, mutation driven
11 tumors, such as basal cell carcinoma and
12 medulloblastoma, abnormal activation of the
13 hedgehog pathways -- primarily through either a
14 loss of the tumor suppressor patched or more rarely
15 through an activating mutation in Smoothened. The
16 small molecule inhibitor, vismodegib, binds to and
17 inhibits the Smoothened receptor, thereby
18 inhibiting hedgehog signaling.

19 This inhibition occurs whether the hedgehog
20 pathway is activated due to hedgehog ligand
21 overexpression, as shown on the left, from loss of
22 function patch mutation, shown in the middle, or

1 from activating Smoothed mutations.

2 We believe that there are two major
3 mechanisms by which abnormal hedgehog signaling is
4 involved in cancer. In the mutation-associated
5 model, the signaling is continuously activated
6 within the tumor cell. This is the mechanism for
7 almost all basal cell carcinomas and in a minority
8 of medulloblastomas.

9 The second model on the right we have called
10 the paracrine signaling model. In this model, the
11 tumor secretes hedgehog ligand which acts in a
12 paracrine manner on neighboring stromal
13 myofibroblasts, shown in blue. These stroma cells
14 in turn secrete growth and proangiogenic factors
15 which support the tumor cell microenvironment. We
16 believe that this is the mechanism of action for
17 most tumor types, including cancer stem cells.

18 Now I will move on to our clinical
19 development program with vismodegib. Our
20 vismodegib program began in 2007 with our first
21 phase 1 study for adults in solid tumors. Since
22 then, we have completed phase 2 studies in

1 colorectal and ovarian cancer and a registrational
2 study in advanced basal cell carcinoma for which a
3 new drug application was submitted in September.

4 We also began pediatric investigations in
5 2007 with a single pediatric patient who was
6 treated without a response. However, we
7 subsequently initiated a collaboration with the NCI
8 and the Pediatric Brain Tumor Consortium. In April
9 of 2009, the PBTC began their phase 1 study in
10 pediatric medulloblastoma. Recently this year, the
11 PBTC began enrolling a phase 2 pediatric
12 medulloblastoma study. These studies are ongoing
13 and have not yet been published, so what I will
14 summarize later is the information that is publicly
15 available. Because our recently submitted NDA is
16 for a cancer affecting adults, the cancer advanced
17 basal cell carcinoma, we have requested a waiver
18 for pediatric development.

19 Now I will describe the results of our
20 clinical studies with vismodegib. In our phase 1
21 solid tumor study, we saw early activity in our
22 patients with locally advanced and metastatic basal

1 cell carcinoma and enrolled an expanded cohort of
2 advanced BCC patients. Vismodegib demonstrated
3 activity in patients with both locally advanced and
4 metastatic BCC as seen in these pre- and post-
5 treatment pictures, with an overall response rate
6 of 58 percent and a median duration of response of
7 over 12.8 months. These promising observations
8 prompted the design of a confirmatory pivotal phase
9 2 study in advanced basal cell carcinoma.

10 The primary endpoint of the pivotal phase 2
11 study in metastatic and locally advanced BCC
12 patients was objective response rate as measured by
13 independent review. These waterfall plots
14 demonstrate the independent review assessment of
15 best response in the metastatic and locally
16 advanced patients in which the vast majority of
17 patients have had some tumor shrinkage.

18 The most common adverse events seen in the
19 pivotal study were muscle spasms, the loss of head
20 and body hair or alopecia, changes in the
21 perception of taste or dysgeusia, weight loss and
22 fatigue. Only a small minority of these adverse

1 events were considered severe. We believe these
2 adverse events are related to the mechanism of
3 action of hedgehog pathway suppression, and we
4 believe these are also relevant to long-term
5 treatment in children.

6 Hedgehog activation is thought to be
7 involved in a large number of malignancies. In
8 contrast to the experience we have had with a
9 mutation-driven disease of advanced basal cell
10 carcinoma, we have not seen similar activity in the
11 paracrine-driven diseases of colorectal and ovarian
12 cancer as shown on the graphs on the left. In both
13 of these randomized placebo-controlled studies,
14 despite the compelling preclinical data, there was
15 insufficient activity in these clinical trials to
16 move forward with further development.

17 There are a number of other phase 1 and
18 phase 2 studies ongoing with vismodegib in other
19 indications, primarily through our collaboration
20 with NCI-CTEP. Although there is literature to
21 suggest these and other tumor types, such as
22 rhabdomyosarcoma and neuroblastoma may be

1 responsive to hedgehog inhibition, the mechanism of
2 action is not through patched or Smoothened
3 mutations, and so the role of vismodegib in
4 treating these tumors remains unclear.

5 Now I'd like to turn our attention to an
6 area where we have seen activity that would be
7 relevant to pediatric patients. In our phase 1
8 dose escalation study, we enrolled a 26-year-old
9 patient who had recurrent disseminated
10 medulloblastoma, metastatic to bone and soft
11 tissues. In the upper left image, you can see that
12 the baseline PET scans shows widespread disease
13 present in the bone marrow and soft tissues, and
14 the MRI below that demonstrates matted
15 supraclavicular lymphadenopathy at the arrow.

16 On the right side in the scans taken two
17 months after the patient began treatment with
18 vismodegib, you can see that there was a remarkable
19 improvement in his tumor burden. At the same time,
20 the patient had substantial clinical improvement as
21 well with resolution of pain from 5 out of 10 to
22 zero out of 10 on a subjective pain scale. He also

1 had a return to a normal level of activity and a
2 reduction in transfusion frequency. We were able
3 to sequence his genes for patched 1, and he had a
4 loss of function mutation in his primary tumor and
5 in his metastatic disease and demonstrated up
6 regulation of the hedgehog pathway.

7 Unfortunately, his remarkable tumor
8 shrinkage was relatively short-lived. In the
9 confirmatory scan planned after the two-month
10 scans, although some lesions remained in response,
11 he was already demonstrating recurrence of tumor in
12 multiple locations. He was removed from study, and
13 after rapid progression on subsequent therapies, he
14 died approximately two months later.

15 A biopsy of a recurrent lesion was obtained
16 at progression, and a new mutation was found in
17 this Smoothed gene which prevents binding of
18 vismodegib to Smoothed, providing a mechanism for
19 drug resistance. Although we have continued to
20 evaluate other resistant tumors from patients with
21 basal cell carcinoma in our other studies, we have
22 not found a similar mutation from other biopsies.

1 Now I would like to give you an overview of
2 our thoughts on pediatric development with
3 vismodegib. I've already described the lack of
4 clinical activity that has been seen in colorectal
5 and ovarian cancer, and ongoing trials will review
6 whether activity is seen outside of the mutation-
7 driven tumors of basal cell carcinoma and
8 medulloblastoma. Therefore, the remainder of my
9 presentation will concentrate on where there is
10 evidence of activity, and in pediatrics that would
11 be medulloblastoma.

12 Medulloblastoma is the most common CNS tumor
13 in childhood, comprising 15 to 30 percent of
14 childhood CNS tumors. Approximately 500 patients
15 per year are diagnosed in the United States.
16 Frontline therapy is optimal surgical excision plus
17 adjuvant radiochemotherapy in children older than
18 three years. And children under the age of three
19 usually receive a radiation-sparing regimen to
20 reduce long-term side effects.

21 Sixty to 80 percent of patients treated in
22 this frontline setting will have long-term

1 survival. However, for the smaller proportion of
2 patients who relapse or are refractory, treatment
3 is often chemotherapy, and clinical trials with
4 investigational agents are appropriate as long-term
5 control becomes unlikely.

6 Recently, medulloblastoma has been
7 characterized by molecular phenotypes by a number
8 of different academic groups and by a number of
9 different methods. In this table, we have tried to
10 combine these clinical pathologic and genetic
11 associations into three molecular subtypes:
12 hedgehog pathway dependent, Wnt pathway dependent,
13 and all others. It is important to note that many
14 of the recently published reports have different
15 classifications, so these are generalizations
16 across the literature.

17 Approximately 15 to 30 percent of newly
18 diagnosed medulloblastoma is thought to be hedgehog
19 pathway dependent. Although desmoplastic and
20 nodular histology has been associated with hedgehog
21 pathway dependent tumors, a significant proportion
22 are other histologies, including large cell and

1 anaplastic, which also appear to be driven by the
2 hedgehog pathway.

3 In mice with patched heterozygous
4 allografted medulloblastoma tumors, vismodegib is
5 very effective. In this study, vismodegib is dosed
6 for the first 28 days, and these tumors remained in
7 durable remission. However, inhibition of the
8 hedgehog pathway in very young animals have
9 resulted in defects in growing bones and teeth as
10 demonstrated in our own toxicology studies as well
11 as in this publication by Kimura, et al., shown on
12 the left, which demonstrated that short treatment
13 periods, as little as four days, resulted in
14 permanently altered growth in these mice.

15 In the figures on the left, treatment with a
16 hedgehog pathway inhibitor leads to alterations in
17 the differentiation of chondrocytes, leading to
18 premature growth plate closure in the long bone in
19 rats.

20 Hedgehog pathway inhibitors, such as
21 cyclopamine, are also known teratogens, and, in
22 fact, cyclopamine was initially identified because

1 of the fetal malformation caused in lambs born from
2 pregnant sheep that ingested cyclopamine. Although
3 the hedgehog pathway is largely silent in adults,
4 there may be the potential for inhibition of this
5 pathway to cause serious adverse events in
6 developing children. And, thus, the benefit-risk
7 potential needs to be seriously considered in
8 pediatric studies, and specific evaluations for
9 these potential adverse events should be
10 incorporated into studies.

11 So how will we identify patients who have
12 hedgehog pathway activation in their
13 medulloblastoma? This is an area of active
14 research with multiple recent publications
15 describing how to subtype medulloblastoma on a
16 molecular basis.

17 Because of the large number of ways that the
18 hedgehog pathway can be activated, a mutation-based
19 test for the hedgehog pathway mutation is not
20 feasible. First, multiple genes are involved, and
21 there are no hot spots to concentrate on. In
22 addition, these genes may be silenced in ways that

1 don't show up in sequencing assays, such as by
2 epigenetic silencing.

3 A number of approaches have been used, such
4 as immunohistochemistry, which utilizes a set of
5 antibodies to classify medulloblastoma subtypes,
6 such as shown here on the left. However, there are
7 other methods as well, including gene expression
8 profiling and quantitative RTPCR to try to
9 characterize these patients.

10 Although these assays appear to be highly
11 correlated with each other for hedgehog pathway
12 signaling, a clear standard assay has not yet
13 emerged. There's even more limited data around how
14 any of these assays correlates with clinical
15 activity with hedgehog pathway inhibitors, and the
16 early stage clinical trials, including those from
17 other sponsors, are using different methods to
18 identify their patients.

19 Genentech began a collaboration with
20 NCI-CTEP and the Pediatric Brain Tumor Consortium
21 in 2008 to better understand how to develop a
22 predictive diagnostic test and how to treat

1 patients with medulloblastoma, and how to best
2 evaluate children for potential toxicity specific
3 to the pediatric age group.

4 The PBTC has chosen to use a
5 immunohistochemistry-based molecular profiling
6 assay to identify patients with hedgehog pathway
7 activation in their tumors. There are now three
8 studies, a pediatric phase 1 dose-finding study,
9 two pediatric, two phase 2 studies in adults and
10 children.

11 The pediatric phase 1 study evaluated 85 and
12 170 milligrams per meter squared dosing and
13 switched to flat dosing of 150 milligrams and
14 350 milligram daily dosing. In the phase 1
15 pediatric medulloblastoma study, all dose levels
16 were tolerated. No dose limiting toxicities were
17 seen at 85 milligrams per meter squared, and single
18 unrelated DLTs were seen at other doses. No bone
19 toxicities were seen. And like what was seen in
20 the adult patients treated with vismodegib, PK
21 levels are primarily correlated with plasma,
22 alpha-1 acid glycoprotein, or AAG levels, and not

1 due to body size. Thus, the same phase 2 dose
2 recommendation has been made, 170 milligrams per
3 meter squared, which is similar to the
4 150 milligram daily dosing used in adults.

5 The Pediatric Brain Tumor Consortium is
6 currently conducting a pediatric phase 2 study in
7 patients between the ages of 3 and 21. This study
8 enrolls patients with relapsed or refractory
9 medulloblastoma with measurable disease to assess
10 efficacy by confirmed objective response.

11 Patients' tumors are tested for hedgehog pathway
12 activation by immunohistochemistry. They're
13 assigned to the appropriate cohort, hedgehog
14 pathway activated or not, based on this testing,
15 and treated with vismodegib.

16 The statistical study design is a Simon two-
17 stage minimax design. After the first 13 patients
18 in a cohort are enrolled and evaluated for
19 response, a decision is made as to whether the
20 activity merits continuing the study. If there are
21 no responses in the first 13 patients, the cohort
22 is closed. However, if there is at least one

1 response, then the enrollment will continue to a
2 total of 20 patients. We have been notified that
3 only patients with hedgehog pathway activation on
4 the IHC test are able to be enrolled on to this
5 study as the hedgehog pathway negative cohort has
6 been closed.

7 To summarize, we have a case report of
8 transient but dramatic efficacy seen in a young
9 adult with hedgehog pathway mutated medulloblastoma
10 with vismodegib. The ongoing phase 1 study is near
11 completion with initial reports of safety having
12 been established at the recommended phase 2 dose,
13 which is similar to the adult dose. Pediatric
14 phase 2 study is ongoing with vismodegib with
15 patients assigned to cohorts based on a diagnostic
16 assay, and the response rate endpoint will provide
17 an estimate of activity in this diagnostically
18 selected population.

19 The questions being posed to the ODAC are
20 areas that are challenges in pediatric
21 medulloblastoma. There is strong rationale for a
22 patient selection assay for medulloblastoma.

1 Abnormal signaling of the hedgehog pathway is only
2 thought to be implicated in approximately 15 to
3 30 percent of medulloblastoma cases. Data is
4 limited regarding the long-term effects vismodegib
5 may cause in young children, raising concern about
6 the benefit-risk assessment of evaluating this
7 investigational medicine in children.

8 Although there are already many diagnostic
9 tests being proposed to identify these patients,
10 this remains an active area of investigation.

11 Genentech feels that the hedgehog pathway has been
12 adequately characterized in the current
13 investigational assays so that the benefit-risk of
14 treating additional hedgehog pathway negative
15 patients with vismodegib is no longer appropriate.
16 However, this will mean that the negative
17 predictive value of an eventual validated assay may
18 not be robustly characterized.

19 Genentech acknowledges that further studies
20 may be appropriate if the ongoing PBTC phase 2
21 study shows compelling evidence of activity.
22 However, there appears to be a very small number of

1 patients, perhaps 30 to 60 diagnosed each year in
2 the U.S., with hedgehog driven relapsed refractory
3 medulloblastoma. This limited population should be
4 carefully utilized, which may mean using surrogate
5 endpoints such as response rate or progression-free
6 survival to determine clinical benefit. We are
7 interested in further input in this area from this
8 subcommittee.

9 Thank you for the opportunity to present our
10 data and our perspective. We look forward to
11 hearing this ODAC's recommendations on how to move
12 forward in this complex area.

13 DR. BALIS: Thank you, Dr. Low.

14 Dr. McKee, could you introduce yourself
15 since you joined the table since this morning?

16 DR. MCKEE: Hi, I'm Dr. McKee. I'm a
17 medical officer and pediatric oncologist at the
18 FDA.

19 **Clarifying Questions from Subcommittee**

20 DR. BALIS: Thank you.

21 The floor is open for questions from the
22 sponsor's presentation. Dr. Arndt.

1 DR. ARNDT: You mentioned that there were no
2 bone toxicities seen in the phase 1 pediatric
3 trial. In the context of phase 1 pediatric study,
4 could you please comment on whether these patients
5 were actually followed long enough to see bone
6 toxicities?

7 DR. LOW: I think that that's a very fair
8 question. This was a phase 1 study, and the
9 majority of patients did not have hedgehog pathway
10 activated tumors. Our understanding from the
11 information that's communicated to us by the PBTC
12 is that there's been at least one patient who's
13 been treated as long as 500 days, but the median
14 duration of treatment was approximately 55 days.
15 So the patients were assessed with MRIs to the knee
16 and dental x-rays, but the follow-up is admittedly
17 short.

18 DR. BALIS: Dr. Mascarenhas.

19 DR. MASCARENHAS: What is known about the
20 ability of this agent to penetrate the central
21 nervous system?

22 DR. LOW: So we have looked at the

1 penetration of this drug in CNS in a single patient
2 that we treated, a 9-year-old who had a catheter in
3 place, and we also have information that was
4 presented by the PBTC regarding CNS penetration.

5 The penetration at first looks relatively
6 low. It's about .3 percent, but this is also
7 comparable to the amount of free drug that is
8 available in the plasma in our patients. This drug
9 is very highly protein bound. And so we believe
10 that the free drug concentration that is
11 represented in the CSF is actually similar to the
12 free drug concentration in the plasma, and so we
13 would expect that there would be the potential for
14 activity.

15 DR. BALIS: Can you discuss a little
16 bit -- and there's some discussion in the written
17 material about the dose that was selected. I know
18 on your slide up there, you said that it was not
19 related to body surface area. Was that meant in
20 children or in adults?

21 DR. LOW: In both cases. Vismodegib is very
22 unusual in its PK in that it is highly bound to AAG

1 and also binds to a certain degree to albumin and,
2 in fact, saturates binding of AAG. And so the drug
3 concentrations are very much dictated by the levels
4 of AAG in the patient, regardless of whether it's a
5 child or adult.

6 I'm going to have my colleague Dr. Graham
7 answer in a little more detail for you.

8 DR. GRAHAM: Good morning, Richard Graham,
9 clinical pharmacology. If I could just have backup
10 slide T-1 to further illustrate the point, I think
11 it will be pretty clear in that case.

12 So what we're looking at here on the
13 left-hand panel is total concentration of
14 vismodegib versus AAG concentration, and this is in
15 adult patients. Now, you can see there's a
16 remarkable correlation between vismodegib in plasma
17 and AAG in plasma, and this explains about
18 75 percent of the variability in PK. So this is
19 different than most drugs that are based on body
20 surface area where body surface area can explain
21 variability in PK.

22 Now, the panel on the right is the similar

1 relationship between vismodegib and AAG, but this
2 is from the PBTC study. And you can see here as
3 well that that similar correlation exists.

4 DR. BALIS: So were you proposing in the
5 written material that you dose children at a fixed
6 dose or at that 170 milligram per meter squared
7 dose?

8 DR. LOW: We recommend the fixed dose, and
9 that is the dose that's being used in the phase 2
10 studies by the PBTC.

11 DR. BALIS: So I guess the question I have
12 is that drug exposure, granted protein bindings can
13 have some impact on that, is really going to be
14 determined by the clearance of the drug in the end.
15 Obviously, it's slow in this case because you have
16 a very prolonged half-life. But excretory organ
17 size is related to age and body size. And so
18 giving the same dose to a 1- or 2-year-old is not
19 going to give you, I don't believe, the same levels
20 as giving it to an adult. At least we don't have
21 any precedence for that being the case.

22 So how young a group of children have you

1 treated with this fixed dose, and what's been the
2 outcome?

3 DR. LOW: The youngest age is three. The
4 age ranges for this study was 3 to 21, and there
5 were younger children enrolled.

6 DR. BALIS: And they were treated at the
7 fixed dose or at the --

8 DR. LOW: Yes, they were.

9 DR. BALIS: Dr. Sekeres.

10 DR. SEKERES: Thank you, Dr. Balis.

11 Could you present some of the preclinical
12 data in animals that has raised some concerns about
13 the developmental effect on children?

14 DR. LOW: Can we bring back up slide 18,
15 please? So the studies that have been done
16 previously with vismodegib include an embryo-fetal
17 study, which is a teratology study, as well as
18 routine clinical toxicology studies, animal studies
19 that are similar to -- that complete our package.

20 This did include some juvenile animals, and
21 some of the adverse events that we saw in these
22 animals are similar. We've been able to see all

1 the on-target toxicities in animals that have been
2 recapitulated in humans in our adult studies.

3 For pediatrics, there are two areas where we
4 believe that there is the potential for defects
5 that we've only seen in animal studies but have not
6 been seen in the adult patients that we've treated.
7 And that is the changes to the growth plate by the
8 maturation of chondrocytes, which could result in
9 premature growth plate closure or fusion of the
10 bones so that they no longer extend in length and
11 could potentially result in short stature. And
12 then the other notable finding was in developing
13 teeth. And in rodents, there are some continuously
14 developing incisors, and those became deformed in
15 shape. And so we believe that the same potential
16 exists for developing teeth in children.

17 DR. SEKERES: Thank you.

18 DR. BALIS: Dr. Reaman.

19 DR. REAMAN: Thanks.

20 Can you just clarify, were those
21 developmental abnormalities seen in the embryo
22 studies or in the juvenile animal studies, or both?

1 DR. LOW: These were seen primarily in the
2 juvenile animal studies and also in adult animal
3 studies because of the way the rodents -- they have
4 continually developing teeth, and their growth
5 plates don't actually close until much, much later
6 in life. The embryo fetal study showed other
7 substantial abnormalities with midline defects.

8 DR. BALIS: Dr. McKee.

9 DR. MCKEE: This is regarding the PBTC 032
10 study. You said that the hedgehog pathway negative
11 arm had been closed, and I just wanted to clarify
12 if you can tell us, is that due to safety reasons
13 or due to lack of efficacy?

14 DR. LOW: We've been told it's due to lack
15 of efficacy. We have not been told of any safety
16 issues.

17 DR. BALIS: Dr. Sekeres.

18 DR. SEKERES: Just to follow up on that
19 study, how is hedgehog positivity being determined
20 in that study, and has the method by which it's
21 been determined been validated?

