FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC)

Tuesday, February 8, 2011

8:00 a.m. to 4:30 p.m.

FDA White Oak Campus

Building 31, The Great Room

White Oak Conference Center

10903 New Hampshire Avenue

Silver Spring, Maryland

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GUEST SPEAKER (Non-Voting, Presenting Only)

Hilde Boone, Pharm, MSc

European Medicines Agency

Liaison Official at the US FDA

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C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(7:58 a.m.)

Call to Order and Introduction of Committee

DR. WILSON: Why don't we go ahead and get started? We really have a very long day. I'd like to welcome you all to this ODAC meeting. To start with, I'd like to go around the room. Let's start on the right side with Dr. Curt. Please state your name into the record and where you're from.

DR. CURT: Gregory Curt, medical oncologist and industry representative to ODAC.

DR. MARTINO: Silvana Martino, medical oncology, from the Angeles Clinic in Santa Monica.

DR. RICHARDSON: Ron Richardson, medical oncologist, Mayo Clinic, Rochester, Minnesota.

DR. MORTIMER: Joanne Mortimer, medical oncologist, City of Hope.

DR. LYMAN: Gary Lyman, medical oncologist, Duke University.

DR. D'AGOSTINO: Ralph D'Agostino, statistician, from Boston University

DR. LOGAN: Brent Logan, statistician, from

the Medical College of Wisconsin.

DR. FREEDMAN: Ralph Freedman, gynecologic oncologist, M.D. Anderson Cancer Center.

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

DR. WILSON: Wyndham Wilson, medical oncologist, National Cancer Institute.

DR. VESELY: Nicole Vesely, designated federal officer, ODAC.

DR. LOEHRER: Pat Loehrer, medical oncologist, Indiana University Medical Center.

DR. KELLY: William Kelly, medical oncologist, Thomas Jefferson University.

MS. MASON: Virginia Mason, oncology nurse and breast cancer advocate with the Inflammatory Breast Cancer Research Foundation.

MS. MAYER: Musa Mayer. I'm the patient rep for this meeting, and I'm a breast cancer advocate from New York City.

DR. SMITH: Malcolm Smith, pediatric oncologist, Cancer Therapy Evaluation Program, NCI.

DR. DEMKO: Suzanne Demko, medical team

leader, Office of Oncology Drug Products, FDA.

DR. PAI-SCHERF: Lee Pai-Scherf, medical officer, Office of Oncology Drug Products, FDA.

DR. KLUETZ: I'm Paul Kluetz, a medical officer at the Office of Oncology Drug Products, FDA.

DR. MURGO: I'm Anthony Murgo, FDA.

DR. PAZDUR: Richard Pazdur, Office of Oncology Drug Products.

DR. WILSON: Thank you. Welcome. Now, I have a statement to read into the record.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory

Committee Act and the Government in the Sunshine Act, we ask that advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussion of the meeting topics during breaks or lunch. Thank you.

Now, we have another statement, conflict of interest statement, to be read.

Conflict of Interest Statement

DR. VESELY: The Food and Drug Administration is convening today's meeting of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

All members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and

are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by, but not limited to, those found at 18 USC Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act, is being provided to participants in today's meeting and to the public. FDA has determined that members and temporary voting members of this committee are in compliance with Federal ethics and conflict of interest laws.

Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees

with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and, for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

At today's meeting, the committee will hear updates on new drug applications and biologic license applications approved under 21 CFR 314.500 and 601.40, subparts H and E, respectively, accelerated approval regulations prior to January 1st, 2009. These updates will provide information related to the, one, status of Phase 4 clinical studies and, two, difficulties associated with the completion of Phase 4 commitments.

Phase 4 studies are post-marketing studies to confirm clinical benefit of a drug after it receives accelerated approval.

Based on the updates provided, the committee will have a general discussion centering on possible ways to improve the planning and conduct of trials to confirm clinical benefit. The overall goal will be the optimization of the accelerated approval process, with a focus on decreasing the amount of time to confirm or failure to confirm clinical benefit, while continuing to provide early availability of promising oncology products.

This is a particular matter of general applicability meeting during which general issues will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they

have made concerning the issues before the committee.

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

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

FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firms that could be affected by the committee's recommendations.

Thank you.

DR. WILSON: I'd like to recognize that Dr. Frank Balis just entered. So, Frank, could you please state your name into the record and your affiliation, and then we'll hear from Dr. Pazdur.

DR. BALIS: Frank Balis, Children's Hospital, Philadelphia.