22 DR. LOW: So the method being used by the

1 PBTC is an assay that originated out of St. Jude's
2 Children's Hospital, and one of the papers that I
3 showed you -- that would be slide 19 -- this is the
4 Ellison publication in Acta Neuropathology. That
5 describes actually the assay that is being used.
6 It's an immunohistochemistry assay based on four
7 antibodies. It has not been validated in the sense
8 that it has -- that the clinical studies are still
9 ongoing. However, it has been validated against
10 other internal assays with regard to hedgehog
11 pathway activation, including sequenced tumors from
12 their tumor banks.

13 DR. SEKERES: And do you have a sense about
14 its test characteristics?

15 DR. LOW: I've heard that they're very good.
16 They're very, very highly correlated, but I can't
17 give you those numbers.

18 DR. BALIS: Dr. Smith, go ahead.

19 DR. SMITH: Could you comment on how you
20 might propose to detect the hedgehog pathway
21 alterations that are downstream from Smoothed
22 that patients wouldn't be predicted to benefit from

1 use of a Smoothened inhibitor?

2 DR. LOW: I think that that is an excellent
3 point and one of the limitations to the diagnostic
4 assays that are currently in use right now. Our
5 molecule hits and activates Smoothened, which is
6 upstream of some of the molecules that are known to
7 be activated in medulloblastoma, including SUFU,
8 for example. There have been SUFU mutations
9 described for medulloblastoma, which will led to
10 hedgehog pathway activation.

11 We believe that over half of
12 patients -- approximately half of patients with
13 hedgehog pathway activated medulloblastoma would
14 have their -- that the defects would be in patched
15 and not downstream. But identifying which patients
16 those are will be challenging with the current
17 diagnostic assays.

18 DR. BALIS: Can I get back to the
19 pharmacology because, to me, it's a very unusual
20 way of dosing the drug? To follow up with the
21 slides that you showed, what's the correlation
22 between free drug concentration and protein levels?

1 Is it the reciprocal of what we see there, meaning
2 are free drug concentrations higher when the AAG
3 level is lower?

4 DR. LOW: The free drug levels are related
5 to the total drug levels when the drug has
6 saturated AAG. And so prior to saturation of AAG,
7 there is a slightly lower proportion of drug that
8 is free. But once AAG is saturated, which is why
9 the dosing regimen that we have described is
10 essential, then the free drug level does increase
11 by about threefold and is maintained, and is
12 proportional to the total drug levels. And we have
13 described this in adult patients in a number of
14 clinical pharmacology studies, and the data that we
15 have from the PBTC on the pediatric patients
16 confirms and is entirely consistent with us.

17 So I appreciate it. It's a very unusual
18 pharmacology and an unusual way of dosing. I would
19 also point out that the PBTC has chosen to dose at
20 both 150 and 300 milligrams, but the adult dose is
21 150 milligrams per day.

22 DR. BALIS: Have you looked at relationships

1 between free drug concentration and pharmacodynamic
2 effects, particularly toxicity?

3 DR. LOW: Yes. We have looked for
4 pharmacodynamic effects in association with
5 efficacy, and what we do know is that in efficacy,
6 based on animal models and our PD markers, there is
7 a very sharp on-off switch in the way that
8 Smoothened reacts to vismodegib. And so it seems
9 to be an all or none phenomenon in terms of being
10 able to block Smoothened.

11 In terms of safety, we have looked at free
12 drugs versus safety from our adult patients, and
13 there's been no correlation for the on target
14 effects that we have evaluated, which are the most
15 common effects, which would be the taste changes,
16 the muscle cramping and the fatigue and weight
17 loss.

18 DR. GRAHAM: Can I have backup slide T-4,
19 please? And I think this may address your
20 question, Dr. Balis, because the pharmacokinetics
21 of vismodegib are nonlinear. This has a lot to do
22 with why we're proposing the same fixed dose at

1 150 milligram per day to children as we do in
2 adults.

3 The Y axis on this figure shows unbound
4 concentration of vismodegib, and the X axis
5 represents different dosing schedules. So we
6 tested three dosing schedules in a clinical study
7 in adult patients, daily dosing, three-times-per-
8 week dosing, and once-weekly dosing.

9 It's a bit difficult to see. I guess on the
10 projection you can see the horizontal gray line.
11 This horizontal gray line is our predicted
12 efficacious exposure. Now, Dr. Low mentioned that
13 in animals, there's a very narrow concentration
14 range that if you drop below, it's an on-off switch
15 for efficacy.

16 You can see that with three-times-per-week
17 dosing and once-weekly dosing, unbound plasma
18 concentrations are starting to come near that
19 efficacious exposure, whereas with daily dosing, in
20 each patient in this study, the concentrations were
21 above that threshold, although not folds above that
22 threshold. So at least in adult patients, this is

1 why we believe 150 milligram daily dosing is
2 important to maintain efficacious concentrations.
3 And that also has to do with saturation of AAG. We
4 talked a little about that binding protein. It's
5 very important for the daily dose to saturate AAG
6 to keep these unbound levels where they are.

7 DR. BALIS: I'm sorry. But do you have a
8 graph or another relationship between age
9 and -- you mention in the paper qualitatively the
10 relationship between age and AAG levels. There's
11 some mention that it's higher in younger children,
12 but I didn't get a sense quantitatively how much
13 that was.

14 DR. GRAHAM: Could we pull up backup
15 slide 3, please? So your question, just so I
16 understand, is AAG levels in young children
17 relative to AAG levels in adults?

18 DR. BALIS: Yes.

19 DR. GRAHAM: Okay. So this has been
20 published in a few papers that are listed here at
21 the bottom, and the key point on this slide is that
22 in infants, ages 2 to 12 months, AAG levels are

1 lower than in adult patients, in adults. However,
2 from age 1 year onward, they stabilize. These
3 levels are consistent with levels in adults. And
4 in the PBTC study, the youngest patient treated was
5 three years of age.

6 DR. BALIS: Thank you.

7 Any other questions for the sponsor?

8 Dr. Mascarenhas?

9 DR. MASCARENHAS: Is there any effect of
10 vismodegib on GLI, which is downstream?

11 DR. LOW: Yes, for tumors that are activated
12 with hedgehog signaling when they are treated with
13 our hedgehog pathway inhibitor, GLI levels do go
14 down.

15 DR. BALIS: Dr. McKee.

16 DR. MCKEE: So some of your questions are
17 related to this, which is why I'm going to ask
18 this. So if you go forward, if you find efficacy
19 in your phase 2 trial in medulloblastoma and you go
20 forward with another trial, would you use the same
21 IHC assay that you're currently using in the
22 phase 2 trial to identify patients who are hedgehog

1 pathway positive?

2 DR. LOW: Right now we have our active
3 collaboration with the Pediatric Brain Tumor
4 Consortium and St. Jude's, but we're also aware
5 that there are a number of other assays being
6 developed both by that group and by other groups.
7 And there have been other published assays.

8 We feel right now that this is still a
9 rapidly evolving area and that there are -- there's
10 certainly the potential for new assays that may be
11 considered more robust to be coming out. Some of
12 these publications that I've presented to you have
13 only been presented this year.

14 So I think that as these data mature and as
15 the research moves forward on an assay to identify
16 hedgehog pathway activated tumors, that we would
17 like to reassess and figure out which would be the
18 most appropriate assay to move forward with.

19 DR. BALIS: Dr. Arndt.

20 DR. ARNDT: Is there any data on combining
21 chemotherapy with this agent?

22 DR. LOW: We have a phase 2 study. This was

1 a study run in first-line metastatic colorectal
2 cancer in which this drug was combined with FOLFOX
3 or FOLFIRI with Avastin. So we do have the safety
4 profile associated with that. And there were no
5 obvious new toxicities identified with the
6 combination. We did see the toxicities that we
7 normally see with vismodegib.

8 So we have data from that study, and as
9 well, there are a number of ongoing NCI-CTEP-
10 sponsored studies, including a small cell lung
11 cancer study and other studies that combine with
12 other chemotherapies. So far, there has not been
13 any evidence of a drug-drug interaction.

14 DR. ARNDT: So it doesn't increase the
15 toxicity of the chemotherapy-like agents?

16 DR. LOW: I think that our experience has
17 been relatively limited, but at this point, we
18 don't have any evidence that it increases the
19 toxicity of other chemotherapeutics.

20 DR. BALIS: Dr. Tassinari.

21 DR. TASSINARI: Yes. In your phase 2 trial
22 that's ongoing right now, how are the potential for

1 toxicities being monitored, particularly for bone,
2 and how long do you intend to follow these
3 patients, and again particularly for the
4 pre-pubertal children?

5 DR. LOW: I would like to clarify that the
6 study that I'm referring to is being run by the
7 Pediatric Brain Tumor Consortium under the
8 sponsorship of the NCI, and so we consider them
9 collaborators, but we don't have access to the
10 degree of information that I do for our sponsored
11 studies.

12 My understanding for the Pediatric Brain
13 Tumor Consortium study is that MRIs are conducted
14 of the knee, specifically to look at growth plate
15 abnormalities, and they're conducted approximately
16 every three months.

17 DR. TASSINARI: And for how long, do you
18 know, are they going to be followed?

19 DR. LOW: My understanding is that they're
20 followed until disease progression.

21 DR. BALIS: Dr. Sekeres.

22 DR. SEKERES: Thank you.

1 You present a case report of a patient who
2 had a transient response with metastatic
3 medulloblastoma. Do you have any sense of the
4 durability of responses in patients with
5 medulloblastoma?

6 DR. LOW: So, unfortunately, in the case of
7 that particular patient, he was very heavily
8 pretreated, including autologous stem cell
9 transplant, multiple chemotherapeutic regimens, and
10 radiation. And so we suspect that -- and as you
11 can see from the scan, he had a very heavy burden
12 of disease going into our trial. We suspect that
13 he had -- because of all these DNA-damaging agents
14 that he's had in the past, that he was more likely
15 to have mutations that could induce resistance,
16 and, therefore, our study did bring out the
17 recurrent tumor, the resistant tumors that were
18 resistant to our drug.

19 We only have that experience, but the PBTC
20 has told us that they have at least one patient who
21 has been reported to have a very remarkable
22 clinical benefit and was on study for 500 days.

1 And so we don't believe that this would necessarily
2 be particular to medulloblastoma, in terms of rapid
3 resistance, but we recognize right now that that is
4 an issue that we don't have enough information on.

5 DR. BALIS: Dr. Seibel.

6 DR. SEIBEL: You mentioned some of the
7 development of newer assays, particularly that may
8 be more robust. Do they have to be done on fresh
9 and frozen tissue, or can -- I know the assay that
10 you're doing now, or that they're doing now, is
11 immunohistochemistry. So with getting tissue, it
12 could be a challenge, depending.

13 DR. LOW: I agree. I am not clear on the
14 details necessarily of all of the other assays that
15 are currently in development, but obviously,
16 something that could be done on fixed tissue would
17 be preferable.

18 DR. BALIS: Dr. Smith.

19 DR. SMITH: One of the papers, we had
20 mentioned the kind of future clinical trials'
21 design and single-arm studies as an option. Have
22 you had internal discussions about the type of

1 study, and if there were a single-arm study, have
2 you had discussions of what that might be in the
3 pediatric population?

4 DR. LOW: Actually, we haven't. We are
5 still awaiting the results of the ongoing phase 2
6 study before we make other decisions about how to
7 move forward here. However, we'd love to have your
8 feedback on what would make sense.

9 **Questions to the Subcommittee and Discussion**

10 DR. BALIS: Okay. There were no registrants
11 for the open public hearing or forum, so we'll
12 proceed on to the questions.

13 Dr. McKee, would you read these for us,
14 please?

15 DR. MCKEE: So question number 1, given the
16 potential for increased development-related
17 toxicity in children and the lack of scientific
18 rationale for testing vismodegib in pediatric
19 patients without activated hedgehog pathway
20 medulloblastoma, does the committee have concerns
21 if the negative predictive value of a diagnostic
22 assay is not tested in hedgehog diagnostic negative

1 patients?

2 DR. BALIS: Any comments about that? That's
3 kind of a double negative question. I have to sit
4 here and read it three times to figure out what's
5 being asked.

6 Dr. Shurin.

7 DR. SHURIN: I think in general with the
8 targeted therapy, you ought to be having some idea
9 of whether you've got a target. So I would say
10 that I do have concerns looking at this double
11 negative question, but I do have concerns about not
12 testing for that.

13 DR. BALIS: Dr. Smith.

14 DR. SMITH: Yes. My concern would be that
15 if you're concerned about the diagnostic negative
16 patients, you're exposing them to this agent that
17 could have adverse effects in that young
18 population. So I'm less concerned about the
19 diagnostic negative patients and that focusing on
20 trying to make an assay that is as valid as
21 possible at detecting true mutated or hedgehog
22 pathway activated cases, and focusing on the

1 patients that are positive for that assay, and
2 avoiding exposing children who are diagnostic
3 negative to the potential adverse effects of the
4 agent would be my preference.

5 DR. BALIS: Dr. Sekeres.

6 DR. SEKERES: I'm going to be an
7 epidemiologic purist and say I think you have to
8 test it in both populations to get the true test
9 characteristics and develop a true sensitivity and
10 specificity and negative and predictive value
11 within subpopulations.

12 DR. BALIS: I think the other perspective to
13 take on that is that, initially, if this is a proof
14 of principle study to determine that it's active,
15 one way to approach it is to do it in a population
16 most likely to respond. And I think you can
17 address the issues about whether it has any
18 potential efficacy in the negative population after
19 you've demonstrated it's active in those that are
20 most likely to respond.

21 Dr. Smith.

22 DR. SMITH: But the PBTC study has looked at

1 13 patients who were diagnostic negative, and they
2 did not respond. And so that stratum has been
3 stopped. So they did that in these 13 patients. I
4 guess the question would be whether more than that
5 is needed.

6 DR. SEKERES: I'm sorry. But I think the
7 question is about the assay, not about treating
8 hedgehog negative patients, so testing the assay on
9 negative patients.

10 DR. SMITH: I would assume the issue is
11 treating patients who test negative with the agent
12 to show that the agent is, in fact, truly,
13 ineffective in test-negative patients is the
14 question.

15 DR. BALIS: If you read it again -- I sat
16 here and read it two or three times.

17 [Laughter.]

18 DR. BALIS: It says would we be concerned if
19 the negative predictive value of the diagnostic
20 assay was not tested in diagnostic-negative
21 patients. That's why I interpret it also that if
22 you don't treat that population, is that okay.

1 DR. SEKERES: I guess we could always ask
2 the person who wrote the question what it means.

3 DR. MCKEE: So the way you are interpreting
4 it is appropriate. I believe the intent of the
5 question is, would the committee agree that with
6 the evidence at hand, that not further treating
7 patients who are hedgehog negative in
8 medulloblastoma, appropriate in the context of
9 development of an assay for identifying these
10 patients?

11 So we do have examples in oncology
12 where -- in adult oncology where we have approved a
13 drug with an assay where it's only approved in the
14 test-positive population, and that's what this is
15 directed at in further development. Do you have to
16 further develop the assay in a test-negative
17 population if you don't think there's any efficacy
18 for the drug in the test-negative population?

19 Does that clarify it?

20 DR. BALIS: Yes. Thank you.

21 DR. SEKERES: I'm still a little confused.

22 [Laughter.]

1 DR. SEKERES: Sorry. I don't think there's
2 a need to try to continue to give this drug to kids
3 who are hedgehog negative, but the assay, I think
4 if you're going to get more of an experience than
5 13 patients to develop your test characteristics, I
6 think you do need that.

7 DR. BALIS: Yes, Dr. Gorlick?

8 DR. GORLICK: I think in these cases, also,
9 the adult trials can be informative. If there have
10 never been responses in an adult who is hedgehog
11 negative, then I think you're more compelled that
12 this isn't necessary, meaning many targeted agents
13 aren't targeted and the sort of assay doesn't
14 predict reliably. I think the adult data will be
15 informative.

16 DR. BALIS: I think we reached a consensus
17 on that, whatever it was asking.

18 Sorry, Amy. You want to go into the second
19 question?

20 DR. MCKEE: If the current Pediatric Brain
21 Tumor Consortium phase 2 study evaluating
22 vismodegib treatment shows promising tumor response

1 rates in children with medulloblastoma, does the
2 committee have comments on the most appropriate
3 primary endpoint to establish efficacy in a
4 confirmatory study? Further, does the committee
5 have comments on the appropriateness of using a
6 historical control or single-arm study?

7 DR. BALIS: I think one point of clarity
8 based on the slides that we saw that we might get
9 from Dr. Low is what the intended indication would
10 be in moving this drug forward, because I got the
11 impression from your slide that you were talking
12 about using this only in a relapsed patient
13 population.

14 Is that true, or would you consider upfront
15 therapy as well?

16 DR. LOW: I think at this point, we're open
17 to a number of different possibilities for how to
18 move forward in this indication. We understand
19 that the pathway is activated in a very small
20 minority of patients, and we've also been told that
21 the benefit may actually be better in the upfront
22 treatment setting. However, that needs to be

1 balanced, in our opinion, with the potential
2 toxicities in this patient population that is
3 largely cured of their disease. And so trying to
4 find the right balance of providing efficacy in a
5 new targeted agent in a targeted disease while
6 balancing the safety concerns that are concerned
7 with this drug, these are issues that we're
8 struggling with and would really like to understand
9 better what would be useful to the pediatric
10 community.

11 So I think that at this point we've chosen
12 the relapse refractory setting simply because we
13 felt that the benefit-risk in that patient
14 population is most appropriate, but we would
15 welcome feedback on when would be the right time to
16 move to a different setting or whether this is the
17 appropriate setting.

18 DR. BALIS: Dr. Reaman.

19 DR. REAMAN: Just ask one other question
20 about the data that you provided and from what we
21 understand, the incidence of the hedgehog activated
22 medulloblastoma is most commonly seen in younger

1 patients, infants. And yet the experience to date
2 is only with children over the age of three.

3 Are there any plans for evaluating the drug
4 in infants? And I know neuro-oncologists define
5 infants as three years of age, but to those of us
6 who aren't neuro-oncologists, what about these
7 younger children, and really infants with respect
8 to the potential for toxicity?

9 DR. LOW: I think my answer is going to be
10 very similar. It's the benefit-risk associated
11 with this molecule. Obviously, we're concerned
12 that the toxicities associated, especially around
13 bone growth, around development issues, may be much
14 more acute the younger that you go. And so this is
15 going to be a challenge to also decide what would
16 be the best time to move forward in to a younger
17 patient population, if it's appropriate.

18 But right now, again, the benefit-risk, the
19 assessment was made for the phase 2 that 3 to 21
20 would be more appropriate. And it is -- I should
21 also point out that a lot of the data around the
22 epidemiology around hedgehog pathway activated

1 tumors is also very recent, which is in the last
2 couple of years; and so part of that is also us
3 reacting to the new data that's coming out every
4 year.

5 DR. BALIS: Dr. Freedman.

6 DR. FREEDMAN: So in looking at whether a
7 randomized-control study would be practical, have
8 you looked at internationally what number of
9 patients you could get from reasonable centers,
10 centers that could do reasonable studies of this
11 drug? And also, are there any logistic issues
12 related to the testing that would be required if
13 you did such a study? In other words, the
14 availability, and where would these tests be done?

15 DR. LOW: We have talked a little bit
16 internally about the testing issue, but at this
17 point, we're concerned about how rapidly evolving
18 this field is. And it's very difficult for us to
19 commit to a test that may not be an appropriate one
20 a year from now. And so that's going to continue
21 to be a challenge with this field for probably
22 quite some time. But we would anticipate that the

1 patients would need to be centrally tested in some
2 manner.

3 In terms of the number of patients, at this
4 point the data that we have is approximately 500
5 patients with medulloblastoma in the U.S., and we
6 estimate a comparable number in the E.U., of which
7 15 to 30 percent would be considered hedgehog
8 positive. And so the numbers that I gave you,
9 about 30 to 60 patients was in the relapsed
10 refractory setting. So if you take that and
11 estimate that only 30 to 40 percent of patients
12 will relapse, then the numbers drop down very
13 dramatically.

14 DR. FREEDMAN: So you would need to extend
15 the study overseas if you wanted to do it?

16 DR. LOW: We would anticipate that that
17 would be necessary.

18 DR. BALIS: Dr. Mascarenhas.

19 DR. MASCARENHAS: I think another issue to
20 be considered is that these patients who have these
21 mutations, mainly the desmoplastic subtype,
22 actually have excellent prognosis, and many of them

1 can be cured with chemotherapy alone in the very
2 young age group. So with the addition of this
3 agent, it may be hard to show a difference unless
4 you would consider eliminating chemotherapy, and I
5 don't know how you would do that study.

6 DR. BALIS: Dr. Smith.

7 DR. SMITH: I would second that point.
8 There was just a publication from the HIT 2000
9 trial that described 19 patients less than four
10 years of age with the desmoplastic nodular variant
11 of medulloblastoma and the five-year EFS was
12 90 percent, and the five-year survival was
13 100 percent with a regimen that did not include
14 plain radiation treatment. So it's hard to take
15 that outcome for this younger group that probably
16 is primarily hedgehog pathway mutated and think
17 about exposing to an agent that we don't know the
18 toxicity profile and for which there's concern that
19 there could be permanent effects.

20 So I think the relapse population then would
21 be the population. There probably would not be
22 many patients from that age group, but there will

1 be some, and then there will be children, older
2 children, who relapse.

3 DR. BALIS: Yes, Dr. Mascarenhas.

4 DR. MASCARENHAS: However, I don't have an
5 idea of the numbers because I'm not a neuro-
6 oncologist, but the other group where this drug may
7 have efficacy is in the anaplastic large cell
8 medulloblastomas, and they're spread out across all
9 the ages. So, potentially -- and those patients,
10 even with traditional therapy, which in the over-
11 three age group who also received cranial spinal
12 radiation still have a poorer outcome. But I'm
13 unclear of the number of patients who may be
14 available for such a trial.

15 DR. BALIS: So the questions posed relate to
16 the endpoint and then the appropriateness of a
17 historical control or single-arm study. And I
18 think, obviously, the discussion about which
19 population it's going to be done in -- it frames
20 the rest of that discussion purely because of the
21 patient numbers that are available. You've already
22 done those calculations in terms of how many

1 relapse patients you'd expect to see, and I think
2 in that setting, it's going to be very difficult to
3 do anything but a single-arm study. And I think if
4 it's patients with disease that is measurable, it
5 probably makes the most sense if you have responses
6 already to look at that at least as one of the
7 primary endpoints in the trial. But, obviously,
8 other opinions here would be helpful, too.

9 [No response.]

10 DR. BALIS: I guess nobody disagrees with
11 that.

12 Yes, Dr. Smith.

13 DR. SMITH: I would agree with that. I
14 think the challenge will be the historical control
15 because -- and would make PFS harder to evaluate in
16 the relapse population because this is a population
17 that we've never studied before. It would take
18 somehow finding tissue blocks from a group of
19 patients treated in the last decade, performing the
20 hedgehog pathway activation assay on that
21 population, and then that becomes your historical
22 control. But it's not clear that that could be

1 done. As far as I know, it doesn't exist at the
2 present time for a relapse patient.

3 DR. BALIS: The other approach would be not
4 to test the control population and assume that the
5 outcome is not going to be that different.

6 Okay. So why don't we move on to the third
7 question.

8 DR. MCKEE: So this is a more general
9 question. If you could identify any other
10 pediatric cancers or subpopulation, i.e., ages or
11 degree of refractoriness to therapy that should be
12 targeted for drug development with this drug.

13 DR. BALIS: Yes, Dr. Mascarenhas?

14 DR. MASCARENHAS: I guess this is what my
15 previous question was aimed at, and I perhaps
16 didn't frame it appropriately. Would this drug
17 have any effect on GLI directly, independent of the
18 hedgehog pathway? I mean, inhibiting Smoothed I
19 mean.

20 DR. LOW: Sure. We know that there's
21 multiple ways of activating GLI, and it can be
22 through the hedgehog pathway, but there are also

1 other pathways that also signal through GLI. And
2 so we would not anticipate that our drug would be
3 able to inhibit non-hedgehog activated GLI, such as
4 with other growth factor receptors.

5 DR. MASCARENHAS: Thank you.

6 DR. BALIS: Okay. I think the issues that
7 you raise about the potential toxic effects are
8 important ones. They're extrapolated, obviously,
9 from the animal models, primarily. And I still
10 don't know personally how well animal models
11 predict for toxicity in children who develop so
12 differently than animals. I mean, animals come out
13 of the womb and are walking. They're fairly fully
14 neurologically developed, and it's not -- children
15 take much longer to develop. There's much more
16 happening with them postnatally than, for example,
17 with other animals.

18 So it's difficult to extrapolate. And we
19 just went through this with VEGF inhibitors, where
20 there was major concern raised because in mice
21 there was expansion of the growth plates in very
22 young animals. And we haven't had really a good

1 opportunity to look long term at growth, but there
2 doesn't seem to be the same concern, at least so
3 far, that we've seen in kids. And, Malcolm, maybe
4 you could address that specifically, if you know
5 more.

6 So from the perspective of somebody that's
7 done pediatric oncology a long time, every drug
8 that we use has significant late effects, and we
9 just had a session right before yours that
10 demonstrates that pretty clearly for older drugs.
11 I don't know that concern about late effects,
12 although we need to monitor them and measure them
13 and everything else, is a stop sign to develop
14 drugs in kids because we've already got that. And
15 if we can find obviously better -- it'd be best to
16 find drugs that didn't have any, but clearly we
17 need to find some that have fewer late effects than
18 the ones that we're using now, even though they may
19 be curative in a large fraction of patients. So I
20 wouldn't be afraid to try them as best you can,
21 even though we start with a relapsed population, if
22 it's really active and continuing to move it

1 forward.

2 Yes, Dr. Smith?

3 DR. SMITH: I guess I wouldn't have concerns
4 about studying this from a toxicity perspective in
5 other relapse patient populations. Moving upfront
6 would be another issue, but we start in the relapse
7 populations, and late effects, we can get some
8 signal, but it's not as great a concern.

9 My major concern, though, is that there
10 really doesn't seem to be any effect of this agent
11 that's beneficial outside of the hedgehog pathway
12 activated patient population. And I think the work
13 that was presented to us from two additional adult
14 cancers focusing on paracrine effects of hedgehog
15 signaling when the pathway wasn't activated by
16 mutation suggests that may not be a profitable way
17 to move with this agent in the pediatric setting,
18 either.

19 So I would want to see more evidence that
20 this agent actually does have some benefit or some
21 promise in another population before moving into
22 other tumor types at this point.

1 DR. BALIS: Dr. McKee, anything else you
2 want us to address?

3 All right. Well, we're ahead of schedule.
4 I don't think anybody will argue with that. We'll
5 take -- 12:45, we'll be back. And as a reminder,
6 panel members, please remember that there should be
7 no discussion of the issues at hand during lunch
8 amongst yourselves or with any member of the
9 audience. Thank you.

10 (Whereupon, at 11:41 a.m., a luncheon recess
11 was taken.)

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A F T E R N O O N S E S S I O N

(12:46 p.m.)

DR. BALIS: Welcome back, and I'd like to invite everybody to take their seats. We'll start in just a minute.

We'll proceed now with topic number 3, which is discussion of pazopanib from GlaxoSmithKline. And before we get started, Amir, would you want to introduce yourself?

DR. SHAHLAEE: I'm Amir Shahlaee. I'm a medical officer with the sarco and melanoma team at the FDA, and I'm a pediatric oncologist.

DR. BALIS: And then I'll recognize that Drs. Smith and Seibel had to leave for another meeting at the NCI, so they won't be with at this session this afternoon.

You want to go ahead with the conflict of interest statement?

Topic 3: Pazopanib - GlaxoSmithKline

Conflict of Interest Statement

DR. BRIGGS: The Food and Drug Administration, FDA, is convening today's meeting

1 of the Pediatric Oncology Subcommittee of the
2 Oncologic Drugs Advisory Committee under the
3 authority of the Federal Advisory Committee Act,
4 FACA, of 1972. With the exception of the industry
5 representative, all members and temporary members
6 of the subcommittee are special government
7 employees, SGEs, or regular federal employees from
8 other agencies and are subject to federal conflict
9 of interest laws and regulations.

10 The following information on the status of
11 this subcommittee's compliance with the federal
12 ethics and conflict of interest laws, covered by
13 but not limited to those found at 18 U.S.C.
14 Section 208 and Section 712 of the Federal Food,
15 Drug and Cosmetic Act, FD&C Act, is being provided
16 to participants in today's meeting and to the
17 public.

18 FDA has determined that members and
19 temporary members of this subcommittee are in
20 compliance with federal ethics and conflict of
21 interest laws. Under 18 U.S.C. Section 208,
22 Congress has authorized FDA to grant waivers to

1 special government employees and regular federal
2 employees who have potential financial conflicts
3 when it is determined that the agency's need for a
4 particular individual's services outweighs his or
5 her potential financial conflict of interest.

6 Under Section 712 of the FD&C Act, Congress
7 has authorized FDA to grant waivers to special
8 government employees and regular federal employees
9 with potential financial conflicts when necessary
10 to afford the subcommittee essential expertise.

11 Related to the discussion of today's
12 meeting, members and temporary members of this
13 subcommittee have been screened for potential
14 financial conflicts of interests of their own as
15 well as those imputed to them, including those of
16 their spouses or minor children, and, for purposes
17 of 18 U.S.C. Section 208, their employers. These
18 interests may include investments, consulting,
19 expert witness testimony, contracts, grants,
20 CRADAs, teaching, speaking, writing, patents and
21 royalties, and primary employment.

22 Today's agenda involves discussion related

1 to pediatric development plans for four products
2 that were either recently approved by the FDA, are
3 in late-stage development for an adult oncology
4 indication, or in late-stage development in
5 pediatric patients with cancer. The subcommittee
6 will consider and discuss issues relating to the
7 development of each product for pediatric use and
8 provide guidance to facilitate the formulation of
9 written requests for pediatric studies, if
10 appropriate.

11 The product under consideration for this
12 session is pazopanib sponsored by GlaxoSmithKline.
13 This is a particular matters meeting during which
14 specific matters relating to pazopanib will be
15 discussed. The subcommittee will not be voting.

16 Based on the agenda and all financial
17 interests reported by the subcommittee members and
18 temporary members, no conflict of interest waivers
19 have been issued in connection with this session.

20 To ensure transparency, we encourage all
21 standing subcommittee members and temporary members
22 to disclose any public statements that they may

1 have made concerning the product at issue.

2 With respect to FDA's invited acting
3 industry representative, we would like to disclose
4 that Dr. Gregory Curt is participating in this
5 meeting as a nonvoting industry representative
6 acting on behalf of regulated industry. Dr. Curt's
7 role at this meeting is to represent industry in
8 general and not any particular company. Dr. Curt
9 is employed by AstraZeneca.

10 We would like to remind members and
11 temporary members that if the discussions involve
12 any other products or firms not already on the
13 agenda for which an FDA participant has a personal
14 or imputed financial interest, the participants
15 need to exclude themselves from such involvement,
16 and their exclusion will be noted for the record.
17 FDA encourages all other participants to advise the
18 subcommittee of any financial relationships that
19 they may have with the firm at issue. Thank you.

20 **Introduction of New Participants**

21 DR. BALIS: Thank you.

22 Both the Food and Drug Administration and

1 the public believe in a transparent process for
2 information gathering and decision-making. To
3 ensure such transparency at the advisory committee
4 meeting, the FDA believes that it's important to
5 understand the context of an individual's
6 presentation. For this reason, FDA encourages all
7 participants, including the sponsor's non-employee
8 presenters, to advise the committee of any
9 financial relationship they may have with the firm
10 at issue, such as consulting fees, travel expenses,
11 honoraria, and interest in the sponsor, including
12 equity interest, and those based upon the outcome
13 of the meeting.

14 Likewise, the FDA encourages you at the
15 beginning of your presentation to advise the
16 committee if you do not have any financial
17 relationships. If you choose not to address this
18 issue of financial relationships at the beginning
19 of your presentation, it will not preclude you from
20 speaking.

21 We'll move on now to the sponsor's
22 presentation, and could you introduce yourself,

1 please, before you speak?

2 **Industry Presentation - Christopher Carpenter**

3 DR. CARPENTER: Good afternoon, I'm Chris
4 Carpenter, director in clinical development at
5 GlaxoSmithKline. On behalf of GlaxoSmithKline, I'd
6 like to thank the FDA and ODAC for the opportunity
7 to tell you about our development plans for
8 pazopanib in pediatric oncology.

9 We recognize that the ultimate goal of
10 pazopanib and all development of new drugs in
11 pediatric oncology is to increase the cure rate,
12 and that is really where we would like to head.
13 I'm going to tell you about the efficacy and safety
14 experience we have in adults, which forms the basis
15 for our pediatric development plans, the
16 preclinical studies we've done to support pediatric
17 development, our current pediatric development
18 plans, the results of our phase 1 study, which is
19 partially complete, and then finally talk to you
20 about the approach we've taken to overcoming the
21 challenges to pazopanib development in pediatric
22 oncology.

1 Pazopanib is a small molecule, oral multi
2 tyrosine inhibitor. The KIs are highest for the
3 VEGF family and PDGF family and c-kit with KIs in
4 the low nanomolar range for all of those molecules.
5 It selectively inhibits VEGF mediated endothelial
6 cell proliferation in preclinical models. It also
7 inhibits angiogenesis in in vivo assays, and
8 arrests growth of human tumor xenografts in mice,
9 again, in preclinical models.

10 This slide summarizes the key milestones in
11 pazopanib development. We began with filing the
12 IND in 2002, and the first-in-human trial began
13 shortly thereafter. I'd just like to highlight
14 when we began our pediatric development. Our
15 phase 1 trial enrolled its first patient in 2009,
16 and also relevant to our pediatric development is
17 the agreement to pediatric investigation plan we
18 came to with the European Medicines Agency at the
19 end of 2010.

20 I'd like to tell you what we've learned
21 about pazopanib in adults, and then I will tell you
22 how that applies to what we're doing in pediatrics.

1 It's administered orally at a dose of
2 800 milligrams once a day. The mean half-life is
3 approximately 31 hours. It's not extensively
4 metabolized, but the metabolism that does occur is
5 primarily mediated through CYP3A so that inducers
6 or inhibitors of CYP3A do affect the exposure to
7 pazopanib.

8 There is a correlation of higher trough
9 plasma concentrations of pazopanib with lower
10 plasma levels of soluble VEGFR-2 and higher blood
11 pressure. Both of these are on-target effects
12 indicating that if the dose's and concentration's
13 achieved, we do have target engagement.

14 We've done several types of biomarker
15 studies, both trying to understand the safety
16 population, patients who might be at increased risk
17 of therapy with pazopanib, and those that might be
18 more likely to benefit, or the efficacy group.
19 We've done both plasma studies as well as
20 pharmacogenomic studies.

21 We've found that in the safety realm that
22 polymorphisms in UGT1A1, the Gilbert's gene, are

1 associated with increases in bilirubin. These are
2 isolated increases in bilirubin, not associated
3 with increases in other ALTs and are benign. In
4 very preliminary data, we found that polymorphisms
5 in the HFE or hemochromatosis gene are associated
6 with increases in ALT, but at this point, the data
7 are too preliminary to consider using these as an
8 exclusion criterion.

9 We've also looked for biomarkers of efficacy
10 as have many investigators in the anti-angiogenesis
11 field and have not been very successful to date.

12 We have identified high plasma levels of IL-6 as
13 being partially predictive of response to pazopanib
14 as opposed to prognostic, meaning that it predicts
15 outcome, either progression-free survival or
16 overall survival regardless of therapy. But we
17 don't think that IL-6 levels can be used as a
18 exclusive biomarker because subjects with low
19 levels of IL-6 also show substantial benefit to
20 treatment with pazopanib.

21 We've also identified polymorphisms in the
22 IL-8 and HIF-1 genes as being associated with

1 outcome, progression-free survival, in the advanced
2 renal cell carcinoma population. But our control
3 population is too small to allow us to determine at
4 this point whether they might be prognostic or
5 predictive markers. We've not been able to
6 identify either prognostic nor predictive markers
7 in other tumor types, including soft tissue
8 sarcoma.

9 This slide summarizes the safety information
10 that we've learned in adults. And on the left are
11 the warnings and precautions contained in our
12 label, and I won't go through those, but I will
13 highlight the most common adverse reactions we've
14 seen in adults, and these are diarrhea,
15 hypertension, hair color changes, nausea, anorexia
16 and vomiting.

17 We've recently completed a phase 3 trial in
18 soft tissue sarcoma, and as a result of that trial,
19 we've identified three new safety signals; one,
20 myocardial dysfunction. And most of these subjects
21 had prior treatment with anthracyclines, which we
22 think may predispose to myocardial dysfunction.

1 There is a higher incidence of venous
2 thromboembolism than we've seen in previous trials,
3 and we've not previously seen pneumothoraces but
4 did in this trial.

5 I'd like to summarize for you the efficacy
6 results we've seen in two phase 3 trials, the first
7 in advance renal cell carcinoma. This trial was a
8 randomized, double-blind, placebo-controlled
9 phase 3 trial. The hazard ratio for progression-
10 free survival was .46, which was statistically
11 significant. The median progression-free survival
12 was 9.2 months for the pazopanib arm and 4.2 months
13 for the placebo arm. The hazard ratio for overall
14 survival was 0.91 but was not statistically
15 significant.

16 As I said, we've recently completed a
17 phase 3 trial, which was, again, a randomized,
18 double-blind, placebo-controlled trial in relapsed
19 or refractory soft tissue sarcoma. The results of
20 that trial are summarized on the next slide.

21 Shown here are the progression-free survival
22 curves for the pazopanib-treated arm in orange and

1 the placebo-treated arm in blue. The median
2 progression-free survival for the placebo-treated
3 arm was 1.5 months. The median progression-free
4 survival on the pazopanib was 4.6 months. The
5 hazard ratio was 0.35, favoring pazopanib and was
6 statistically significant.

7 Based on an interim analysis at which
8 77 percent of the information was available, the
9 overall survival also favors pazopanib with a
10 hazard ratio of 0.82, but it's not statistically
11 significant.

12 We studied a number of histologies in our
13 soft tissues sarcoma study, and those that were
14 included in broad categories -- and there are
15 subcategories under many of these -- are shown on
16 the top half of the slide, and I'd just like to
17 highlight a couple of them.

18 One is leiomyosarcoma, so 43 percent of the
19 patients we enrolled had leiomyosarcoma, the most
20 common soft tissue sarcoma in adults. The next
21 most common histology we enrolled was synovial
22 sarcoma, and that is the most common type of soft

1 tissue sarcoma seen outside the Ewing's and
2 rhabdomyosarcoma realm in pediatrics, so it does
3 overlap there. We also enrolled or allowed
4 patients with alveolar or pleomorphic
5 rhabdomyosarcoma to enroll. We did enroll two
6 patients with those diseases, but they were both on
7 the placebo arm.

8 For the purposes of our analysis of the
9 adult subjects, we've grouped these into three
10 groups, the leiomyosarcoma group, the synovial
11 group, and then all the other histologies have been
12 grouped into other. And it's in this other group
13 that there's most overlap with the histologies that
14 also occur in the pediatric subpopulation exists.
15 A number of histologies were excluded, and those
16 include some that are much more common in the
17 pediatric population such as osteosarcoma and
18 Ewing's sarcoma.

19 We have additional studies going on in
20 adults that I'd like to tell you a bit about. We
21 have two phase 3 studies, one a maintenance trial
22 in ovarian cancer and the second an adjuvant

1 therapy study in renal cell carcinoma. We are
2 considering a first-line study in soft tissue
3 sarcoma, which would be phase 3 study. We've
4 investigated a number of other indications in
5 adults, including non-small cell lung cancer,
6 breast cancer, cervical cancer, bladder cancer,
7 thyroid cancer, and glioblastoma multi-forming.

8 With that background in adults, our safety
9 and efficacy data in particular, I'd like to now
10 tell you what we are planning and have done in
11 pediatrics. So as I said, we have agreed to a
12 pediatric investigation plan with European
13 Medicines Agency at the end of last year. The key
14 elements of this agreement include juvenile
15 toxicity studies, development of an age appropriate
16 formulation, a phase 1 monotherapy study to assess
17 safety and determine the maximum tolerated dose, a
18 phase 2 study in relapsed or refractory soft tissue
19 sarcoma, and a phase 3 study of pazopanib versus
20 investigative choice of therapy, again, in relapsed
21 or refractory soft tissue sarcoma. And there are
22 stage gates between phase 1 and phase 2 and phase 2

1 and phase 3, based on the risk-benefit profile.

2 In addition to the requirements of our PIP,
3 we are doing additional studies. In phase 1, we
4 have two cohorts, one of which is investigating PK
5 in more detail and one which is investigating
6 pharmacodynamics. And we plan to add additional
7 strata to our phase 2 design, which I'll tell you
8 about in a minute. We have both an FDA and EMA
9 class waiver for pediatric development in renal
10 cell carcinoma.

11 As I said, we've done preclinical studies to
12 support pediatric development of pazopanib, and the
13 first set of studies are juvenile toxicity studies.
14 And we found that effects on organ development on
15 preweanling rats indicate that pazopanib has the
16 potential for similar effects on organ development
17 in young children, those less than two years of
18 age. The toxicity profile in older but still young
19 rats, those three to seven weeks of age, is similar
20 to that which we have seen in adults rats. The
21 safety issues to highlight are that we do see bone
22 and tooth effects, which are class effects, and we

1 expect that these would also be seen in children,
2 especially if they were treated for prolonged
3 periods of time, likely six months or greater.

4 We've also done preclinical efficacy
5 studies. Xenograft studies were done in
6 collaboration with the Pediatric Preclinical
7 Testing Program, and we looked at rhabdomyosarcoma
8 and Ewing's sarcoma cell lines. We looked at seven
9 cell lines in total and saw a small positive effect
10 on six of those seven cell lines. Other
11 angiogenesis inhibitors have also been studied, and
12 publications indicate that they do show activity in
13 pediatric sarcomas.

14 So we are partly through -- in fact, a large
15 part of the way through our phase 1 trial of
16 monotherapy in children with relapsed or refractory
17 solid tumors. The study is being conducted by the
18 NCI and Children's Oncology Group. The principal
19 investigator is Dr. Julia Glade Bender, and she's
20 here today and will be able to answer any questions
21 relevant to the trial.

22 Part 1 is the dose escalation part, and it's

1 completed. It used a rolling six trial design.
2 The starting dose was 60 percent of the approved
3 adult dose. Again, the adult dose is 800
4 milligrams orally once a day. The pediatric
5 starting dose was 275 milligrams per meter squared.
6 It was administered once daily in 28-day cycles.
7 Four dose levels were planned to be studied, and
8 all four dose levels were studied. Twenty-seven
9 subjects were enrolled, 23 were eligible, and 23
10 were evaluable in part 1.

11 Part 2-A is a cohort expansion designed to
12 investigate the pharmacokinetics of a 50 milligram
13 per ML powder for oral suspension solution, and
14 accrual to that cohort has also been completed,
15 although we have no results as yet. Part 2-B is
16 designed to investigate pharmacodynamics using DCE-
17 MRI in subjects with recurrent or refractory soft
18 tissue sarcoma. Accrual has also been completed to
19 this cohort, but we, as with the earlier cohort,
20 don't have results yet. Among all three cohorts,
21 53 patients in total have been enrolled in this
22 trial.

1 The maximum tolerated dose was defined as
2 usual by the occurrence of dose-limiting toxicity.
3 So as I said, all four doses levels were studied.
4 At the first dose level, six patients were
5 evaluable. One had a dose-limiting toxicity of
6 increased lipase. At the second dose level study,
7 six patients were evaluable and no DLTs were seen.
8 At what turned out to be the maximum tolerated
9 dose, 450 milligrams per meter squared, six
10 patients were evaluable. One patient had two DLTs,
11 one of hypertension and one of proteinuria. At the
12 highest dose level studied, 600 milligrams per
13 meter squared, five of the evaluated subjects
14 had -- five subjects were evaluable and two had
15 dose-limiting toxicities, one of hypertension and
16 one of increased amylase.