Opening Remarks

DR. PAZDUR: Good morning. I'd like to take this opportunity to welcome you to the third advisory committee meeting on accelerated approvals.

First held in 2003, this recurring meeting is designed to provide an update on accelerated approval applications that have not completed their post-marketing trial requirements, as well as identifying challenges applicants have faced the design, implementation and completion of these required trials. We will conclude the meeting in the afternoon by holding a discussion with the committee to solicit advice in improving the accelerated approval program.

In 1992, the accelerated approval regulations, subpart H for new drugs and subpart E for biologics, were added to expedite the delivery of drug products that would provide a benefit for serious or life-threatening illnesses that lacked satisfactory treatment. The patient population treated must have a serious or life-threatening disease, and the drug must demonstrate a benefit over available therapy.

Approval can be based on a surrogate that is, quote, "reasonably likely," unquote, to predict a clinical benefit. Approval is subject to the requirement to verify clinical benefit with one or more adequate and well controlled trials which are conducted with, quote, "due diligence," unquote. The regulations state that these trials would usually be underway at the time of the accelerated approval.

FDA now has the authority under FDAAA to impose financial penalties to those sponsors who do not conduct their post-marketing trial requirements with, quote, "due diligence," unquote. This

represents a significant change for the accelerated approval of drugs since our last meeting in 2005.

Following my introduction, Dr. Paul Kluetz will provide a presentation on the status of the accelerated approval for oncology drug indications to date. The accelerated approval pathway continues to be widely used for new oncology drug indications.

The average number of approved oncology drug indications per year has increased from approximately 2.9 to 3.3 when comparing the period before 2005 to the period after 2005. The median time from accelerated approval to completed post-marketing trials confirming clinical benefit was 3.9 years. However, the range was up to 12.6 years and eight indications, or 31 percent of the accelerated approvals, exceeded six years to verify a clinical benefit. This would not be a problem if all confirmatory trials verified the benefit. However, as expected, drugs have failed to confirm clinical benefit.

By accepting a surrogate endpoint that is

reasonably likely to predict a benefit, we expect some drugs will fail to confirm a benefit in post-marketing trials. This is beginning to become apparent now with five applications, approximately 10 percent of oncology accelerated approvals, which have failed to verify a clinical benefit.

Whether by completed trials that failed to confirm a clinical benefit or the inability to accrue patients to their post-marketing trials, the failure to verify benefit has led to either restricted distribution, voluntary or involuntary withdrawal of these indications.

As previously noted, by granting accelerated approval based on surrogate endpoints, we do expect a small percentage of drugs to fail to confirm clinical benefit. This is a trade-off for early availability of promising drugs for severe and life-threatening diseases and underscores the importance of due diligence and early integration of post-marketing trial design into a comprehensive drug development program.

For today's meeting, we will begin with

Dr. Kluetz's presentation. Following Dr. Kluetz's presentation, Dr. Jeff Murray, from the FDA Division of Antiviral Drugs, will provide information on the use of accelerated approval regulations in approving antiretroviral drugs.

While we recognize significant differences between HIV and oncology drug development, the experience in HIV with accelerated approvals does have some parallels and may prove to facilitate some of our discussion in the afternoon.

In HIV studies for accelerated approval, two large randomized trials are generally performed. Accelerated approval is granted on the basis of viral load at 24 weeks and then confirmation of clinical benefit is demonstrated in the same trial at 48 weeks. Having several trials ongoing at the time of accelerated approval and the use of an interim analysis of a surrogate endpoint in a randomized trial deserves discussion in oncology.

Dr. Murray's presentation will then be followed by the sponsor presentations, each of which will be followed by a brief period of time

for clarifying questions from the committee.

Our purpose of the sponsor's presentation is to bring the committee up to date with completion of accelerated approval studies. We do not plan to have an in-depth discussion on each of these applications either in the morning or the afternoon session.

In the afternoon session, we will have a brief presentation by Hilde Boone, from the European Medicines Agency, or EMA, on the use of conditional marketing authorization, a recent regulatory mechanism similar to our accelerated approval process. The EMA use of conditional approval relies on the demonstration of a positive benefit-risk ratio based on preliminary evidence from an ultimately comprehensive drug development program.

Like the FDA requirements, there are, quote, "specific obligations," unquote, to provide further confirmatory data. While there are similarities, perhaps the most important difference between accelerated approval and Europe's conditional

approval is that their conditional authorization is valid for one year and expires unless renewed. This allows for regular assessment of these trials and early detection of problems in meeting post-marketing commitments.