17 We've looked further at the toxicities, and
18 the conclusion we've come to is that the AE profile
19 in pediatrics is very similar to that which we've
20 seen in adults. The key toxicities highlighted in
21 the table are those that we anticipated based upon
22 what we knew about our adult subjects. We did see

1 increases in ALT, although most of them were
2 grade 1. We saw left ventricular dysfunction in
3 five subjects, grade 1 and grade 2. We saw
4 hypertension, as expected, as well as proteinuria,
5 also hypothyroidism. QTc interval was studied in
6 nine subjects and was not found to be prolonged.
7 There were numerous other grade 3 AEs, all of which
8 occurred in just one subject, and there was one
9 grade 4 AE, which was a decrease in the
10 neutrophils.

11 We have preliminary data on both the
12 pharmacokinetics and pharmacodynamics from the
13 pediatric phase 1 study. We can say that the half-
14 life appears to be 24 hours, approximately 24 hours
15 in the pediatric population, which is very similar
16 to the 31 hours that we see in the adult
17 population.

18 Plasma biomarkers were studied in the
19 phase 1 trial, and they indicate that there is
20 target engagement. We saw both an increase in
21 plasma VEGF and platelet-induced growth factor
22 levels and decreases in soluble VEGFR-2 and

1 endoglin levels.

2 Although not the primary aim of the study,
3 clinical activity was monitored. The median number
4 of cycles were three. The range was 1 to 17. Two
5 subjects remain on therapy. There was one partial
6 response in a subject with hepatoblastoma, and four
7 patients have had stable disease for six months or
8 more. One had alveolar small part sarcoma.
9 Another had an osteosarcoma. A third had synovial
10 sarcoma, and the fourth patient had myxopapillary
11 ependymoma.

12 Our initial focus is on monotherapy in
13 patients who have exhausted all accepted therapies,
14 and recognizing I said at the beginning that our
15 goal ultimately is cure, this is a step on the way.
16 And we think that it's important with pazopanib to
17 take a stepwise approach. And the reason for this
18 is that when we were initially developing our
19 pediatric development plans, we were obtaining the
20 results of many of our early phase 1 combination
21 therapy trials and saw a lot of toxicity requiring
22 either dose interruptions, or dose reductions, or

1 accentuation of the toxicity of the backbone
2 regimen.

3 So this raised a concern to us that although
4 we recognize children are much more tolerant of
5 cytotoxic therapy, that we still might not be able
6 to combine in children. And so we thought it was
7 prudent to start with monotherapy, show that we can
8 achieve a safe and tolerable dose that approximates
9 the adult dose, and then to move to phase 2 to
10 demonstrate that we can show efficacy, and then
11 decide whether monotherapy and/or combination
12 therapy is the way to go at that point, based on
13 additional data we hope to have from further adult
14 phase 1 combination therapy studies. We thought
15 also that these data, there were not sufficient
16 data to support frontline use of monotherapy in
17 place of effective therapy in pediatric cancers.

18 We focused on sarcoma but are studying other
19 indications as well in phase 2, which I'll show you
20 in just a moment. And this is based in part on the
21 progression-free survival improvement we've seen in
22 our trial in soft tissue sarcoma in adults but also

1 on preclinical data. We planned for our pediatric
2 studies to fulfill worldwide regulatory
3 requirements for pediatric development.

4 We've been talking with the Children's
5 Oncology Group about what the phase 2 trial design
6 will look like, and this is very likely what it
7 will be. We intend for it to be a single-arm,
8 Simon two-stage design to be conducted, again, by
9 the Children's Oncology Group with seven potential
10 strata. They are rhabdomyosarcoma, which is
11 included in the PIP; Ewing family sarcoma, again
12 included in the PIP; and non-rhabdomyosarcoma soft
13 tissue sarcomas, a large group by histology, which
14 is also included in the PIP.

15 Four strata are not included in our PIP but
16 we think are important to study, and these are
17 osteosarcoma, evaluable and measurable
18 neuroblastoma, and hepatoblastoma. The addition of
19 hepatoblastoma is based on the partial response we
20 saw in the phase 1 study.

21 Response rate in the first stage for each
22 stratum will determine whether an additional 10

1 subjects will be enrolled, and that go-no criterion
2 is one or greater responses out of 10 subjects
3 enrolled. Both response rate and progression-free
4 survival in the second stage will determine the
5 characteristics of a phase 3 trial.

6 As I'm sure you're familiar with, there are
7 challenges in pediatric development and oncology,
8 and we've seen some. Among them are the long
9 duration of trials to the limited number of
10 subjects for clinical trials, and we've found that,
11 really, it's extremely important for us to work
12 with cooperative groups to conduct our trials. And
13 that it's also important to consider study design,
14 including what endpoints might allow the most
15 efficient conduct of these trials.

16 There are safety issues that have been
17 unique to VEGF family members, and that certainly
18 includes pazopanib, that may preclude use in
19 younger children because of the effects on organ
20 development, and we think it's important to monitor
21 bone and tooth development in all children.

22 We're continuing our efforts to develop an

1 oral suspension formulation with longer in-use
2 shelf life. So we've been able to develop an oral
3 suspension formulation, but a long shelf life has
4 been a challenge, and we're still working on it.

5 We recognize that in many indications in
6 pediatrics, combination therapy is likely necessary
7 to increase the cure rate, and we plan to build on
8 our monotherapy results and what we learn
9 additionally from adults to move into combinations
10 that we think may be curative if the risk-benefit
11 ratio favors that.

12 In summary, we've completed part 1 of our
13 phase 1 trial in pediatrics and defined the MTD,
14 and showed an acceptable safety profile, which is
15 very similar to that which we've seen in adults.
16 We plan to initiate a single-arm stratified phase 2
17 study in 2012. Further pediatric development of
18 pazopanib will be guided by the results of this
19 study. And I'd like to emphasize that despite the
20 challenges that are inherent in pediatric trials
21 and those we've seen with pazopanib,
22 GlaxoSmithKline truly is committed to pediatric

1 development.

2 We'd be happy to take any questions at this
3 point.

4 **Clarifying Questions from Subcommittee**

5 DR. BALIS: Thank you.

6 Anybody want to start off with a question?
7 If not, I have a couple to get some clarification.

8 One, on your sarcoma study, you showed
9 progression-free survival curves. What about
10 response? Can you give me that --

11 DR. CARPENTER: Response --

12 DR. BALIS: That's the primary endpoint for
13 the pediatric study?

14 DR. CARPENTER: Progression-free survival
15 was the primary endpoint. Response rate was low.
16 It was 4 percent by independent review.

17 DR. BALIS: And could you describe in a
18 little bit more detail this cardio toxicity that
19 you saw, the signal you saw in adults. And, also,
20 there were four patients I think in the pediatric
21 study that had --

22 DR. CARPENTER: I'd be happy to answer for

1 adults. Then I'd like Dr. Glade Bender, if she
2 would, to answer for the pediatric population.

3 So in adults in the soft tissue sarcoma
4 trial, we saw decreases in 4/24:15 EF, and they
5 were almost all reversible, almost all associated
6 with hypertension in the adult population.

7 DR. GLADE BENDER: So first I'd like to
8 introduce myself. I'm Julia Glade Bender. I am a
9 pediatric oncologist at Columbia University in New
10 York City. I was the study chair of the phase 1
11 protocol of pazopanib through the Children's
12 Oncology Group. I do not work for GSK but did
13 accept travel expenses; but, otherwise, I have no
14 financial interests in the company.

15 So with regards to the question about
16 cardiac toxicity in the pediatric phase 1 trial, we
17 saw asymptomatic decreases in shortening fraction
18 by echo in five patients on part 1. In all
19 patients, this was reversible. And in the case of
20 all patients who did not have progression at the
21 time of the changes noted on echocardiogram, they
22 were actually rechallenged with the drug, and it

1 did not recur.

2 So, based on these results, we think that
3 the cardio toxicity is absolutely something that
4 should be monitored but not an insurmountable issue
5 with this agent.

6 DR. BALIS: Was there an association with
7 prior anthracyclines, could you tell?

8 DR. GLADE BENDER: So of those five
9 patients, I believe three of them had received
10 prior anthracyclines, but it wasn't 100 percent.

11 DR. BALIS: Dr. Mascarenhas.

12 DR. MASCARENHAS: You asked the questions I
13 wanted to, but I can actually expand a little bit.

14 In the adult soft tissue sarcoma trial, was
15 cardiac toxicity a targeted toxicity, and did you
16 collect any information in those patients?

17 DR. CARPENTER: I'm sorry. Could you repeat
18 the question?

19 DR. MASCARENHAS: In the adult soft tissue
20 sarcoma trial, was cardiac toxicity one of the
21 targeted toxicities, or do you have more
22 information on the cardiovascular side effects in

1 the adult population, their past history of
2 anthracycline exposure, et cetera?

3 DR. CARPENTER: Was it -- so it wasn't
4 initially a targeted toxicity, but once we
5 identified it, we monitored it very closely with
6 regular echocardiograms or MUGAs.

7 Then the second part of your question was?

8 DR. MASCARENHAS: Was there any correlation
9 with anthracycline exposure in --

10 DR. CARPENTER: Almost all of the subjects
11 had prior anthracycline exposure, so we can't say
12 that there was a correlation. We didn't have
13 enough subjects without prior anthracycline
14 exposure.

15 DR. MASCARENHAS: A second question, I note
16 that in your combination trials, it appears that
17 there were drug -- there were interruptions in
18 pazopanib therapy mainly due to cytopenias. Is
19 that a correct assumption, and if so, how long, in
20 general, were these interruptions?

21 DR. CARPENTER: Yes, you're right. It was
22 generally for cytopenias.

1 If we could have slide A-26 up. This is a
2 summary of our completed trials that are phase 1
3 trials in combination in adults. And, in general,
4 when we combine with cytotoxic therapy, we have
5 seen dose reductions. I can't quote for you
6 exactly how long the dose interruptions would be.
7 Often a cycle, they would skip. For example, even
8 with paclitaxel, which is fairly well tolerated,
9 they can't take day 15 of a day 1, 8 and 15
10 therapy. So there were very frequent dose
11 interruptions and dose reductions, and they could
12 be up to a cycle in length.

13 DR. BALIS: Dr. Freedman.

14 DR. FREEDMAN: There's been a finding
15 recently with bevacizumab of a very high incidence
16 of premature ovarian failure. Since there's some
17 overlap in the mechanisms here, have you got any
18 information on the effects on menstrual cycle, for
19 example, in patients who receive this drug? That's
20 my first question.

21 DR. CARPENTER: Is there interruption of the
22 menstrual cycle?

1 DR. FREEDMAN: Yes, in older, in adults.

2 DR. CARPENTER: I actually don't know that.
3 I'll ask Dr. Lini Pandite if she can provide that
4 information.

5 DR. FREEDMAN: Because, I mean, it's anti-
6 angiogenic effect, and you might expect it to
7 have --

8 DR. CARPENTER: Again, adult cancer
9 patients, often they don't menstruate, and I don't
10 know if we have any data on that.

11 DR. PANDITE: Based on the mechanism, you
12 would expect the menstrual cycle to be interrupted.
13 We don't have -- we haven't collected that data, so
14 we don't have that data.

15 DR. FREEDMAN: It'd be important because you
16 want to treat a population maybe getting into the
17 cycline, and the question will be what long-term
18 effects they might have not only on their menstrual
19 status but on fertility. So there was the one
20 question.

21 The other question is you presented data
22 that so far, your serum biomarkers have not yielded

1 anything really informative. Are you looking at
2 other markers, either in the serum or in the tumor
3 itself, that might help to identify suitable
4 biomarkers for targeting?

5 DR. CARPENTER: We are -- in soft tissue
6 sarcoma, have very small studies. We don't have a
7 lot of patients, between 40 and 60 patients who are
8 doing several biomarker studies, looking both at
9 pharmacogenomics and cytokinin angiogenic factors.
10 We're continuing to do biomarker studies in
11 advanced renal cell carcinoma and have some plans
12 for our adjuvant trial, including more broad
13 pharmacogenomic studies.

14 DR. FREEDMAN: You would expect a process to
15 be taking place within the tumor, IL-6, IL-8.
16 These are all released in the micro-environment of
17 the tumor, and these may be even more critical than
18 what's happening further away.

19 DR. CARPENTER: We agree, and in our renal
20 carcinoma studies, we're considering looking at the
21 tumor rather than at plasma levels as well, or
22 correlating the two to determine which is the

1 better marker. We agree.

2 DR. BALIS: Dr. Mascarenhas.

3 DR. MASCARENHAS: In your soft tissue
4 sarcoma patients, you said there was a 4 percent
5 objective response rate. Did you evaluate response
6 by FTG pattern in any patients? Are you collecting
7 that information?

8 DR. CARPENTER: We did, and I think
9 between -- I can't remember. It's between 40 and
10 50 patients, we've collected information on
11 response based on FTG pat, but we don't have those
12 data yet. They're still being analyzed.

13 DR. BALIS: Dr. Arndt.

14 DR. ARNDT: In your pediatric investigation
15 plan, you comment that ultimately a goal would be
16 to do a study comparing the clinical activity of
17 pazopanib to, quote, "physician's choice of
18 therapy."

19 Can you elaborate on that? That's really
20 not something that we're used to in pediatric
21 oncology.

22 DR. CARPENTER: It does happen in adult

1 trials. Because of the variety of tumor types in
2 soft tissue sarcoma and that it might be a
3 worldwide study where there are different standards
4 of care, we thought it would be important to allow
5 for different therapies to be used. For example,
6 one investigator might think that doxorubicin as a
7 single agent is the best to use, and another might
8 think ifosfamide. So where there is no standard of
9 care, we think allowing investigator choice is an
10 important component of the study design.

11 DR. ARNDT: How can -- so if you're -- would
12 you develop it then in the usual sort of 10 to 20
13 cohort patient strata? So, for example, 10
14 patients with Ewing's, 10 patients with rhabdo, 10
15 patients with osteosarcoma, or how would -- could
16 you elaborate a little bit more on that kind of a
17 study design?

18 DR. CARPENTER: Sure. So the Simon two-
19 stage, the phase 2 is a single-arm trial, so it's
20 not randomized. There is no alternative arm that
21 would be investigator choice, so that is just
22 single arm. And the decision about whether to go

1 forward to phase 3 will be based on the response
2 rate and progression-free survival rates in that
3 trial.

4 So in a phase 3 trial, it will be much
5 larger. There wouldn't be strata. And what that
6 phase 3 trial would look like, it's really too
7 early for us to speculate about. It would truly
8 depend on the results that we saw in phase 2.

9 DR. ARNDT: How would you measure the
10 responses in phase 2? Would you do simple cure
11 measurements, PET measurements? What would be your
12 endpoints?

13 DR. CARPENTER: We're planning to do resist,
14 and I don't know if Julia would like to comment
15 further than that, just by standard resist
16 criteria.

17 DR. BALIS: Dr. Mascarenhas.

18 DR. MASCARENHAS: In the adult soft tissue
19 sarcoma trial, was there any correlation in time to
20 progression based on histological grade of the
21 tumor?

22 DR. CARPENTER: No, there was not.

1 DR. MASCARENHAS: And in your planned
2 phase 2 trial, is there a reason to exclude
3 patients with Wilms' tumor?

4 DR. CARPENTER: I'll turn that one to
5 Dr. Glade Bender.

6 DR. GLADE BENDER: I think the decision to
7 not include Wilms' tumor as a strata had more to do
8 with potential competing trials for the same small
9 patient population.

10 DR. BALIS: It seems like a lot of your
11 strategy was driven by -- at least when reading the
12 report, driven by the issue of your inability to
13 safely combine this with other agents. And I think
14 Carola raised the question -- Dr. Arndt raised the
15 issue that the design that you set out was not one
16 that we're used to. And, actually, the other part
17 of it that we're not used to is we typically add on
18 and compare rather than to drop everything and
19 compare it to a standard regimen. But it seems
20 like the reason you picked that strategy was
21 because of this issue with inability to combine.

22 Do you have any idea what the mechanism of

1 that might be? Because I'm not sure that that's
2 been seen with other anti-angiogenics.

3 DR. CARPENTER: It depends on the anti-
4 angiogenic. So bevacizumab, no, they don't see it.
5 But the multikinase inhibitors do, and it's very
6 likely due to the other kinases that are inhibited.
7 In our case, probably c-kit is the major culprit.

8 DR. BALIS: Other questions?

9 Dr. Sekeres.

10 DR. SEKERES: Thank you, Dr. Balis.

11 In your adult study, how were these patients
12 previously treated, and how does that compare to
13 how pediatric patients would previously be treated
14 in a relapse refractory population?

15 DR. CARPENTER: So these were all previously
16 treated patients. It was a requirement of the
17 trial. Almost all of them had had Adriamycin. I
18 think 70 percent or so had also had ifosfamide
19 beforehand. So they were -- at least had to have
20 one prior regimen, but were allowed to have had
21 more. And then Dr. Bender can address the
22 pediatric population, the pretreatment.

1 DR. GLADE BENDER: So for soft tissue
2 sarcoma, ifosfamide and doxorubicin is very similar
3 to the way that pediatric patients would be treated
4 prior to going on a phase 2 study of this agent.

5 In terms of the phase 1 trial, children
6 generally in pediatrics have been on a multitude of
7 prior therapies. I think the range has been
8 something like 3 to 11 prior regimens; so that,
9 again, that makes you feel a little better about
10 the safety issues, that they're very heavily
11 pretreated patients.

12 DR. SEKERES: So are you saying -- are you
13 anticipating that you'll have a healthier, less
14 heavily pretreated population in moving to a
15 phase 2 setting that would be more similar to the
16 adult population?

17 DR. GLADE BENDER: Yes. I think it would be
18 very similar, if one would prioritize a phase 2
19 trial over a phase 1 trial. So I think that the
20 patients that come to the phase 2 trial will have
21 fewer regimens, but the regimens that they will
22 have received, at least for the non-rhabdo soft

1 tissue sarcoma, will be very similar to the
2 population in adults.

3 DR. BALIS: Yes, Dr. Mascarenhas.

4 DR. MASCARENHAS: Thank you.

5 Are there any preclinical in vivo data of
6 pazopanib with pediatric-type tumors?

7 DR. CARPENTER: Yes, if I could have
8 slide A-13 up. We have a little bit, and it's
9 frankly not a lot. So we did xenograft studies
10 with a pediatric preclinical testing program and
11 looked at five rhabdomyosarcoma cell lines and two
12 Ewing sarcoma cell lines. And all five of the
13 Ewing sarcoma cell lines had small but positive
14 effects favoring pazopanib, and one of the two
15 Ewing sarcoma lines did as well. But that really
16 is the extent of our preclinical data in pediatric
17 sarcoma tumors.

18 DR. GLADE BENDER: I can add there was a
19 recent publication in Neuroblastoma as well. It
20 was single agent, and it also caused delayed time
21 to progression, but modest activity in vivo.

22 DR. BALIS: Okay. Let me ask one other very

1 quick question. Two of the four dose limiting
2 toxicities on the phase 1 study were pancreatic,
3 right, lipase and amylase elevations? So I assume
4 since you listed those as dose limiting, you
5 attributed them to the drug.

6 Is this a target toxicity or one that was
7 seen fairly frequently in adults?

8 DR. GLADE BENDER: Adults, I can't answer.
9 I can just say it seems to be a class effect in
10 pediatrics as well in phase 1. A number of the
11 multi-tyrosine kinase inhibitors that we've studied
12 have had elevations in amylase and lipase, but it's
13 just a chemical finding that's been --

14 DR. BALIS: Right, they don't have clinical
15 pancreatitis.

16 DR. GLADE BENDER: Correct, completely
17 asymptomatic.

18 DR. CARPENTER: This has been seen in adults
19 as well, but it's not common.

20 **Questions to the Subcommittee and Discussion**

21 DR. BALIS: Any other questions before we
22 move on?

1 Again, there are no registrants for the open
2 public forum, so we can move on to discuss the
3 questions at hand.

4 Amir, would you read those for us?

5 DR. SHAHLAEE: So I'll start with the first
6 question. Non-rhabdomyosarcoma soft tissue
7 sarcomas comprise 4 percent of pediatric
8 malignancies and affect approximately 500 patients
9 younger than 20 years old in the United States each
10 year. Despite advances in other areas of pediatric
11 oncology, the cure rate for this subset of patients
12 has remained unchanged in more than two decades,
13 with little change in traditional chemotherapy
14 approaches.

15 Studies in these patients are usually
16 complicated by the rarity of individual subtypes of
17 non-rhabdo soft tissue sarcomas and inadequate
18 response to chemotherapy consisting of
19 anthracyclines and alkylators. Development of
20 novel approaches to treatment of non-rhabdo soft
21 tissue sarcomas is critical to improving the
22 outcomes for this patient population.

1 Does the panel consider pazopanib a viable
2 drug candidate for further study in pediatric and
3 young adult patients with non-rhabdomyosarcoma soft
4 tissue sarcomas? Please comment on potential study
5 designs.

6 Dr. Mascarenhas, you want to take the lead
7 on that?

8 DR. BALIS: Dr. Arndt, you want to go ahead?

9 DR. SHAHLAEE: Dr. Arndt?

10 DR. ARNDT: Obviously, a difficult question.
11 What I've gathered from reading the background
12 material provided, it seems that we don't really
13 expect this agent to have single agent activity.
14 So I think to have newly diagnosed potentially
15 curable patients and sort of deprive them of
16 chemotherapy, for what it's worth, would probably
17 not be an ethical thing to do.

18 What comes to mind is a more difficult
19 patient population like nonresectable tumors or
20 patients with metastatic disease who are currently
21 actually enrolled on the frontline non-rhabdo soft
22 tissue study in COG. And one way to do this might

1 be to have for that stratum of patients, that is
2 the nonresectable patients or the patients with
3 metastatic newly diagnosed disease, treated with
4 chemo plus or minus pazopanib if, in fact, we can
5 determine that combining chemotherapy with
6 pazopanib is feasible in children.

7 DR. BALIS: Dr. Mascarenhas.

8 DR. MASCARENHAS: I think, in general, the
9 non-rhabdo soft tissue sarcoma experience in
10 pediatrics seems to be similar to adults, but we
11 have not had a study which determines the natural
12 history of this disease. So to use time to
13 progression endpoint, there's very limited data to
14 suggest that now. We will probably have that data
15 with chemotherapy probably in the next couple of
16 years. So endpoints may be very hard with this
17 particular agent.

18 I didn't ask this question earlier, but,
19 potentially, integration of this drug in the group
20 of patients may be at the time of radiation therapy
21 since a large of number of these patients do get
22 radiation therapy as an adjunct for local control.

1 And the other potential area may be as maintenance
2 therapy following the completion of cytotoxic
3 chemotherapy. But I think we would need to get a
4 very good strength -- I mean, good sense of what
5 the time to progression is since this is a real
6 mixed bag of tumors.

7 The other potential as a single agent is
8 that chemotherapy is completely ineffective in
9 certain subtypes of soft tissue sarcomas, and many
10 of these patients do present with metastatic
11 disease. So there is potentially a patient
12 population where you could potentially try this as
13 a single agent without chemotherapy.

14 DR. BALIS: Dr. Sekeres.

15 DR. SEKERES: So I was going to say
16 something similar but from a different direction
17 about progression-free survival because one area
18 where you-all do have a lot of data is in an adult
19 population with sarcomas. So if you start out
20 making an assumption -- and I don't know if this is
21 biologically true, but that sarcomas in children
22 are similar to sarcomas in adults, you should be

1 seeing similar effects of the drug. Yet, we're
2 comparing apples to oranges a little bit because
3 the data we have here involve progression-free
4 survival in adults but response rates in kids.

5 So is there a way that you can -- do you
6 have any slides where we can see like to like? So
7 what were the rates of partial responses or stable
8 disease in the adult studies, so we can compare
9 what you're seeing at least initially among 53 kids
10 in the phase 1.

11 DR. CARPENTER: We can show again the slide
12 that we projected that shows the Kaplan-Meier PFS
13 curves, but we don't have data in the pediatric
14 population for sarcoma. Is that what you're
15 asking, if we --

16 DR. SEKERES: Well, it's either that or
17 asking for response rates in adults.

18 DR. CARPENTER: The response rate in adults
19 is 4 percent.

20 DR. SEKERES: So does that include stable
21 disease or --

22 DR. CARPENTER: No, no. This is confirmed

1 partial response. So that if you look at tumor
2 shrinkage, it occurred at 50 percent of patients,
3 if you were to look at a waterfall plot. I'm
4 sorry, I don't have one. There was tumor shrinkage
5 in 50 percent of the patients in the phase 3 trial,
6 but to meet the criterion of 30 percent or greater,
7 that was confirmed subsequently, only 4 percent by
8 independent review.

9 DR. SEKERES: I'm glad you made that point
10 because we could probably spend an entire afternoon
11 arguing about whether the resist criteria really
12 should apply to sarcomas or not, but that's a
13 different ODAC.

14 So in your pediatric population then, what
15 percentage of tumor shrinkage did you see?

16 DR. CARPENTER: Can we have the speaker on
17 here again? I'm having difficulty hearing you.

18 DR. SEKERES: I'm sorry. In your pediatric
19 population, what percentage of patients in the
20 phase 1 study had decrease in tumor size but didn't
21 quite make the 50 percent mark? So how comparable
22 were the responses you saw in the pediatric phase 1

1 compared to the adult phase 3?

2 DR. GLADE BENDER: So, first of all, in
3 phase 1 in pediatrics, it was a very heterogeneous
4 population. About 50 percent of the patients on
5 the phase 1 actually had brain tumors, and we do
6 not routinely -- they didn't request films for
7 central review unless we believe at the
8 investigator level that there's been at least a
9 partial response or there's been stable disease for
10 at least six months. So we don't routinely look
11 for that minor response, if you will.

12 So I can only comment on my patients whom I
13 personally treated, and I have seen shrinkage. But
14 it may not have met the criteria for partial
15 response nor may it have been the duration of six
16 months. I showed one of those slides at ASCO of a
17 patient of mine with alveolar soft part sarcoma,
18 where it was a quite remarkable response in terms
19 of number and size of too many to count pulmonary
20 metastases and also brain metastases. And there
21 was the one partial response in hepatoblastoma that
22 was confirmed.

1 DR. SEKERES: So, again, I hate to keep
2 hammering this. I'm at least struggling. I get
3 some nods around the table, so I sense other people
4 are struggling in trying to make a comparison
5 between the adults and the kids. Is there any way
6 that you can show us that the responses within
7 patients who have sarcomas, even stable disease but
8 some shrinkage of tumors, was comparable, or you
9 just don't have those data?

10 DR. GLADE BENDER: First of all, we may have
11 some of that data in the final strata of the
12 phase 1, which was a designated imaging-driven
13 strata for soft tissue sarcoma. It was a dynamic
14 contrast-enhanced imaging, and I'm presenting that
15 data in two weeks' time in San Francisco at the
16 EORTC meeting, and we certainly saw pharmacodynamic
17 changes. I haven't reviewed those films for
18 resist-type shrinkage. But that I think really is
19 the purpose of the phase 2, is to do just that, to
20 look at response or to look at tumor shrinkage in a
21 homogenous population of different tumor strata.

22 DR. SEKERES: Okay. Thanks.

1 DR. CARPENTER: I would add, too, that we
2 have looked at our response rate by the larger
3 groups that we analyzed in the adult population,
4 and we saw very rare responses in the largest
5 group, leiomyosarcoma. And most of the -- almost
6 all of the responses were in either synovial or the
7 other group, and those are the two groups that
8 overlap with the pediatric population.

9 DR. BALIS: Dr. Arndt.

10 DR. ARNDT: I was starting to think about
11 the comment that you made that some of the patients
12 had PET scans done and wondering, number one, when
13 that data might be available. And, two, in terms
14 of study design, one of the things to consider as
15 sort of a surrogate endpoint would be PET response
16 and going back to whether or not it's feasible to
17 combine this drug with chemotherapy.

18 If it were feasible, one could conceive of a
19 study design where you have a standard chemotherapy
20 and then randomized patients to receive or not
21 receive the pazopanib and monitor them by PET
22 response as a surrogate. Of course, we don't know

1 if PET response predicts ultimate outcome, but it
2 might be one way to look at things.

3 DR. CARPENTER: We hope to have the results
4 from the PET sub-study of the adult study within
5 the next few months.

6 DR. BALIS: Dr. Gorlick.

7 DR. GORLICK: So I think we've talked a bit
8 about rare sarcomas where monotherapy would be
9 appropriate. I think if you are committed to the
10 monotherapy concept, you can imagine there being
11 continuation phase beyond standard chemotherapy in
12 a sort of localized approach.

13 But I think much more relevant for that is
14 actually going ahead and testing combination
15 therapy. I accept that the agent has a fair number
16 of toxicities that we worry about combining, but
17 there's been many examples of agents like that that
18 have been tolerable in the pediatric setting, even
19 when toxicity has been sort of borderline
20 acceptable among sort of the adult population.

21 So I would encourage us going ahead and
22 doing the combination studies of the agents that

1 are relevant to sort of the histologies you're
2 interested, which seems to be include the sarcoma
3 population. You can imagine combining with
4 anthracyclines; you'd be afraid of cardio toxicity.
5 But we've combined drugs like trastuzumab with
6 anthracycline and had no problems in the pediatric
7 population.

8 So I think the approach of monotherapy makes
9 sense in adults but not to the same extent in kids.

10 DR. BALIS: Dr. Mascarenhas.

11 DR. MASCARENHAS: Is there any data about
12 radiation therapy together with this drug with
13 pazopanib?

14 DR. CARPENTER: No, we don't have any data
15 with radiation therapy and pazopanib.

16 DR. BALIS: Dr. Shurin.

17 DR. SHURIN: I would worry about giving
18 radiation with an angiogenesis inhibitor just from
19 the standpoint of the fact that so much of the
20 cytotoxicity relates to the oxygenation of the
21 tissue. And just as you're designing studies, I
22 would wonder if maybe, at least early on, you want

1 to actually avoid that, because if the tissue isn't
2 well-oxygenated, the radiation may not be as
3 effective.

4 DR. BALIS: I think the issue really here
5 that we're asking, particularly the way the
6 question was worded up there by including young
7 adults, is have we learned enough about synovial,
8 which is going to be the most common non-rhabdo
9 soft tissue sarcoma that we would enroll, as
10 opposed to leiomyosarcoma. Is there enough
11 information from the adult trials, enough of a
12 signal? You mentioned that all of the responses
13 were in that group, that we're going to learn
14 something more by doing the same study over in
15 kids.

16 That really comes down to is the data
17 extrapolatable from adults to kids. And if you
18 look upfront, the outcomes are different in younger
19 kids with synovial sarcoma than they are in adults.
20 The kids tend to do better, at least in terms of
21 survival.

22 So I'm not sure that it is, personally, at

1 least based on upfront. And if that's the case,
2 just to answer the question, I think it makes a lot
3 of sense to test this separately in that same
4 population in a pediatric age group, even though
5 you're doing the same or you've done the same in
6 adults, because the outcome could be different from
7 the studies.

8 The endpoint, I think a lot of people here
9 were struggling with using response considering the
10 way that these trials are typically designed in
11 kids sets a very high bar for response, partial
12 response rates of 25 or 30 percent typically to
13 call it positive. And I think we've demonstrated
14 over and over and over again with cytotoxic agents
15 is hopeless.

16 We haven't had a positive phase 2 study in
17 pediatrics in two decades, I would guess, even
18 though a lot of the agents we tested and called
19 negative in phase 2 trials have moved up front and
20 are being used in children, including the
21 camptothecins. So I really do think it's
22 worthwhile considering something other than a

1 resist-driven response as outcome.

2 Now, that's going to be tough because you
3 clearly don't want to do a comparative study, but I
4 think we need more sensitive ways to detect
5 activity of these drugs than using the old
6 traditional method. And I'm also not convinced
7 that these stage 2 designs that you're using are
8 the way to go in pediatrics. The primary thrust of
9 them, the way they were designed was essentially
10 for drug rejection. So the only thing that really
11 comes out of it is that you know a drug is inactive
12 and you drop it.

13 It gives you a hint that it might be active
14 if it's positive study, but you can get -- for
15 example, you can have a response rate that's below
16 your target, and you're calling that study a
17 positive study just because the way the trial's
18 designed. In pediatrics, we don't have the
19 bandwidth to study every drug that might be active.
20 We have the bandwidth to study the most active
21 drug, and we really should be focused on designs
22 that look more to finding that agent than to

1 defining a whole group of drugs that might have
2 some activity.

3 So there are a couple ways that you could
4 look at this in a little more innovative way in
5 terms of trying to move the drug forward. I think
6 Richard's point, also, about the not giving up on
7 combinations because they were too toxic in adults
8 is a good one as well.

9 Dr. Reaman.

10 DR. REAMAN: Just one other thought, and I
11 know that we've been burned historically, at least
12 in rhabdomyosarcoma, looking at upfront window
13 therapy, but is this another opportunity given the
14 fact that we haven't had many positive phase 2
15 studies in years, in large part, because the
16 patients that we enroll on phase 2 studies have
17 been very extensively pretreated.

18 So would this create a potential opportunity
19 for looking in some of these rare subtypes at an
20 upfront window and then moving forward with
21 combination therapy?

22 DR. BALIS: Yes, Dr. Mascarenhas?

1 DR. MASCARENHAS: It did cross my mind -- I
2 guess the one difference after hearing that the
3 response rate was 4 percent, it kind of discourages
4 you against the upfront window with a relatively
5 low response rate as a single agent or refractory
6 patients. And the question is, if there was a
7 correlation with histological grade, and we know
8 that low-grade tumors progress more slowly, I think
9 that would be an excellent way to really proceed.

10 The other concern is the drug -- I mean, the
11 histology, which is most relevant to pediatrics, is
12 synovial sarcoma, and that group of diseases
13 actually has the highest response rate of all non-
14 rhabdo soft tissue sarcomas to chemotherapy. And
15 that's anywhere between 35 to 55 percent. So even
16 if you picked an upper end of a response to show
17 the effect of the addition of an agent and gauge
18 response as your endpoint, it may be quite
19 difficult.

20 DR. BALIS: Dr. Gorlick.

21 DR. GORLICK: Yes. My concern with a window
22 study design wouldn't be the response rate. The

1 problem is you're dealing with an agent that's
2 toxic in the adult population. So my concern would
3 be that if you give this agent during the window
4 and you have an unexpected toxicity that precludes
5 your ability to give subsequent therapy, you can
6 put your patient at risk for not being able to sort
7 of get standard of care. I think agents that are
8 less toxic are probably more appropriate than a
9 window design than a drug like this, where it seems
10 to be a little bit more open ended.

11 DR. BALIS: Okay.

12 DR. SHAHLAEE: So just to summarize what I
13 gathered from the discussion is it seems like the
14 group agrees that there needs to be a histology
15 specific approach when it comes to soft tissue
16 sarcomas.

17 Is that fair enough, Drs. Arndt,
18 Mascarenhas, Gorlick, I think?

19 DR. MASCARENHAS: Can I qualify that?
20 Sorry. I think it depends -- but not generally.
21 It's pick the type of histology rather than
22 separate studies in each subtype.

1 DR. SHAHLAEE: So I guess what I'm getting
2 at is Dr. Bender's study, you're going to have 10
3 unspecified non-rhabdo soft tissue sarcoma that
4 potentially can get 10 that are from histologies
5 that are known to be less responsive, and all of a
6 sudden, we're going to be writing off a drug that
7 potentially may be active.

8 DR. BALIS: I think that is a good question
9 going forward. What would happen if -- is it the
10 usual zero out of 10, stops at the first stage? If
11 there were zero out of 10 who met the partial
12 response criteria, but if you have the same
13 50 percent who have a decrease in tumor size, what
14 are you going to do at that point with the
15 development? Are you going to still plan on
16 carrying it forward to look at a different endpoint
17 in a randomized study?

18 I think if you think ahead about those kinds
19 of outcomes, it kind of tells you, in an indirect
20 way, that maybe your endpoints aren't the right
21 ones to be looking at, or at least the bars you've
22 set aren't the right ones to be looking at. Think

1 about really what evidence would make you move this
2 drug forward into the next step.

3 DR. SHAHLAEE: And I guess the second
4 question I was going to pose back to the group was,
5 it seems like, again, everyone was leaning towards
6 that this may be a good add-on agent in the context
7 of an Adri-ifos backbone.

8 Is that fair to say or?

9 DR. BALIS: Dr. Gorlick. Go ahead,
10 Dr. Gorlick.

11 DR. GORLICK: So I think trying to do
12 histology specific trials within non-rhabdo soft
13 tissue sarcomas in peds is challenging just because
14 of the relative number. The agent that comes
15 forward is the one that Dr. Balis -- or the entity
16 that already comes forward is the one that
17 Dr. Balis already mentioned, which is synovial
18 sarcoma, which is the most common of that group.
19 Ifos-dox would be the typical chemotherapy for
20 synovial. Hence, looping back to, yes, that would
21 be the answer.

22 DR. BALIS: Dr. Arndt.

1 DR. ARNDT: I agree. But, again, the
2 problem is the data we've seen that suggests that
3 combining this agent with chemotherapy is a
4 challenge.

5 DR. BALIS: Dr. Sekeres.

6 DR. SEKERES: So I would follow up on that
7 by saying the data we've seen would not justify a
8 combination therapy in a phase 2 setting yet, but
9 instead would suggest not excluding the possibility
10 of combination therapy in pediatric patients but
11 looking at it in a phase 1 setting and seeing if
12 there's anything to the add-on.

13 DR. BALIS: Dr. Mascarenhas.

14 DR. MASCARENHAS: And also not ruling out
15 the possibility of continuation phase 2 therapy and
16 then looking at overall rate with this drug
17 because, potentially -- I mean, with synovial
18 sarcoma, if they respond, they don't progress that
19 early. But, potentially, you could throw this drug
20 out if you find out that it's actually too toxic to
21 be given in chemotherapy but may actually have an
22 effect, because I think some further thought to

1 clinical trial design with this agent and
2 good -- or developing another surrogate to allow
3 continuation therapy may be worth --

4 DR. BALIS: Yes, Dr. Arndt.

5 DR. ARNDT: In synovial sarcoma, though, the
6 response rates aren't that great, either. They're
7 about 30 percent. So -- yes, with conventional
8 therapy, dox-ifos.

9 DR. BALIS: Yes, Dr. Sekeres.

10 DR. SEKERES: That actually begs the
11 question I alluded to earlier, is looking at
12 response rate even really valid in this tumor
13 subtype, or should the company be generating data
14 on progression-free survival and maybe have a link
15 to the data you alluded to earlier about PFS in
16 chemotherapy approaches, or cytotoxic chemotherapy
17 approaches.

18 DR. BALIS: Okay. Do you want to go on to
19 the second question?

20 DR. SHAHLAEE: Thank you. Rhabdomyosarcoma
21 is the most common soft tissue sarcoma in children
22 and adolescents, affecting nearly 350 patients in

1 the U.S. annually. Although cure rates for most
2 subtypes for rhabdomyosarcoma have drastically
3 improved with multimodal therapy, patients who
4 relapse at metastatic disease continue to fare
5 poorly, despite attempts at treatment
6 intensification with cytotoxic chemotherapy.

7 Upfront window approaches for testing new
8 agents in rhabdomyosarcoma have in the past helped
9 identify active agents and agent combinations.
10 This approach, however, has not led to any
11 improvements in survival rates of patients with
12 high-risk disease. Novel therapeutic approaches
13 with targeted agents may offer an alternative
14 approach worthy of further exploration in this
15 patient population.

16 Does the panel consider pazopanib a viable
17 drug candidate for further study in pediatric and
18 young adult patients with rhabdomyosarcoma? Please
19 comment on potential study designs.

20 DR. BALIS: Okay. So this is a similar
21 question to the one we looked at, although I think,
22 obviously, we don't have adult data to extrapolate

1 downward here. We're looking at a disease that
2 we're not going to be able to base on. And short
3 of having phase 2 data, which is obviously not
4 available yet, the only thing we're left with is
5 what happened on the phase 1 trial, and whether
6 there were patients and what happened to them.

7 Julie, do we have an answer to -- do you
8 know -- have data from the phase 1 study regarding
9 the patients with rhabdo?

10 DR. GLADE BENDER: So on part 1 of the
11 study, there were no rhabdomyosarcoma patients
12 enrolled.

13 DR. BALIS: Okay.

14 Dr. Neville. I'm sorry.

15 DR. NEVILLE: I'll comment. It's quiet.

16 So just to echo, I would echo the previous
17 conversation about the other sarcomas, that with
18 monotherapy, I think the drug might get killed
19 unnecessarily if you look into a single agent
20 therapy in these relapse refractory patients. I
21 mean, it's crazy to think that single agent therapy
22 is going to meet the criteria, especially if it's

1 resist. I mean, we've all seen those kids on
2 phase 2 who we think would benefit from the drug,
3 and then the drug goes on to get killed. So I
4 would argue for a phase 1 with multiagent therapy.

5 DR. BALIS: Dr. Mascarenhas.

6 DR. MASCARENHAS: So I really think that the
7 apples and oranges over here and that
8 rhabdomyosarcoma is a completely different tumor
9 from soft tissue sarcoma. The other huge advantage
10 we have with rhabdomyosarcoma is that we've done
11 clinical trials with rhabdomyosarcoma now for
12 almost 40 years. So things like time to
13 progression and event-free survival and overall
14 survival are well known, both in the upfront
15 setting in the different risk groups, and
16 potentially, very, very soon, we'll have even more
17 data in the relapse setting with these drugs.

18 So, potentially, we may be able to see -- we
19 may be able to use this in a time-to-progression
20 model a little more effectively I think than in the
21 adult-type soft tissue sarcoma in pediatrics.

22 The one concern is that even though

1 doxorubicin and ifosfamide is intensive therapy,
2 the usual duration of therapy is much shorter than
3 that of rhabdomyosarcoma. Rhabdomyosarcomas tend
4 to be treated for at least a year rather than six
5 months in most cases. I mean, 40 weeks is usually
6 the minimum, and now high-risk patients are
7 potentially treated a little longer. And towards
8 the end of therapy, toxicity becomes more
9 prominent. The acute toxicity rate in the
10 treatment of rhabdomyosarcoma in general is over
11 80 percent, hematological acute toxicity. And
12 radiation therapy is used extensively in the
13 treatment of these patients. About two-thirds of
14 them will receive radiation therapy.

15 So the answer is not as clear. To me, a
16 bigger concern in rhabdomyosarcoma is have we seen
17 enough of a signal to see if this is a drug which
18 we would be willing to put relatively precious
19 patients on. I mean, there are a total of 350, 400
20 new patients with rhabdomyosarcoma every year, of
21 which about 25 to 30 percent will be metastatic or
22 high risk. But that being said, it's the most

1 common sarcoma in childhood, and the majority of
2 patients come from that group of patients.

3 DR. BALIS: Dr. Sekeres.

4 DR. SEKERES: So from the pediatric
5 oncologists, is it reasonable to enroll rhabdo and
6 non-rhabdo patients on to the same phase 1 study in
7 combination with chemo, or no, in a relapse
8 refractory setting?

9 DR. MASCARENHAS: I don't think so.

10 DR. ARNDT: Unless you do totally separate
11 strata.

12 DR. BALIS: I think here the difficulty
13 with --

14 DR. ARNDT: But even so, would this be
15 something sort of within enough of a signal that
16 people would be excited to do this instead of
17 pursuing some other active chemotherapy agent that
18 has more of a signal? I mean, I don't know.