The EMA presentation will be followed by an open public hearing.

In the afternoon, we have identified four key areas we would like discussion from the committee. These areas include the use of single-arm trials to gain accelerated approval, the number of confirmatory trials that should be conducted, the timing of confirmatory trials, and, lastly, unique issues using cooperative groups either in the United States or Europe to conduct and complete these required regulatory obligations.

Regarding single-arm trials, single-arm trials have formed the basis for over half of the accelerated approvals for oncology drugs to date. While single-arm trials often require less resources and time to complete, they provide limited data on clinical benefit and safety.

Single-arm trials for accelerated approval have usually performed in refractory populations, where no available therapy exists. As a greater number of drugs are approved, identification and documentation of a refractory population is increasingly problematic. In addition, marginal response rates observed in single-arm trials in the refractory setting make it difficult to determine whether these findings are reasonably likely to predict clinical benefit.

Alternatives to a single-arm trial in a refractory population include the following: randomized trials in a less refractory population against an active control using a surrogate endpoint, analyzed at an earlier time, or a randomized trial in a refractory population comparing the investigational agent to best supportive care or various agents selected by the investigator. Randomized trials provide the opportunity to take a look at a wider variety of endpoints and allow for an improved characterization of safety.

We will be asking the committee to discuss settings where a randomized study should be required for accelerated approval, and, alternatively, to discuss situations where a single-arm trial may be appropriate to support accelerated approval.

With regard to our second topic, number of confirmatory trials, the time from either a successful completion of a required post-marketing study or withdrawal of the indication can be prolonged.

For drug approval in most therapeutic areas outside of oncology, two well designed, well controlled, randomized trials are usually required. In oncology, FDA has frequently approved drugs on the basis of a single, well conducted trial. FDA usually receives proposals for a single trial to be conducted post-approval to demonstrate clinical benefit for drugs receiving accelerated approval.

Since these studies are generally performed in related but different disease settings, positive studies may allow the applicant to obtain

supplementary indications in addition to fulfilling their commitments under accelerated approval.

In the setting of accelerated approval, when only one confirmatory post-marketing trial is conducted, there is the increased risk that clinical benefit will not be demonstrated in a timely manner if that single trial fails to confirm a benefit or does not accrue patents as rapidly as planned. This may lead to either earlier withdrawal of the indication or the need to conduct a second trial, resulting in substantial delays.

We will be asking the committee to discuss whether applicants should be required to conduct at least two adequate and well controlled clinical trials as their accelerated approval commitments to verify clinical benefit. As previously noted, because these trials are performed in related, but different disease settings, these trials, if successful, may lead to supplemental indications in addition to fulfilling the requirements to demonstrate clinical benefit.

With regard to the additional topic for this

afternoon's discussion, that is, timing of confirmatory trials, accelerated approval regulations clearly state that post-marketing trials would, quote, "usually be underway," unquote, at the time of accelerated approval.

Once a drug gains accelerated approval in a refractory disease state, accrual to a confirmatory trial in the same setting is difficult. Pursuing a confirmatory trial in a less refractory setting can potentially circumvent this problem; however, changes in science, accrual challenges, and other hurdles may lead to delays.

FDA believes that more timely completion of accelerated confirmatory trials can be enhanced if accelerated approval is granted when the confirmatory trial is ongoing. This is the paradigm that is used in the HIV setting.

Given the regulations state that the trials would be usually underway at the time of accelerated approval, we will be asking the committee to discuss whether an approval should be delayed until such trials are ongoing, keeping in

mind that access to drugs can be accomplished under expanded access programs if a delay is anticipated.

Regarding our last topic, that is, confirmatory trials and the cooperative groups, FDA recognizes that cooperative groups, both in the United States and Europe, are critical to drug development and encourages their participation throughout the drug development process. Applicants may engage a cooperative group to design and execute a confirmatory trial to fulfill their regulatory obligation. However, the ultimate responsibility of completing the confirmatory trial with, quote, "due diligence," unquote, rests with the application. This fact may hold importance, added importance, to the sponsors with the introduction of financial penalties in 2007 for lack of timely completion of these trials at their agreed-upon date.

We will be asking the committee to discuss the use of cooperative groups to conduct clinical trials required to demonstrate clinical benefit to fulfill the sponsor's specific accelerated approval

obligations. And if the cooperative group is used, we will ask you to discuss if additional trials should be conducted under the direct supervision of the applicant to ensure adherence to complete the post-marketing requirement by a specified date.