19 DR. SHAHLAEE: Dr. Arndt, I totally agree
20 with you. We don't have any data up to now that
21 suggests activity in rhabdomyosarcoma, but then
22 when you look at high-risk patients, as was

1 extensively discussed at CTAS (ph) over the last
2 few days, we have no improvement over VAC. So the
3 40 weeks of therapy that you're talking about has
4 not really improved anything for a really long
5 time, as both you guys well know.

6 DR. BALIS: Dr. Arndt.

7 DR. ARNDT: So I think one of the comments
8 Leo made earlier was to look at this agent in the
9 setting of maintenance chemotherapy. The Europeans
10 are looking at other agents, Navelbine and Cytosan,
11 in high-risk patients as maintenance chemotherapy.
12 And I suppose that would be one avenue to approach
13 to look at it in terms of maintenance, but then in
14 very high-risk patients. But then, of course,
15 you're weeding out those patients who relapse
16 before they ever get to maintenance.

17 DR. BALIS: Dr. Neville.

18 DR. NEVILLE: I was just going to clarify to
19 Dr. Mascarenhas' comments. I was not advocating
20 necessarily an upfront window, but I just think as
21 a single agent, I agree with you that we don't even
22 know if there's a signal. So to think this agent

1 will go forward as a single agent in the relapse
2 refractory setting is unrealistic.

3 DR. BALIS: Dr. Mascarenhas.

4 DR. MASCARENHAS: The other thing is we've
5 treated high-risk rhabdomyosarcoma, metastatic
6 rhabdomyosarcoma for so many years and not had any
7 improvement. And perhaps our paradigm of treating
8 them is wrong. It's going to -- we may need to
9 relook at how we investigate that group of
10 patients, and, potentially -- our problem with
11 rhabdomyosarcoma is not getting a response; it's
12 keeping the disease away. And so aborting
13 chemotherapy early with earlier local control and
14 then starting an agent like this earlier, rather
15 than continuing with the entire year of therapy and
16 then thinking of maintenance, may be a potential
17 way to look at incorporating these agents in this
18 group of patients; so if local control was done at
19 three months or something immediately after local
20 control was done, because we don't have one iota of
21 data to suggest that the continuation of
22 chemotherapy in this group of patients benefits

1 them, either from progression-free survival or
2 overall survival.

3 DR. BALIS: I think you raised the issue,
4 and we've heard it here a couple times about
5 looking in a window setting, meaning up front. The
6 other limitation, besides the ones that have been
7 raised, in doing that is that you're limited in
8 terms of what your endpoint can be because it's
9 such a short period of time that you're observing.
10 And generally it's going to be one cycle or
11 potentially two, which is one or two months, which
12 means you're limited to looking at response. And I
13 think you have to be convinced that that's the
14 appropriate endpoint for a drug that works the way
15 this one does to consider that. Otherwise, I think
16 you're stuck in looking at other places.

17 We probably ought to be careful, when we
18 have these discussions, about whether we're talking
19 about upfront therapy versus in a relapse setting.
20 And one of the questions that Dr. Sekeres asked was
21 about the same combinations. Part of the problem
22 is that the diseases are different enough that we

1 use very different frontline therapy with them, and
2 so the drugs that are then available in a relapse
3 setting are not going to overlap very much to allow
4 us, I think, to do that, unless we pick other new
5 agents, and then what do we learn from that?

6 So I don't necessarily disagree with the
7 thought of looking at this in a relapse setting as
8 a single agent to start with, to look for activity.
9 At least what I think, and I think I'm hearing from
10 the rest of the group here, is that what really
11 needs careful consideration is what the endpoint of
12 that study is going to be.

13 Dr. Mascarenhas.

14 DR. MASCARENHAS: The present relapse
15 rhabdomyosarcoma study is a randomized phase 2
16 trial with time to progression as the primary
17 endpoint. So that model with another similar
18 agent, or really even a classic phase 3 design in
19 the relapse I think may be a potential way, if
20 there is some interest generated either based on
21 response or other preclinical data.

22 DR. BALIS: Can we get an FDA perspective on

1 the use of a historically controlled progression-
2 free survival endpoint for moving a drug along?

3 Everyone is looking for Dr. Pazdur.

4 [Laughter.]

5 DR. REAMAN: He is supposed to be back here
6 by now. But I'm not sure that there is much of a
7 perspective to really provide, and certainly in
8 pediatrics. And in this particular tumor, I'm not
9 sure that we have much in the way of a good
10 historical control.

11 Having said that, if there are robust data
12 that can be collected and put together, given the
13 difficulty with the studying new drugs in select
14 populations of rare diseases, I think there is some
15 openness and flexibility about looking at new
16 possibilities.

17 DR. BALIS: Dr. Arndt.

18 DR. ARNDT: But there is data available on
19 the event-free survival of patients with recurrent
20 rhabdomyosarcoma.

21 DR. BALIS: Right.

22 DR. ARNDT: I mean, that's clearly

1 available, and, frankly, it hasn't changed at all
2 over the past decades.

3 DR. BALIS: Okay. Any other questions? I'm
4 sorry. Go ahead.

5 DR. REAMAN: So given that, and I think we
6 do have the luxury of -- although we don't have
7 large numbers of patients, we generally have pretty
8 good access to data, and given the fact that
9 patients are very frequently treated in a standard
10 fashion on study.

11 So I think if that is, in fact, available,
12 then considering historical control design wouldn't
13 be absolutely out of the question.

14 DR. BALIS: Any other questions or comments?
15 Yes, I'm sorry.

16 DR. REAMAN: The only other thing to be
17 concerned about is that there is rhabdomyosarcoma
18 and there's rhabdomyosarcoma. And we talk about it
19 like it's a homogenous disease, but it's no more
20 homogenous than lumping together the soft tissue
21 sarcomas. So that's the only thing we would have
22 to be careful about I think.

1 DR. SHAHLAEE: I was going to make the exact
2 same comment. In Dr. Bender's study, there's one
3 stratum for all rhabdomyosarcoma. And, again,
4 going back to the same issue that we raised with
5 the previous study, what if these are adolescents
6 with stage 4 alveolar?

7 Exactly. And then you don't really know if
8 you have activity in the embryonal subset.

9 DR. MASCARENHAS: You could potentially
10 overcome that with a randomized design and
11 stratification, unless you're expecting a
12 completely differential effect based on histology.

13 DR. SHAHLAEE: So I guess my question was,
14 would we have enough patients at COG to have a
15 strata for embryonal relapse and one for alveolar
16 relapse?

17 DR. MASCARENHAS: No.

18 DR. SHAHLAEE: That's what I'm --

19 DR. MASCARENHAS: I would say in a uniform
20 relapsed trial, first relapse trial, you could
21 potentially think of doing a three-year study or a
22 four-year study.

1 DR. SHAHLAEE: But before getting to that,
2 in the Simon two-stage design, I mean, we're
3 looking for any evidence right now; we have none,
4 before we even get there.

5 DR. BALIS: Dr. Mascarenhas.

6 DR. MASCARENHAS: There are plenty of
7 patients. We have no relapse strategies. So I
8 think in second progression, you'll fill up the
9 strata very quickly.

10 DR. BALIS: Dr. Arndt, did you have a
11 comment?

12 DR. ARNDT: In terms of relapsed rhabdo, I
13 mean, we do know that there is bad relapsed rhabdo
14 and good relapsed rhabdo. And, frankly, the
15 difference between the subgroups of the bad
16 relapsed rhabdo isn't really that much.

17 DR. SHAHLAEE: The other question I was
18 going to ask actually of GSK is, the patients with
19 rhabdo are going to have had exposure to a lot of
20 actinomycin, which has risk of VOD. Any concerns
21 about potentially when you add pazopanib on the
22 patients who have had exposure to another hepato

1 toxic drug?

2 DR. CARPENTER: I think at this point we
3 don't know, and we just require very close
4 monitoring to begin with.

5 DR. BALIS: Okay. Good.

6 Thank you very much. This session is now
7 adjourned. We'll take a 10-minute break. We're
8 still way ahead, so, actually, why don't we say
9 2:15 we'll reconvene. And remember, please, there
10 should be no discussion of the issues at hand
11 during the break amongst yourselves or other
12 members of the audience.

13 (Whereupon, a recess was taken.)

14 DR. BALIS: If everybody could please take
15 their seat, let's move on to the last session this
16 afternoon, and we can maybe get out early. Thank
17 you.

18 Dr. Curt has recused himself for this final
19 discussion.

20 So the topic for the last discussion is
21 MEDI-573 from MedImmune.

22 Caleb, would you read off the disclosures?

1 **Topic 4: MEDI-573 - MedImmune**

2 **Conflict of Interest Statement**

3 DR. BRIGGS: The Food and Drug
4 Administration, FDA, is convening today's meeting
5 of the Pediatric Oncology Subcommittee of the
6 Oncologic Drugs Advisory Committee under the
7 authority of the Federal Advisory Committee Act,
8 FACA, of 1972. With the exception of the industry
9 representative, all members and temporary members
10 of the subcommittee are special government
11 employees, SGEs, or regular federal employees from
12 other agencies and are subject to federal conflict
13 of interest laws and regulations.

14 The following information on the status of
15 this subcommittee's compliance with federal ethics
16 and conflict of interest laws, covered by but not
17 limited to those found at 18 U.S.C. Section 208 and
18 Section 712 of the Federal Food, Drug and Cosmetic
19 Act, FD&C Act, is being provided to participants in
20 today's meeting and to the public.

21 FDA has determined that members and
22 temporary members of this subcommittee are in

1 compliance with federal ethics and conflict of
2 interest laws. Under 18 U.S.C. Section 208,
3 Congress has authorized FDA to grant waivers to
4 special government employees and regular federal
5 employees who have potential financial conflicts
6 when it is determined that the agency's need for a
7 particular individual's services outweighs his or
8 her potential financial conflict of interest.

9 Under Section 712 of the FD&C Act, Congress
10 has authorized FDA to grant waivers to special
11 government employees and regular federal employees
12 with potential financial conflicts when necessary
13 to afford the subcommittee essential expertise.

14 Related to the discussions of today's
15 meeting, members and temporary members of this
16 committee have been screened for potential
17 financial conflicts of interests of their own as
18 well as those imputed to them, including those of
19 their spouses or minor children, and, for purposes
20 of 18 U.S.C. Section 208, their employers. These
21 interests may include investments, consulting,
22 expert witness testimony, contracts, grants,

1 CRADAs, teaching, speaking, writing, patents and
2 royalties, and primary employment.

3 Today's agenda involves discussions related
4 to pediatric development plans for four products
5 that were either recently approved by the FDA, are
6 in late-stage development for an adult oncology
7 indication, or in late-stage development in
8 pediatric patients with cancer. The subcommittee
9 will consider and discuss issues relating to the
10 development of each product for pediatric use and
11 provide guidance to facilitate the formulation of
12 written requests for pediatric studies, if
13 appropriate.

14 The product under consideration for this
15 session is MEDI-573, sponsored by MedImmune. This
16 is a particular matters meeting during which
17 specific matters relating to MEDI-573 will be
18 discussed. The subcommittee will not be voting.

19 Based on the agenda and all financial
20 interests reported by the subcommittee members and
21 temporary members, no conflict of interest waivers
22 have been issued in connection with this session.

1 To ensure transparency, we encourage all
2 standing committee members and temporary members to
3 disclose any public statements that they may have
4 made concerning the product at issue.

5 With respect to FDA's invited acting
6 industry representative, Dr. Gregory Curt is
7 recused from participating in the discussions.
8 Dr. Curt is employed by AstraZeneca.

9 We would like to remind members and
10 temporary members that if the discussions involve
11 any products or firms not already on the agenda for
12 which an FDA participant has a personal or imputed
13 financial interest, the participants need to
14 exclude themselves from such involvement, and their
15 exclusion will be noted for the record. FDA
16 encourages all other participants to advise the
17 subcommittee of any financial relationships that
18 they may have with the firm at issue. Thank you.

19 **Introduction of New Participants**

20 DR. BALIS: And for the last time today,
21 both the Food and Drug Administration and the
22 public believe in a transparent process for

1 information gathering and decision-making. To
2 ensure such transparency at the advisory committee
3 meeting, FDA believes that it's important to
4 understand the context of an individual's
5 presentation.

6 For this reason, FDA encourages all
7 participants, including the sponsor's non-employee
8 presenters, to advise the committee of any
9 financial relationships that they may have with the
10 firm at issue, such as consulting fees, travel
11 expenses, honoraria, and interest in the sponsor,
12 including equity interest, and those based upon the
13 outcome of the meeting.

14 Likewise, FDA encourages you at the
15 beginning of your presentation to advise the
16 committee if you do not have any financial
17 relationships. If you choose not to address the
18 issue of financial relationships at the beginning
19 of your presentation, it will not preclude you from
20 speaking.

21 We'll now proceed with the sponsor's
22 presentation.

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Industry Presentation - Robert Sikorski

DR. SIKORSKI: Good afternoon, I'm Dr. Robert Sikorski, a senior director of clinical development at MedImmune and a board certified medical oncologist. With me today is Dr. Jaye Viner, a director of oncology clinical development at MedImmune.

Before we begin, I would first like to thank the agency and the advisory committee for inviting us here today to participate in this important discussion regarding the development of new therapies for children with cancer.

As you will see, our presentation focuses on MEDI-573, a novel antibody in our oncology portfolio. MEDI-573 is designed to inhibit growth by blocking the insulin-like growth factors known as IGF-1 and IGF-2. MEDI-573 is currently in the early stages of clinical development, and to date, our studies have involved only adult subjects. However, a growing body of evidence suggests that IGF pathway inhibition may offer potential therapeutic benefit for pediatric subjects as well,

1 specifically those having a rare tumor, which we
2 will refer to as Ewing sarcoma. This actually
3 represents a family of tumors, as you know.

4 As we will discuss, beyond initial
5 exploration, pivotal studies with Ewing sarcoma
6 would be challenging. Our goal here today is to
7 obtain clarity on an integrated clinical and
8 regulatory path that can be used to advance
9 MEDI-573 as a potential therapy for Ewing sarcoma.

10 I will first summarize the major findings
11 obtained with the IGF-targeting agents tested in
12 the clinic to date, as well as select preclinical
13 experiments performed with MEDI-573. Dr. Viner
14 will then discuss our experience with MEDI-573 in
15 the clinic. I'll return and discuss items
16 pertinent to the development of MEDI-573 in Ewing
17 sarcoma.

18 We have one external advisor with us today,
19 Dr. Katherine Janeway. Dr. Janeway is a pediatric
20 oncologist at the Dana Farber Cancer Institute.
21 She will serve as a potential responder to
22 questions.

1 Let's start with a brief overview of the IGF
2 pathway. A basic understanding of the key
3 components of this pathway is needed to interpret
4 preclinical as well as clinical data from the
5 various inhibitors that have been used to date.
6 The basic membrane-bound components of the IGF
7 pathway are as follows: first, the homodimeric
8 IGF-1 receptor; a non-signaling receptor IGF-2; the
9 conical insulin receptor called IRB; a splice
10 variant of the insulin receptor called IRA; and two
11 heterodimers between the insulin receptor and the
12 IGF-1 receptor.

13 These receptors are differentially activated
14 by three circulating ligands, IGF-1, IGF-2, and
15 insulin. IGF-1 has high affinity for all IGF-1
16 receptor species. IGF-2 binds to a broader set of
17 targets that includes IRA and the IGF-2 receptor.
18 Insulin binds to both of the insulin receptor
19 variants, IRA and IRB.

20 Now, ligand binding can activate two
21 divergent functions, depending on the specific
22 receptors, which have been engaged, cell growth or

1 glucose homeostasis, cell growth for the first four
2 receptors or glucose homeostasis for IRB. Many
3 antibodies in small molecule inhibitors of the IGF
4 pathway have been tested in the clinic. MEDI-573
5 is unique in that it targets the IGF ligands and
6 not the receptor.

7 Here we have summarized the clinical
8 activity reported for monotherapy studies of IGF
9 targeting agents. Clearly, Ewing sarcoma stands
10 out in that multiple agents have shown responses in
11 this particular setting. Independent trials
12 testing five different agents have shown at least
13 one objective response in Ewing sarcoma.
14 Sporadically objective responses have been seen in
15 other types of sarcoma as well.

16 Next, we have summarized the magnitude and
17 the reproducibility of the clinical activity
18 reported to date with IGF pathway inhibitors in
19 Ewing sarcoma. Objective responses have been
20 demonstrated in approximately 5 to 17 percent of
21 subjects treated. In addition, suggestions of
22 disease stabilization and longer than expected

1 response durations have been reported with the
2 various IGF pathway inhibitors.

3 For example, three subjects with figitumumab
4 had stable disease for nine months or greater.

5 While encouraging, we do note that most of these
6 trials were relatively small and that none were
7 randomized. As a result, it is not possible to
8 draw statistically-based conclusions regarding the
9 significance of these observations.

10 Dose limiting toxicities are one overall
11 measure of safety. Within the initial phase 1
12 trials of the IGF pathway inhibitors, no dominant
13 patterns of DLTs have emerged. Of note,
14 thrombocytopenia was seen with two agents and
15 hyperglycemia with one.

16 Another way to gauge safety with respect to
17 IGF pathway inhibition is to examine the largest
18 monotherapy clinical data set that has been
19 reported to date. This comes from a phase 2 trial
20 of figitumumab, an IGF-1 receptor-targeting
21 antibody. This trial includes 165 subjects with
22 colorectal cancer. Here, for example, grade 3 or 4

1 hyperglycemia, an adverse event which we will
2 discuss shortly, occurred in 22 percent of the
3 subjects in the higher dose.

4 Using our mechanism of action diagram, we
5 will now highlight the challenges presented by IGF
6 pathway inhibition. Antibodies to the IGF-1
7 receptor binds to an inactivate signaling of three
8 IGF-1 receptor containing species. However,
9 antibodies do not bind to IRA and, therefore,
10 cannot completely inhibit IGF-2 base signaling.
11 This is important since IRA may serve as an escape
12 mechanism by which tumors can resist the inhibition
13 of IGF-1 receptor-based therapies.

14 Small molecules present a different
15 challenge. They're designed to inhibit the
16 tyrosine kinase domains of these receptors. Since
17 these domains are all strongly related, it's hard
18 to create a small molecule that both inhibits the
19 IGF-1 receptor and does not inhibit insulin
20 signaling. An undesired result of this would be
21 impaired glucose homeostasis.

22 We have developed an alternative approach to

1 inhibit the IGF pathway. Unlike targeting the
2 IGF-1 receptors directly by antibody or small
3 molecule, we target inhibition of the IGF-1 and 2
4 ligands themselves. The potential benefit of this
5 approach is a more complete blockade, while at the
6 same time sparing the inhibition of insulin
7 signaling and maintaining normal glucose
8 homeostasis.

9 I will now walk you through selected
10 biochemical characterizations of MEDI-573.
11 MEDI-573 is a human antibody that, as I mentioned,
12 binds both IGF-1 and 2. This slide demonstrates
13 the potent inhibition produced by MEDI-573 in a
14 cell culture system whose growth is driven by IGF-1
15 or IGF-2 and the IGF-1 receptor. Furthermore,
16 MEDI-573 potently inhibits the core mechanism of
17 receptor signaling, phosphorylation. Shown here is
18 the inhibition of IGF-1-induced phosphorylation of
19 two downstream signaling components, the IGF-1
20 receptor itself and AKT.

21 This slide shows that MEDI-573 also inhibits
22 IGF-2-induced phosphorylation of these same

1 components. Additionally, this inhibition of
2 signaling translates to inhibition of tumor growth
3 in an animal model system. Shown here is the dose
4 proportional inhibition of a subcutaneous tumor
5 that is driven by IGF-1. The same magnitude of
6 tumor inhibition was seen in the IGF-2-driven model
7 as well. Again, this demonstrates that MEDI-573
8 can block the tumor-promoting activity of both IGF
9 ligands.

10 Now, using a cell culture model, we will
11 compare the inhibition produced by MEDI-573 to that
12 of an antibody blocking the IGF-1 receptor. Cell
13 growth is driven here by an autocrine signal
14 involving IGF-2 and the IGF-1 receptor. Both
15 MEDI-573 and the IGF-1 receptor antibody can
16 clearly inhibit this type of signaling. However,
17 blocking IGF signaling through the IGF-1 receptor
18 alone may not be sufficient to maximally inhibit
19 the pathway. As illustrated previously, IGF-2 can
20 bind and can signal through IRA as well. This
21 provides a possible mechanism of resistance for all
22 antibodies that target the IGF-1 receptor. IRA

1 messenger RNA is highly expressed in many tumor
2 cell lines. In fact, greater than 95 percent of
3 the insulin receptor transcript can be the IRA
4 variant.

5 In a different cell culture model driven by
6 autocrine IGF-2 and IRA, we can now see a clear
7 difference between the inhibition produced by
8 MEDI-573 as compared to receptor-targeting with an
9 antibody. We have initiated clinical trials to
10 test if more complete inhibition of IGF-2 signaling
11 produced by MEDI-573 preclinically translates to
12 more potent antitumor activity in the clinic.

13 To support these human studies, the safety
14 of MEDI-573 was examined in cynomolgus monkeys.
15 Even at the highest dose tested, 60 milligrams per
16 kilogram given weekly, no toxicities were observed.
17 In particular, the lack of metabolic perturbations,
18 such as no changes in fasting glucose levels, were
19 notable.

20 Dr. Viner will now present our initial
21 clinical trial experience with MEDI-573.

22 Dr. Viner.

1 **Industry Presentation - Jaye Viner**

2 DR. VINER: Thank you.

3 Four clinical trials are underway with
4 MEDI-573. Today, we will present data from the
5 first-in-human trial. This is a phase 1
6 multicenter, open label, dose escalation and
7 expansion trial in adults with advanced solid
8 tumors, refractory to standard therapy or for which
9 no standard therapy exists. Enrollment was
10 completed earlier this year.

11 In this three plus three dose escalation and
12 expansion trial, MEDI-573 was tested on a weekly
13 schedule at doses of 0.5 milligrams per kilogram
14 through 15 milligrams per kilogram. It was also
15 tested on an every three-week schedule at a dose of
16 30 milligrams per kilogram.

17 Today, we will be presenting interim data
18 for a total of 37 adults. These subjects ranged
19 from 37 to 83 years of age. Most of them were
20 heavily pretreated, having received two to nine
21 prior regimens with various therapies. This trial
22 recruited subjects 18 years or older with advanced

1 solid tumors that were measurable or evaluable.
2 Eligibility also required adequacy of organ
3 function. We excluded subjects with uncontrolled
4 diabetes or those who had been exposed to
5 antibodies directed against the IGF-1 receptor.

6 These subjects had the tumors listed here.
7 Subjects with bladder cancer were enrolled into a
8 biomarker-rich expansion phase that mandated tumor
9 biopsies before and after the first dose of
10 MEDI-573. The trial enrolled four subjects with
11 sarcoma, details of which are described on the
12 following slide.

13 In these heavily pretreated subjects, no
14 objective responses were observed. The interval
15 between the time of diagnosis and treatment with
16 MEDI-573 ranged from 4 to 13 years. A summary of
17 the number of lines of prior therapy received with
18 best clinical response to treatment is provided
19 here. These subjects were treated at doses ranging
20 from 5 to 15 milligrams per kilogram on a weekly
21 schedule. Stable disease was the best response in
22 three of the subjects and ranged from 126 to 647

1 days.

2 At all dose levels tested, MEDI-573 fully
3 suppressed the IGF-2 ligand. The IGF-1 ligand was
4 also fully suppressed at all dose levels tested
5 except for one subject in a lower dose group in
6 whom suppression was greater than 90 percent.

7 Twenty-seven of the 37 subjects were
8 evaluable for activity. While no objective
9 responses have been seen to date, 40 percent or 11
10 subjects met criteria for stable disease, which was
11 defined as no objective response or progression of
12 disease at 12 weeks.

13 Serious adverse events occurring in the
14 first-in-human trial are summarized here. Two of
15 these events, hypoglycemia and weight loss, were
16 considered to be related to MEDI-573. Both of them
17 occurred in a diabetic who continued to take her
18 hypoglycemic medications despite poor oral intake
19 in the context of antibiotic treatment for an
20 infection. All other SAEs were considered not
21 related to the study drug.

22 No dose limiting toxicities were reported on

1 the trial. This was defined as any grade 3 or
2 higher treatment-related adverse event that
3 occurred during the first treatment cycle. The
4 most common adverse events, defined as those
5 occurring in 10 percent or more of the subjects,
6 are listed here. Of note, all of these events were
7 grade 1 to 2 in severity.

8 Two cases of hyperglycemia occurred in two
9 subjects. One was grade 1 and was deemed not
10 related. The other was grade 3 and occurred in a
11 subject with a prior history of untreated
12 hyperglycemia. This event was deemed remotely
13 related to the investigational product.

14 In addition to the first-in-human trial just
15 reviewed, another phase 1 trial is being conducted
16 in Japan. Two other trials were recently initiated
17 to advance MEDI-573 in breast cancer and
18 hepatocellular carcinoma. These are both global
19 phase 1B-2, randomized, open label trials.

20 Dr. Sikorski will now provide an overview of
21 the potential of advancing MEDI-573 in the
22 pediatric setting.

1 **Industry Presentation - Robert Sikorski**

2 DR. SIKORSKI: Thank you, Dr. Viner.

3 This slide underscores why we are all here
4 today. You can see the relatively poor prognosis
5 of those patients with refractory Ewing sarcoma.
6 Treatment of Ewing sarcoma involves chemotherapy,
7 radiotherapy, and surgery at the early stages.
8 Once refractory, however, the median survival can
9 be less than one year, depending on the exact type
10 of relapse. Refractory Ewing sarcoma represents a
11 significant unmet medical need.

12 We are present studying MEDI-573 in adults
13 and have made no decisions regarding pediatric
14 subjects at this date. However, given the activity
15 detected with IGF inhibitors in Ewing sarcoma, it's
16 logical to consider the possible path by which
17 MEDI-573 could be developed in this setting. As an
18 initial study, we can envision a trial of 6 to 12
19 pediatric-age patients, enrolling a variety of
20 sarcomas, including Ewing sarcoma, osteosarcoma and
21 rhabdomyosarcoma. Such a study would provide the
22 requisite safety, pharmacokinetic and

1 pharmacodynamic data to enable future pediatric
2 clinical development. It would also provide a
3 limited opportunity to obtain an activity signal as
4 well.

5 After this initial study, there are
6 challenges to advancing a new therapy like MEDI-573
7 in Ewing sarcoma. We have grouped these challenges
8 into four main issues for the committee's
9 consideration.

10 First, the rarity alone of Ewing sarcoma
11 represents a unique challenge to clinical
12 development. In the United States, for example,
13 the annual incidence of Ewing sarcoma at all ages
14 is less than 500 with a prevalence under 2,000. In
15 patients under age 14, the prevalence falls well
16 below a thousand. Enrolling a sizeable clinical
17 study in a refractory population, which represents
18 only a subset of these patients, would require a
19 global and collaborative approach.

20 The regulatory expectations for an advanced
21 trial remain to be defined. Key requirements, such
22 as the age range of the subjects, whether to focus

1 only on Ewing sarcoma or a mixed population of
2 tumors, the need for randomization or the
3 acceptability of a single-arm monotherapy study
4 require careful deliberation. These choices would
5 have a major impact on advancing MEDI-573 in the
6 pediatric setting.

7 In addition to the issues of study design,
8 the most appropriate endpoint to demonstrate a
9 meaningful clinical benefit in pediatric sarcoma is
10 unclear. Given the relatively poor prognosis of
11 refractory patients with Ewing sarcoma, would, for
12 instance, objective response rate alone be viewed
13 as endpoint of regulatory importance in an advanced
14 study?

15 Collectively, the IGF-1 receptor class of
16 inhibitors as monotherapy have produced an
17 approximately 10 percent response rate in Ewing
18 sarcoma. While the scientific progress made in
19 this disease is highly encouraging, the magnitude
20 of the clinical benefit delivered to Ewing sarcoma
21 patients by this class of agents remains open to
22 interpretation. Due to differences in mechanism of

1 action, extrapolating these data directly to
2 MEDI-573 is really not possible.

3 In conclusion, we thank the FDA and the
4 committee for their interest in MEDI-573 and for
5 inviting us here to participate in today's meeting.
6 We recognize the unmet medical needs of children
7 and the dire situation facing patients with
8 refractory Ewing sarcoma and their families,
9 particularly. Through discussions with the agency
10 and the committee, we seek clarity on the
11 integrated clinical and regulatory path by which
12 MEDI-573 could be developed for these patients.

13 Thank you, and I welcome your questions that
14 you may have.

15 **Clarifying Questions from Subcommittee**

16 DR. BALIS: Thank you, and I'll open the
17 floor up for questions.

18 Dr. Gorlick.

19 DR. GORLICK: Is there data preclinical
20 using xenograft models or cell lines that the
21 activity spectrum of this drug is similar to the
22 agents that targeted IGF-1R antibody, or is this

1 totally different?

2 DR. SIKORSKI: Yes. I can answer that in
3 two ways. First, what I presented today were cells
4 that were genetically engineered to create, for the
5 most part, autocrine loops between the receptor
6 versus the agents and the ligands. And as you can
7 see, we've shown that autocrine loops, particularly
8 with IRA, obviously cannot be blocked by the
9 insulin-like growth factor receptor binding
10 antibodies. Those antibodies simply do not bind to
11 IRA.

12 Now, as far as a more broad description of
13 the trials' preclinical experience with cell lines,
14 I'd like to call up one of our directors of our
15 translational department, Dr. Teresa LaVallee to
16 comment.

17 DR. LAVALLEE: Thank you, Dr. Sikorski.

18 Teresa LaVallee, MedImmune, translational
19 sciences. And we have looked extensively
20 preclinically at cell lines for inhibition of IGF-1
21 and IGF-2 produced either by the cell line or added
22 exogenously and can show inhibition of

1 IGF-stimulated proliferation as well as downstream
2 signaling activation.

3 In vivo, we are challenged due to lack of
4 cross-reactivity with the murine IGF-1. So we are
5 unable to block the signaling and have not been
6 able to show any antitumor activity with usual
7 human tumor cell lines. Using the engineered cell
8 line that was presented by Dr. Sikorski earlier, we
9 have been able to show robust inhibition of the
10 ligands and also pharmacodynamic effects in vivo.

11 DR. BALIS: It sounds like you have a number
12 of studies, but we heard really about the phase 1
13 trial in adults. What do you see as your path
14 towards registration or licensing of this drug in
15 adults at this point?

16 DR. SIKORSKI: I think -- let's reflect on
17 where we are in the program. Obviously, we're
18 early. We have treated 37 -- we've reported on the
19 dosing of 37 adults to date. We clearly have
20 completed a phase 1 study and this year have
21 launched a phase 2 study in breast cancer and a
22 phase 2 study in hepatocellular. They're both

1 sizeable randomized studies. So we await the data
2 from those two studies. We've obviously
3 optimistic, but we don't know that data yet.

4 We think the pediatric setting represents a
5 different path for this drug. We were hoping that
6 a discussion such as this we could initiate some
7 clarity on what that path would look like. We're
8 looking forward to discussion. And as I mentioned,
9 both from a clinical and a regulatory perspective,
10 we're very interested in the integrated path that
11 would take this drug forward.

12 DR. BALIS: The drug that you stopped at in
13 the adult trial, phase 1 trial, I gather it wasn't
14 because of dose limiting toxicity. How do you
15 decide where to quit the escalation? What was it
16 that drove that?

17 DR. SIKORSKI: So this was driven by
18 obviously toxicities, which we did not see, that
19 was one way to look at it, but also the
20 pharmacodynamic monitoring of particularly the
21 IGF-1 and IGF-2 ligands themselves. So
22 suppression, I think as Dr. Viner has shown, was

1 rather complete throughout those studies.

2 DR. BALIS: Dr. Arndt.

3 DR. ARNDT: Maybe you already touched on
4 this, but how well or how much do the adult tumor
5 types that you were targeting in your studies
6 express and depend on IGFR for proliferation? And
7 by consequence, how informative can they be for
8 pediatric studies in Ewing's and rhabdo, where we
9 do know that IGFR is heavily expressed, or IGF is
10 expressed?

11 DR. SIKORSKI: Again, I think I can have
12 two-part answer here. First, for Ewing's, in
13 particular, as we provided in our briefing
14 document, Affymetrix-based expression data showing
15 that the receptor and the ligands are themselves
16 expressed in Ewing's sarcoma.

17 Now, to address some of the other tissue
18 types I think that you're interested in, again,
19 I'll call Dr. Teresa LaVallee up to discuss what
20 we've done to date and how we view this.

21 DR. LAVALLEE: Thank you, Dr. Sikorski.

22 Our phase 1 study was an all-comer phase 1

1 with no selection, so there was no enrichment for
2 IGF-1R, high expressers, or ligand expressers. In
3 our phase 2 studies, we've chosen two patient
4 populations that have looked at both -- the whole
5 algorithm, if you will, of the family for breast
6 cancer that has a high level of IGF-1R, as well as
7 IRA expression with the ligands. And we'll be
8 looking in that study at the levels of the
9 receptors in relationship to activity, as well as
10 other studies have reported that circulating levels
11 of ligand are predictive for the IGF-1R targeting
12 antibodies. So we'll be looking at that as well.
13 In liver cancer, it is well reported to have high
14 levels of IGF-1R, IRA, and IGF-2, which is the
15 ligand that would drive both those receptors.

16 So we have an interest in sarcoma for the
17 Ewing sarcoma, rhabdomyosarcoma, as well as
18 osteosarcoma, given the high levels of IGF-1R, IRA,
19 and the ligands.

20 DR. GORLICK: Do you have any expectations
21 with regard to toxicity in a younger child that's
22 still growing?

1 DR. SIKORSKI: I think we're well aware of
2 the pathway and the potential for inhibition of
3 growth that -- it is obviously insulin-like growth
4 factor. To date, we have not observed throughout
5 the studies being done any significant effect.
6 Obviously, we want to take that into careful
7 consideration in designing any of these studies.
8 That does impact the selection of patients, whether
9 we go into post or prepubertal setting for our
10 initial studies or not. So we have obviously no
11 data on this but are well aware of the
12 implications.

13 DR. BALIS: The study that you described as
14 a starting point in pediatrics clearly wasn't a
15 traditional phase 1 design from what I saw in the
16 sense that you were just -- you basically said you
17 were going to look at safety and pharmacokinetics.
18 Does that mean you don't intend to do a dose
19 escalation in that study, and if not, what dose are
20 you going to pick?

21 DR. SIKORSKI: Yes. I think the point of
22 that slide was to show that we would have a phase 1

1 study as part of the initial monotherapy component,
2 and I'll ask our gentleman from our PK group to
3 discuss that in a second, how he would choose that
4 dose.

5 But the purpose of that phase 1 study was to
6 show that we have thought of a phase 1 study, but
7 we struggle with the follow-on studies, more than
8 actually that study.

9 So, Dr. Yu, if I can ask you to comment,
10 particularly on how we would envision the starting
11 dose and the dose escalation and pharmacodynamic
12 aspects.

13 DR. YU: My name is Xiangqing Yu. I'm a
14 MedImmune clinical pharmacologist doing PK.
15 Currently, there are two phase 2 trials we use in
16 studies, 10 milligram per kilogram. 10 milligram
17 per kilogram dose has been shown efficacious in
18 preclinical in monkeys, also in the phase 1 trial
19 that Dr. Viner just presented, the IGF-2 was fully
20 suppressed over 90 percent undetectable level.

21 DR. BALIS: While you're up there, can I
22 just ask one other question? I've been involved in

1 studies looking at other antibodies, including
2 antibodies directed at IGF-1R, and the experience
3 that we had was that the clearance was more uniform
4 if it's normalized to body surface area than body
5 weight. And it's always been traditional to dose
6 antibodies based body weight, I think, because most
7 people thought that the distribution was plasma
8 volume and that relates to body weight.

9 But in actuality, what we saw in the younger
10 kids on the other studies was that the clearance
11 was more rapid if it's normalized per kilo, and
12 they fell below our target levels more frequently.
13 So we did a simulation looking at what would have
14 happened if we dosed them at the body surface area
15 dose that was picked to be equivalent to the adult
16 dose, and we saw a much more uniform plasma drug
17 exposure and clearances when we did that.

18 Have you looked at relationship to weight
19 versus body surface area with the data that you
20 have so far?

21 DR. YU: We don't have any PK data from that
22 pediatric population yet. MEDI-573 currently from

1 the preclinical to the adult patients shows quite
2 linear PKs, especially at 10 milligram per
3 kilogram, which shows a consistent clearance across
4 species and from also the 10 milligram across
5 that -- and also can improve cohorts.

6 Regarding if we will go with that kilogram
7 per body surface area, we will do the phase 1
8 trials including 6 to 12 patients first and see
9 what will be the suitable dose for our final trial.

10 DR. BALIS: Dr. Freedman.

11 DR. FREEDMAN: Just trying to understand how
12 this drug might work and also how it might
13 contribute to the toxicity that you described, the
14 fatigue, weight loss, and so forth. Is there a
15 tumor phenotype that expresses the array of
16 receptors? Is there a potential paracrine effect?
17 Are there -- have you tested this against normal
18 cells, even in short-term cultures? Have you
19 looked at its effect on different -- whether it
20 targets any other tissues in the body that are
21 perhaps more proliferating in their manner?

22 Can you -- I'm trying to see if this is a

1 distinctive, true antitumor-specific effect, or is
2 there potential for other interactions, and
3 particularly in relation to the toxicity?
4 Obviously, there must be some other effects of the
5 drug on normal tissues.

6 DR. SIKORSKI: Again, I would like to call
7 Dr. LaVallee to discuss our preclinical studies.

8 DR. LAVALLEE: So our evaluation of looking
9 at normal tissues and effects were mostly done in
10 our cynomolgus monkey studies of which we did not
11 see any effects that we could relate to MEDI-573
12 treatment. We did show that we had pharmacodynamic
13 activity in monkeys and looked at effects on
14 fibroblasts that we would stimulate with IGF-1 and
15 could show that we blocked signaling. So to date,
16 we have not uncovered any effects.

17 DR. FREEDMAN: Did you look histologically
18 at the different organs?

19 DR. LAVALLEE: Yes.

20 DR. FREEDMAN: And you saw no evidence of
21 tissue damage?

22 DR. LAVALLEE: Correct, yes.

1 DR. FREEDMAN: How do you explain the
2 fatigue effect?

3 DR. LAVALLEE: I'll let Dr. Sikorski answer
4 that.

5 DR. SIKORSKI: I think we have to take that
6 under consideration. These are phase 1 patients.
7 I think that was reported here, a small subset,
8 heavily pretreated. So it's hard to interpret the
9 significance, I think, of fatigue in that setting.
10 It will be more important, I think, to see as we
11 play out these phase 2 studies, which are, as I
12 pointed out, randomized, whether that holds up once
13 we randomize to a different population. But,
14 currently, I don't have an explanation or a sense
15 of why that would be important going forward.

16 DR. FREEDMAN: Is it possible that when the
17 antibody binds to the ligands on the cell, that you
18 may get a modulation of that target and that that
19 could contribute to resistance? Have you studied
20 that in any model to see if modulating the effect
21 on tumor cell lines could eventually lead on to
22 resistance?

1 DR. SIKORSKI: I'm not aware of any studies.
2 I think the resistance mechanisms that we discussed
3 focused on IRA and the IGF-1 receptor class.

4 DR. FREEDMAN: I mean, that effect has been
5 observed.

6 DR. SIKORSKI: That's well known, as you
7 know, potential effect. Whether that plays out in
8 the clinic, we have to see, but that model has been
9 put forward.

10 I don't know -- obviously, we block the two
11 ligands. This is a dual-targeting antibody. It's
12 unique. It blocks both of those ligands. And so
13 the resistance mechanism, if there is any, is not
14 currently known.

15 DR. BALIS: Any other questions?

16 Dr. Reaman.

17 DR. REAMAN: Clinical experience with some
18 of the other IGF-1 receptor antibodies have shown
19 some increased cardio toxicity in patients
20 previously exposed to Adriamycin. Do you have any
21 data from your early phase studies to date?

22 DR. SIKORSKI: Yes, excellent question.

1 We're well aware of that data, and we -- I will
2 again ask another -- this is a two-part answer. My
3 first part will be that we have launched a two
4 phase 2 trials. One of those is in breast cancer.
5 One of those will include pretreated patients with
6 Adriamycin in the adjuvant setting. So we await
7 that data.

8 We also have some patients who have been
9 treated with Adriamycin that were part of our
10 initial experience presented by Dr. Viner. And
11 I'll ask Dr. Viner to come up and comment on those
12 patients.

13 DR. VINER: Five patients on the phase 1
14 study had been exposed to that class of agents.
15 There were only three cardiac events on the study
16 that were grade 1 tachycardias. One of those
17 tachycardias occurred in a patient with a prior
18 exposure to that class of agents.

19 As Dr. Sikorski just mentioned, we
20 anticipate that as our safety database enlarges
21 with the phase 2 trials, if there's a signal there,
22 we'll have a better opportunity to assess it.

1 DR. BALIS: Okay. Thank you very much.

2 There were no registrants again for the open
3 public hearing for this, so we'll move on to the
4 questions.

5 **Questions to the Subcommittee and Discussion**

6 DR. SHAHLAEE: Do you consider the modest
7 activity of IGF-1R inhibitors seen to date
8 sufficiently compelling to warrant more definitive
9 evaluation in children, adolescents, and young
10 adults with specific sarcoma subtypes?
11 Specifically, how do you think the different
12 mechanism of action of MEDI-573 impacts further
13 investigation of this agent in bone and soft tissue
14 sarcomas in children, adolescents, and young
15 adults?

16 DR. BALIS: Rich, I'm going to call on you
17 to start the discussion.

18 DR. GORLICK: So I think in the community,
19 there's been some sarcoma -- bone sarcoma
20 community, let me qualify it further, there's been
21 considerable interest in developing the IGF-1R
22 antibodies, meaning there has been interest in

1 doing trials either in the recurrent or the upfront
2 metastatic setting. And we can go into more
3 details of those.

4 But I think because of the non-overlapping
5 spectrum of toxicity relative to the agents that we
6 utilize, with a hint of activity, there's interest
7 in combining them with standard chemotherapy
8 because they wouldn't preclude the ability to give
9 what we consider to be standard, which is sort of
10 the critical issue.

11 I think for this compound in particular,
12 you've hit on the right point, which is I think it
13 still remains to be shown that the MEDI-573 has the
14 same activity level in the sarcomas that we saw
15 with the IGF-1R antibodies, meaning I appreciate
16 that the mechanism is the same pathway but it's not
17 identical.

18 I sort of appreciate the challenges I heard
19 in the answer to the question that obviously non-
20 overlapping species issues may make this hard to do
21 in the preclinical setting. And so it may
22 necessitate clinical development in a sort of

1 multistep path where you validate that 10 percent
2 activity level and then proceed to randomized
3 trials in order to get a more precise signal of
4 activity.

5 So I think the answer, as far as I would see
6 it, would be, yes, there's definitely interest in
7 the class of compounds, and hopefully this is in
8 the class.

9 DR. BALIS: Dr. Shurin.

10 DR. SHURIN: One of the things that would be
11 particularly helpful -- I was very impressed with
12 the comment about the challenges with the different
13 models -- would be a better preclinical, not
14 necessarily model, but something in which you could
15 test to determine whether or not this actually
16 makes sense.

17 I think Dr. Arndt's comment about the high
18 level of expression of IGF and these factors in
19 general in pediatric tumors may make it so that it
20 actually makes some real sense to pursue this as a
21 target. But an in vitro analysis to be able to
22 sort of see if you could find some correlate of

1 drug effect, maybe in parallel with the clinical
2 studies, might be really helpful in deciding where
3 this goes eventually.