In summary, accelerated approval allows for earlier marketing of promising drugs at the expense of increased uncertainty. While almost 10 percent of the oncology indications approved under accelerated approval were unable to demonstrate a clinical benefit, this should not be thought of as a failure of the accelerated approval paradigm. Rather, this highlights that by granting accelerated approval based on a surrogate that is reasonable likely to predict clinical benefit, we expect a small percentage of products to fail to confirm clinical benefit.

This is a trade-off, again, of early availability of promising agents for severe and life-threatening diseases. We continue to point out that the accelerated approval, with the initial trials to seek accelerated approval, as well as the

trials to confirm clinical benefit, should be a part of a well thought out, comprehensive drug development program that is discussed with the FDA from its inception. These confirmatory trials are as important, if not more important, than the initial trials leading to accelerated approval.

Thank you.

DR. WILSON: Thank you. I would now like to invite Dr. Kluetz.

FDA Presentation - Paul Kluetz

DR. KLUETZ: Good morning. My name is Paul Kluetz, and I'm a medical officer here at the FDA, Office of Oncology Drug Products. The goal of this advisory committee meeting, as was stated by Dr. Pazdur, is to provide an update on the status of accelerated approvals for oncology.

Today, we'll hear from several sponsors regarding their outstanding post-marketing commitments, and have a discussion regarding the accelerated approval process, with a focus on ways to make the program better.

My talk today will begin with a brief

overview and regulatory background of the accelerated approval process. I'll then update the committee on the status of the accelerated approval indications to date. This will be followed by a few brief conclusions, at which point I'll end my talk with the remaining agenda, including sponsor presentations and questions.

In the United States, drugs are approved on adequate and well controlled clinical trials demonstrating substantial evidence of clinical benefit based on prolongation of life, a better life, or an established surrogate for either of the two. This is known as regular approval.

In 1992, the accelerated approval regulations, subpart H for new drugs and E for biologics, were added in an effort to hasten the delivery of drug products which appeared to provide a benefit for serious or life-threatening illnesses that lacked satisfactory treatments.

Subpart H and subpart E allow for accelerated approval of a product based on the use of a surrogate endpoint, which is reasonably likely

based on epidemiologic, therapeutic, pathophysiologic or other evidence to predict clinical benefit, or on an effect on a clinical endpoint other than survival or irreversible morbidity.

Because accelerated approval is granted on the basis of less substantial evidence than regular approval, it is subject to the requirement that the applicant study the drug further to verify and describe its clinical benefit. This is also known as a post-marketing requirement.

With respect to the timing of these clinical requirements, post-marketing trials would usually be underway. The studies would also be adequate and well controlled, and the applicant shall carry out any such studies with due diligence.

So to summarize the critical elements of an accelerated approval application, the population should have a serious or life-threatening disease; the drug must demonstrate a benefit over existing or available therapy.

Approval can be based on a surrogate

endpoint that is reasonably like to predict a clinical benefit, but the sponsor is subject to the requirement to verify this benefit with one or more adequate and well controlled trials. Post-marketing trials would usually be underway; and, finally, the applicant should carry these out with due diligence.

Importantly, if post-marketing studies fail to demonstrate clinical benefit or the applicant fails to perform these trials with due diligence, the FDA may withdraw approval following a public hearing.

With respect to available therapy, the accelerated approval regulations require that the drug provide meaningful therapeutic benefit to patients over existing or available therapy. And in order to clarify what was meant by available therapy with respect to accelerated approval, in July of 2004, the FDA released a guidance for industry.

This guidance states that available therapy and the terms "existing treatments" and "existing

therapy" should be interpreted as therapy that is specified in the approved labeling of regulated products, with only rare exceptions. However, exceptions may include well established oncologic treatments.

Post-marketing trials are required when there's uncertainty. More commonly, the uncertainty in accelerated approval exists regarding the relationship of the surrogate endpoint to true clinical benefit. For instance, does an improvement in response rate or progression-free survival translate into an overall survival benefit?

But post-marketing trials may be required not only for surrogate endpoints which are not well established, but also when there is uncertainty that a recognized, observed clinical benefit correlates with an improved ultimate outcome. This is illustrated with the dexrazoxane application, the first oncology drug approved in 1995.

While it met its clinical benefit endpoint with respect to reduced cardiac toxicity during

treatment with doxorubicin-based therapies for breast cancer, there was concern that there may be protective effects on the tumor, and, thus, the sponsor was required to conduct post-marketing clinical trials to verify that the reduced cardiac toxicity was not outweighed by a potential decrement in antitumor efficacy.