4 DR. BALIS: Other questions or comments?

5 Dr. Mascarenhas.

6 DR. MASCARENHAS: I think one of the
7 struggles with this agent is that there's been so
8 much of preclinical data for the IGFR pathway and
9 inhibition, especially in Ewing's sarcoma, and it's
10 translated to approximately a 10 percent response
11 rate, which doesn't -- which is small. And I think
12 the key would be to really combine it with
13 cytotoxic chemotherapy. And I think there is
14 emerging data to suggest that this is likely
15 feasible.

16 I guess my question is that, at least based
17 on my knowledge, the side effects of IGFR
18 inhibition seem to be a class effect rather than an
19 individual drug effect. And could a pediatric
20 trial be envisioned where based on preclinical
21 modeling, that you would embark directly on a
22 phase 2 trial and assess pharmacokinetics,

1 potentially to move this up a little faster?

2 DR. SHAHLAEE: So the question I was going
3 to actually ask you was instead of a pediatric-
4 specific study, how about a adolescent, young
5 adult, considering the patient population? I mean,
6 that's been a frequent discussion for this class of
7 drugs, 13 and above, 15 and above. I guess I want
8 to hear what your thoughts are.

9 DR. GORLICK: Yes. I was avoiding the soft
10 tissue sarcoma part of the discussion with my
11 colleagues' delight. I think in the context of
12 bone sarcomas, you're very capable of doing a trial
13 that's exclusively in post-pubescent patients,
14 which avoids the growth sort of toxicity issue. I
15 think it is a view of the sarcoma community, to
16 some extent, which is maybe a little different from
17 the pediatric -- I guess this is a pediatric
18 meeting. But you don't necessarily in those late
19 post-pubescent patients need a phase 1 trial
20 particularly for that population, that you're able
21 to use the adult dose for the above 13 or above 14,
22 or maybe above 16 population. Given the peak ages

1 of incidence of osteosarcoma and Ewing's sarcoma,
2 excluding the younger patients doesn't create
3 tremendous uproar, largely because there's going to
4 be only a small affected population.

5 Soft tissue sarcoma, typically, what you're
6 thinking about is now rhabdomyosarcoma. As soon as
7 you bring rhabdomyosarcoma into the equation,
8 you're talking about much younger children. And,
9 clearly, you need to do a pediatric phase 1 trial
10 as sort of an essential.

11 The problem with pediatric phase 1 trials
12 that are looking to assess growth is by nature of
13 the phase 1 trials, the prognosis of those patients
14 are poor, and long-term follow-up to assess those
15 later effects may not be there.

16 DR. SHAHLAEE: So, potentially, the sponsor
17 may want to pursue a two-pronged approach, one with
18 the bone sarcomas and a different one with the
19 pediatric going to soft tissue.

20 DR. BALIS: Dr. Mascarenhas, you want to
21 address that?

22 DR. MASCARENHAS: I think in

1 rhabdomyosarcoma, particularly, given the potential
2 effect based on IGF-2 signaling, it makes sense.

3 DR. SHAHLAEE: And the other thing that,
4 Dr. Mascarenhas, you touched upon, and, again, I
5 want to hear your thoughts on, you said combining
6 with a cytotoxic agent. My question is what about
7 with targeted agents like we've seen some other
8 attempts with other members of this family? Any
9 comments on a phase 1 using a combination like
10 that?

11 DR. MASCARENHAS: I think again that would
12 require early phase testing. It's
13 certainly -- with the mTOR inhibitors, there's been
14 a lot of interest. There hasn't been significant
15 response data generated in sarcomas with a
16 combination, though there have been anecdotal
17 evidence of response. There have been some
18 challenges with toxicity, which have precluded
19 giving the optimal doses of both agents together.
20 And I believe testing is still underway with both
21 trials in adults in sarcomas, I think, at M.D.
22 Anderson and within the Children's Oncology Group,

1 but it remains to be seen if that would be a way to
2 proceed. But biologically, it makes sense.

3 DR. BALIS: Dr. Gorlick.

4 DR. GORLICK: I think most of the reason you
5 bring up the issue of cytotoxic chemotherapies and
6 their combination is in the context of bone
7 sarcomas and rhabdo, there's a standard of care for
8 frontline therapy as well as recurrent. So the
9 issue is you're not going to run as a sort of final
10 study two experimental agents against each other
11 study. Ultimately, it's going to be cytotoxic
12 plus- minus this addition. So you have to think
13 about your ultimate trial and sort of the early
14 stage development.

15 DR. BALIS: Yes, Dr. Mascarenhas.

16 DR. MASCARENHAS: And, again, the model
17 potentially could be the addition of continuation
18 therapy because in these studies, we do have
19 sufficient data now with time to progression in the
20 relapse setting.

21 DR. BALIS: Dr. Reaman.

22 DR. REAMAN: Dr. Gorlick, can you just

1 comment on the mechanism of action as far as
2 inhibition of both the IGF-1 and 2, and the likely
3 applicability to osteo as well as Ewing's sarcoma?
4 Do you think there's some benefit here?

5 DR. GORLICK: Yes. I'm not sure how this is
6 going to work entirely. What I think you're
7 bringing up is the fact that the existing IGF-1R
8 antibodies have variable efficacy, inhibiting
9 binding of IGF-1 versus IGF-2 ligand to the one
10 receptor. So some of the antibodies out there had
11 a little bit more of a preferential IGF-1 effect
12 versus an IGF-2 effect, meaning this is, again,
13 always one receptor but to two or one ligand.

14 Osteos seemed to be more of an IGF-2 ligand-
15 driven malignancy whereas rhabdo seem to be a
16 little bit more IGF-1 ligand driven. This
17 particular agent seems to inhibit both, so if
18 you're just thinking about it mechanistically, I'm
19 guessing its efficacy would be equivalent.

20 DR. BALIS: From a pharmacologic
21 perspective, the other -- I don't know if it's
22 major, but you'd think the major difference between

1 this antibody and those that we've looked at that
2 are binding receptors is just that fact. It may
3 not need access to the tumor to produce an effect.

4 So it's producing an effect by binding a
5 ligand, and that can be done at a site distant from
6 where the tumor is actually located, which may make
7 some difference in terms of its efficacy in solid
8 tumors, especially where you may have limited
9 access of antibodies getting directly in and
10 binding to the tumor cell itself.

11 Is that something, from the company's
12 perspective, that you addressed in terms of your
13 preclinical studies and looked at?

14 DR. LAVALLEE: Yes, we're very interested in
15 that. And, in fact, I think Dr. Viner described
16 our phase 1 study has an expansion phase with
17 biopsies. So we're looking at it in our clinical
18 studies, so the two doses that have been selected
19 is the dose that maximally suppresses the ligand in
20 the periphery and then threefold above it to
21 establish the dynamic range, and then look in the
22 tumor for the effects and modulation of the

1 pathway, and also maybe early on to get some
2 insights into compensatory pathways.

3 DR. BALIS: The other comment I'd make,
4 there was a -- I think which Dr. Gorlick was
5 talking about moving forward without a separate
6 pediatric phase 1 study. And I think the one
7 circumstance, and this fits it where I think is
8 more feasible, is one where you're not at the edge,
9 meaning that you're not already treating at the
10 maximum-tolerated dose. So you have a safety
11 margin, even if there ends up being a difference in
12 children and adults, or adolescents and adults,
13 such that, for example, if the levels ended up for
14 some reason being higher or there was more
15 sensitivity to the drug, you still have some range
16 because you're probably well below whatever the
17 maximum-tolerated dose is with this agent, that it
18 would still be safe to do that.

19 Yes, Dr. Sekeres?

20 DR. SEKERES: Can I just ask a quick
21 question of Dr. Gorlick? So it looks like the
22 field for this class of agents is fairly crowded.

1 Are you excited about what you're seeing here
2 enough that in a limited number of pediatric
3 patients, this would be a consideration for a
4 phase 1 study?

5 DR. GORLICK: I wish the field were crowded.
6 When this whole issue of IGF-1R antibodies and some
7 excitement about activity in pediatrics and
8 sarcomas arose, that was a major concern, that
9 there were a lot of antibodies being developed and
10 there weren't a lot of patients.

11 I believe it is attributed to many of these
12 antibodies not having activity in their pivotal
13 adult studies, but the vast majority of the
14 antibodies are no longer in clinical development.
15 And, actually, I think it's at this point a little
16 bit the reverse scenario where people have gotten
17 an excitement about this class, and there is not a
18 drug that will fill the niche.

19 So I don't think it's -- so short answer is
20 no; it won't be hard to do trials.

21 DR. SEKERES: And are the data you've seen
22 here compelling enough to justify a phase 1 in

1 pediatric population?

2 DR. GORLICK: Yes, I think certainly.

3 DR. BALIS: We're going to move on to the
4 next question.

5 DR. SHAHLAEE: I think we have already
6 touched upon it, but what recommendations do you
7 have regarding the most appropriate pediatric
8 patient populations in which to study these agents.
9 I think we discussed that the bone tumors, we may
10 be able to lump it with adult side, while in the
11 rhabdos, we're going to have to have a pediatric
12 phase 1.

13 Is that a fair conclusion?

14 DR. GORLICK: Yes, I think that's a fair
15 conclusion. I think the most consistent activity
16 across all of these sort of class trials, again,
17 with the caveat that this drug is, in fact, in that
18 class, has been in the Ewing sarcoma population.

19 Again, I think if the field was crowded, you
20 would need to consider avoiding it, largely because
21 of the issues of competitor antibodies already
22 being there. Given what's occurred, I think the

1 primary focus should be Ewing's sarcoma and just go
2 ahead where you've seen the most activity.

3 DR. BALIS: Yes, Dr. Mascarenhas?

4 DR. MASCARENHAS: I guess my concern is
5 that, yes, this is a very interesting class of
6 drugs to study in the patient population we have.
7 I mean, the biggest question is that ultimately we
8 may see the effect of this drug only in a phase 3
9 trial, and is a drug like this going to be around
10 to be tested in the phase 3 setting, given the
11 chances that you could see significant efficacy in
12 an early phase trial? I think we'd be able to test
13 toxicity. Efficacy, I have big questions about,
14 just given what we have already, unless it's done
15 again in the relapsed setting where you actually do
16 show a difference. But then the relapsed setting
17 is also not the best setting to test a drug like
18 this, which might have less efficacy than what we
19 expect with cytotoxic therapy.

20 DR. BALIS: I think we take that risk all
21 the time. There's always an issue of the timing
22 for starting pediatric studies, the appropriate

1 time. If we start too early, the drug may, as many
2 of these have, die on the vine because there's no
3 indication from adults from the pivotal trials.
4 But if we wait too late, particularly if it reaches
5 the market, then it may get more difficult to test
6 it at that point.

7 So it's always a risk in terms of
8 determining when to start. My inclination is once
9 there's good safety data in adults, if there's a
10 good rationale for doing it -- and I think in this
11 case, I think everybody here agrees that there
12 is -- that's probably the point to move ahead with
13 it.

14 In terms of the tumor types, I mentioned
15 that I agreed that we may not need to have phase 1
16 data necessarily in an adolescent and young adult
17 population, but that doesn't preclude the fact that
18 we may need that kind of data in children,
19 particularly if we're going to look at other
20 sarcomas. And once these drugs get into pediatric
21 studies, there's always interest in looking at
22 tumors other than a particular target tumor. So I

1 think it's still important at this point to look
2 carefully at a wide age range in terms of
3 pharmacokinetics and safety.

4 Yes, Dr. Mascarenhas.

5 DR. MASCARENHAS: I guess just given the huge
6 amount of preclinical data in this biological
7 pathway, is there a mechanism, at least with the
8 FDA, investigating one of these drugs with an
9 orphan status, that it would last the duration and
10 see a trial through where it's more likely to show
11 an effect?

12 DR. BALIS: You want to address that,
13 Dr. Reaman?

14 DR. REAMAN: Well, this certainly would be a
15 potential orphan status by definition, bone sarcoma
16 in the pediatric age group. Bone sarcomas in
17 general would classify in the agency's definition
18 of orphan diseases. Whether that provides any real
19 advantage to the agent's development or to actually
20 moving this forward and making it available, I'm
21 not really sure.

22 But I think that Dr. Balis did mention

1 getting the toxicity data or at least doing a
2 phase 1 study in younger children. And maybe this
3 question really shouldn't be study and agents,
4 agents being plural, but actually studies being
5 plural with this agent. So I would definitely say
6 that there would be a simultaneous need for not
7 only doing a phase 2 study in an adolescent/young
8 adult population, but at the same time considering
9 a phase 1 study in younger children as well, and be
10 able to move forward.

11 DR. BALIS: Other comments?

12 [No response.]

13 DR. BALIS: You're set?

14 DR. SHAHLAEE: Move on to the last question?

15 DR. BALIS: Oh, there's another one. I'm
16 sorry. Yes, please.

17 DR. SHAHLAEE: I think we've kind of
18 partially answered this one, too. What
19 recommendation do you have regarding the
20 appropriate study design to efficiently evaluate
21 the safety and activity of this class of agents in
22 this pediatric population?

1 DR. BALIS: Go ahead, Dr. Gorlick.

2 DR. GORLICK: So I think the key thing in
3 that is efficiently, and that's the hard thing to
4 try to define when you're talking about a rare
5 disease. I think that's kind of the point Leo was
6 getting at. Ewing sarcoma is a rare disease.
7 That's a good thing. That said, it makes trials
8 more difficult.

9 Really, pivotal phase 3 trials are either
10 going to be a comparison in the recurrent setting,
11 where you have a disease where only a subset recur,
12 or it's going to be an upfront comparison of an
13 addition. And either study in the context of this
14 sort of large cooperative groups that exist are
15 feasible, but even with large cooperative groups,
16 it may require international sites in order to get
17 the numbers that you need to do it in a relatively
18 smaller time period, and it requires some
19 realization -- reality check that even as an
20 international group, it's likely to be a couple of
21 years to get the numbers of patients that you're
22 going to need to address the question in a

1 definitive way. So I think the efficiently part is
2 the hard part.

3 DR. SHAHLAEE: How about in osteogenic
4 sarcoma in an, again, relapse setting?

5 DR. GORLICK: Osteosarcoma is a little
6 more -- I think in some ways, it's a little bit
7 more wide open because there's less in the way of
8 standard of care. I think the studies that are
9 typically done are comparisons to other new agents
10 or comparisons to -- like the typical frontline
11 recurrent regimen as an addition, which would be
12 the ifosfamide, etoposide and the patient has
13 gotten cisplat-dox, high-dose methotrexate up front
14 as a plus or a minus. Ultimately, given the
15 similar incidence and the similar rate of
16 recurrence, I'd imagine the rates and the durations
17 of the studies are probably not that wildly
18 different.

19 I think the plus of the upfront setting in
20 osteosarcoma is it's a little bit wider open,
21 meaning there's not a lot of other questions that
22 are sort of burning to be asked, so it's easier to

1 get to the upfront setting. I think the
2 complications are osteosarcoma therapy is very
3 doxorubicin dense, so you have to be comfortable
4 about cardiac toxicity. And that's probably your
5 biggest issue. And you have a little bit less data
6 that there's activity with this class, in the
7 osteos. But for whatever that's worth.

8 DR. BALIS: Dr. Sekeres.

9 DR. SEKERES: I was stuck on the
10 efficiently, also. We've talked before about rare
11 disease indications and pathways for efficient
12 study conduct to reach an approvable risk-benefit
13 ratio. This does satisfy some of those criteria.
14 It's a rare disease, a patient population that
15 needs something.

16 What would get in the way is we don't have
17 enough data supporting a really wow effect here.
18 We're seeing some stable disease, some patients who
19 live a long time without their tumor growing, but
20 nothing that's just blowing you out of the water
21 where you could see, gee, let's do a quick phase 1
22 to 2 design, where if you meet certain markers at

1 the end of phase 1, you could progress to a phase 2
2 with a possible registration strategy. That's the
3 part that I'm just not seeing yet. I'd love to see
4 more data in combination in phase 1 with this.

5 DR. BALIS: Dr. Mascarenhas.

6 DR. MASCARENHAS: Just a couple of comments.
7 I think if you're going to use response as a
8 surrogate of activity, osteosarcoma is always a
9 hard model to do that in, number one. And, number
10 two, the point I was trying to make earlier is that
11 if there's a lot of strong biology, we may need to
12 look at other models. And I think one of the
13 examples which I could throw out is the use of
14 retinoic acid in neuroblastoma. There were no
15 responses in the phase 2 setting. It made a
16 difference in the phase 3 setting. There was very,
17 very strong biology to support that, and we may
18 need to think of potential trials like this for
19 Ewing sarcoma or rhabdomyosarcoma, which are driven
20 tremendously by biology.

21 The other concern is I think -- I mean, all
22 of us in the room probably recognize that in

1 sarcomas, we've probably reached out plateau as to
2 what we can achieve with cytotoxic therapy. And if
3 you're going to take it to the next level, some of
4 these trials may need to be done with some act of
5 faith, but provided we've taken the safeguards of
6 patient safety in consideration.

7 DR. BALIS: Dr. Reaman.

8 DR. REAMAN: To address Dr. Sekeres'
9 concern, I think efficient, we weren't looking for
10 an efficient or a rapid road to approval. We were
11 really looking at a mechanism by which we could
12 efficiently evaluate this agent before it
13 disappears, because that's sort of been our history
14 to date.

15 [Laughter.]

16 DR. REAMAN: So with all due respect to the
17 sponsor, that was the reason for the efficiency
18 here.

19 DR. BALIS: I think the thing that we -- I
20 guess I should say, you can see how we think in
21 pediatric oncology. We don't think of developing
22 drugs for a second line indication. We talked

1 about this before. We think about curing our
2 patients. If you prolong a 70-year-old's life by
3 four or five years, you've done a great thing, but
4 we have 4-year-olds, and we need to prolong their
5 life by 70 years, not by months or years.

6 So you can see the thought is going right to
7 a phase 3, and that means that they're in the
8 relapse setting. Those studies are a
9 steppingstone. They're not the way that we see a
10 drug to reach its final resting place in terms of
11 where it's indicated.

12 But I think it's still an issue when we talk
13 about this, the same as it was with the last one,
14 is do we need a phase 2 study, or is there enough
15 biology to move this forward? And if we're going
16 to do a phase 2 study, what would it take as a
17 result of that to interest us in moving it up into
18 the initial frontline setting for both -- and it
19 may be disease specific. It may be different for
20 osteo versus Ewing's.

21 But the one thing for both of those diseases
22 that we tend to do is neo-adjuvant therapy, which

1 is kind of like a window, and then we get tumor
2 tissue. Actually, in osteo, it's a very
3 important -- we've used it in some ways, although
4 we don't know for sure if it works, to guide our
5 therapy even, to look at response. But we may have
6 access to tumor tissue in all of those patients
7 after initial therapy to look at biologic effects
8 of this drug as well in a frontline setting, where
9 we wouldn't be able to do that in a relapse
10 setting.

11 So I'll ask you, Rich. What do you think
12 about for Ewing's, let's say specifically, a
13 phase 2 study before looking at it up front?

14 DR. GORLICK: I think you can think about
15 doing it in the classic way just to get a response
16 rate to verify that it's sort of that same
17 10 percent, or people have proposed randomized
18 phase 2 trials that are effectively phase 3 trials.
19 So even though it's atypical for pediatric
20 oncology, doing it at this scale that it
21 definitively answers the sort of change in survival
22 question --

1 DR. BALIS: So is it in a relapse or newly
2 diagnosed?

3 DR. GORLICK: They have thought about doing
4 it in the relapse setting, meaning there have been
5 designs developed where you can answer it
6 definitively in that sort of setting. It sort of
7 bypasses -- to bring it into the frontline setting,
8 you're usually going to have two phase 2 trials,
9 one to basically define that your response rate is
10 at sort of the activity level that you're
11 interested in, and a second basically, which is
12 sort of a phase 1-2, combining it with standard
13 chemotherapy, making sure you don't modify your
14 ability to deliver standard of care.

15 I think the challenge in adding something to
16 the localized setting of Ewing's sarcoma is right
17 now there is a belief, based on the last Children's
18 Oncology Group study, phase 3 study, that intensive
19 timing of Ewing sarcoma improves its therapy as
20 opposed to standard timing every three weeks. Any
21 agent that's going to compromise the timing of
22 standard therapy is going to raise the question

1 that it's going to compromise the benefits that
2 have been achieved through that. So whatever you
3 add has to be very nontoxic.

4 I think this certainly has the possibility
5 of doing it, but that's something you'd have to
6 prove.

7 DR. BALIS: Dr. Mascarenhas.

8 DR. MASCARENHAS: So I think one of the
9 strategies which we've sort of thought about and
10 spoken a lot with this soft tissue sarcoma
11 committee of the Children's Oncology Group is to
12 really screen agents in their relapsed setting with
13 their randomized phase 2 design and accept a
14 relaxed alpha to show a slight effect, and that
15 would be sufficient for us to consider running a
16 formal phase 3 trial in the intermediate group
17 strategy.

18 Potentially, this could be addressed in that
19 setting. And, presently, we're investigating three
20 targeted agents, one in the high-risk setting and
21 two in the standard-risk setting. And it's
22 unlikely that all three of them are going to be

1 winners. But I think if one of them shows
2 sufficient amount of interest, that would be
3 sufficient information to consider investigating it
4 in the upfront setting in a group of patients which
5 has an intermediate prognosis; not in the low-risk
6 patients, but I think in the intermediate- or high-
7 risk patients.

8 DR. BALIS: Okay. Any other comments?

9 [No response.]

10 DR. BALIS: Great. Thank you very much.

11 Do we have a closing comment from the FDA?

12 DR. BRIGGS: No, nothing additional.

13 **Adjournment**

14 DR. BALIS: All right. Well, thank you all
15 for being here today. I think some of you will be
16 back tomorrow for a quite different discussion.
17 Those who aren't attending, thank you for your
18 participation today, and this concludes the final
19 session. The committee is again reminded that this
20 is an open forum, and we have our discussions here
21 at the table and not amongst ourselves.

22 Thank you again, and we'll see some of you

1 back tomorrow.

2 (Whereupon, at 3:49 p.m., the meeting was
3 adjourned.)

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