In short, the accelerated approval process allows for early marketing of promising drugs, but at the cost of increased uncertainty regarding the ultimate clinical benefit, and this highlights the importance of the timely completion of post-marketing trials to verify that benefit or a complete trial to fail to confirm benefit, in which case, the product could be removed.

A presidential communication was drafted in March of 1996 by then President Bill Clinton, entitled "Reinventing the Regulation of Cancer Drugs." This was created to highlight the commitment to expand and speed up access to new cancer drugs. The document further defined what was meant by a surrogate endpoint reasonably likely

to predict clinical benefit under accelerated approval, stating, "The FDA will substantially expand the use of the accelerated approval process for cancer treatments based on verified and recognized demonstration of objective tumor shrinkage, including partial response.

It recognized that objective tumor shrinkage and the frequency in magnitude of this effect as an accelerated approval endpoint should outweigh the drug's toxicity, and that, as mentioned before, accelerated approvals are subject to confirmatory studies to verify the relationship of this to clinical benefit.

The presidential communication went on to describe several other ways to facilitate accelerated approval. First, because it may be difficult to conduct a confirmatory trial in the initial refractory population for which it gained accelerated approval, a confirmatory trial may be conducted in a more front-line, less refractory setting. Stated another way, post-marketing studies need not be carried out in the same

population for which the drug was approved.

Additionally, highlighting a point made in the available therapy guidance, a drug approved under accelerated approval that has not yet completed its post-marketing trials and verified its benefit is not considered available therapy. Thus, prior to the confirmation of clinical benefit, accelerated approval of one drug for a patient population should not preclude the accelerated approval of additional therapies for that population.

The European Medicines Agency, or EMA, our European regulatory counterpart, has also developed a mechanism to attempt to speed delivery of promising agents to the market. A more comprehensive review of the EMA conditional marketing pathway will be provided by Hilde Boone this afternoon.

There are three approval types in Europe currently, including normal, exceptional and conditional approval. The conditional approval is most akin to our accelerated approval process, came

into effect in April of 2006. Similar to accelerated approval, it's based on preliminary evidence demonstrating a positive benefit-risk ratio. And like the FDA post-marketing requirements, there are specific obligations to provide further confirmatory data regarding this preliminary evidence.

While there are similarities, the most important difference, as stated earlier, is that Europe's conditional approval is valid for one year only and expires unless renewed. Again, this allows for regular built-in analysis of due diligence and detection of any problems that they may encounter early on.

The EMA also notes that there is clear information to patients and health professionals on the conditional nature of the authorization; and, finally, that there may be financial penalties if sponsors fail to fulfill their obligations.

Although not contained in the FDA accelerated approval regulations, failure to conduct a required post-marketing study under the

accelerated approval regulations is now deemed to be a violation of the Food and Drug Administration Amendments Act of 2007, also known as FDAAA. Drafted to amend the FD&C Act to enhance the post-marketing authorities of the FDA, violations can be subject to financial penalties. Thus, with respect to accelerated approval, failure to perform post-marketing trials with due diligence is now subject to financial penalties.

In 2003, the first ODAC was held to discuss the progress of the accelerated approval program and, at that time, Dr. Pazdur made it clear that the meeting would -- that the accelerated approval process would benefit from continual review with these meetings to shed the light of day on accelerated applications; not only to identify and provide an update for applications that were delayed in fulfilling their post-marketing requirements, but, also, to discuss challenges unique to these applications and, really, to solicit input to attempt to improve the accelerated approval program.

In 2003, there were 19 indications for 16 drugs approved in oncology under the accelerated approval regulations and of those, seven out of 19 were recently approved, within 18 months; 21 percent had satisfied their post-marketing requirements and verified benefit; and the remainder were presented as indications that had not yet completed their post-marketing requirements.

Because of the complexity of confirmatory trial design, including endpoint selection and patient population, it was stressed at the 2003 ODAC, and, indeed, will continue to be highlighted today, that early integration of accelerated approval planning into a comprehensive drug development plan is critical.

Two years later, in 2005, the second accelerated approval ODAC was held, and at that time, there were 28 indications for 24 drugs that were approved under accelerated approval.

By 2005, 10 of 28 had completed post-marketing requirements verifying benefit, and an

equal number were approved less than 36 months. At this point, we had begun to see what was to be expected with surrogate endpoints that were reasonably likely to predict clinical benefit in that two indications, amifostine and gefitinib, were 7.1 percent of oncology indications under accelerated approval, had failed to confirm the benefit, resulting neither with the voluntary withdrawal of the indication or, in the case of gefitinib, restricted distribution, allowing access only to patients already obtaining benefit from gefitinib. And it has been recently announced by the company that gefitinib will be voluntarily withdrawn from the U.S. market in September of this year.

Now, five years since the last ODAC update, I'll present the most current status of the accelerated approvals for oncology drug products.

Since the first accelerated approval in 1995, there are now 49 new indications for 37 oncology drug products. Twenty-seven of 49, or 55 percent, have verified clinical benefit in

completed post-marketing trials. Seven of 49 were recently approved within the last two years. Five indications, or 10.2 percent, have failed to confirm a benefit. Four of these have failed to verify benefit in completed post-marketing trials. And the fifth, celecoxib, for reduction in colonic polyps for familial adenomatous polyposis, has not completed accrual to their confirmatory trial in now over 11 years, and the sponsor has announced they plan to voluntarily withdraw the indication. Celebrex will continue to be marketed for its other approved indications.

We've asked the sponsors of six indications granted accelerated approval prior to 2009 to present an update on the status of their post-marketing requirements.

With respect to the trial design for the initial accelerated approval of the 49 indications, 20 indications were based on a randomized comparative trial design and 29 were based on single-arm studies. The surrogate endpoints used for accelerated approval were response rate and

duration in 36 indications; time to event endpoints in 10 indications, including progression-free survival, disease-free survival, and time to progression; and, other endpoints, including measures of cardiomyopathy, creatinine clearance, and colonic polyp incidence were used for the remaining three indications.

Post-marketing trial designs that led to confirmation of benefit were nearly all randomized, with the exception of three; imatinib for pediatric Philadelphia positive CML; nilotinib for imatinib-resistant or intolerant Philadelphia positive CML; and a liposomal doxorubicin for Kaposi's sarcoma, which were all based on single-arm trial data.

The endpoints used for confirmatory trials that verified clinical benefit were mostly survival and time to event endpoints, again, PFS, TTP and DFS. And of the six indications that used response rate for confirmation of benefit, the disease indications include Kaposi's sarcoma, cutaneous T-cell lymphoma, lymphomatous meningitis, and three with Philadelphia positive CML.

The number of indications approved for oncology under the accelerated approval process has remained relatively consistent over time, with a slight uptick. This bar graph shows the number of indications approved under accelerated approval over time, with the number of indications on the Y-axis and the year of approval on the X-axis.

At the 2005 accelerated approval ODAC, there were 29 indications approved over 10 years, an average of 2.9 approvals per year; and the average yearly approval rate has remained relatively constant, with a slight increase to an average of 3.3 approvals per year from the period 2005 through 2010.

The interval of time between the accelerated approval of a product and the completion of confirmatory trials with verification of benefit is an important metric. This interval of accelerated approval to verification of benefit can be thought of as the time saved during drug development to get effective drugs to patients and really represents the mission of the accelerated approval process.

Of the 49 accelerated approvals, there have been 27 indications which completed post-marketing trials and verified their benefit, and this slide shows each of the 27 indications sorted from left to right by the date of their accelerated approval, ranging from 1995 through 2008. Time in years is on the Y-axis, and so each bar is one individual indication and its length of time it took from accelerated approval to verification of benefit.

As you can see, while the median time from accelerated approval to confirmation of benefit is 3.6 years -- earlier, Dr. Pazdur had said 3.9, but we recently had an approval that had verification of benefit. It is 3.6 years. The range was up to 12.6 years, and, in fact, eight indications, or 30 percent of approvals, took over six years to verify clinical benefit.

This would not be a problem, obviously, if all trials verified benefit, but as expected and as we see today, a number of indications have failed to confirm benefit, making it clear that accelerated approval post-marketing requirements

need to be done with due diligence and these times need to be shortened.

The completion of post-marketing trial requirements is to be undertaken with due diligence. And as of December 31st, 2010, of the accelerated approval indications that have not yet completed confirmatory trials, the five longest times since accelerated approval have ranged from 5.2 to 11 years.

The longest of these, celecoxib, has announced they will voluntary withdraw the indication. Of note, the removal of the indication is not due to any new efficacy or safety data that alter benefit-risk profile of Celebrex, and all other indications remain approved and unchanged for Celebrex. The sponsor also intends to continue the CHIP trial. The status of the other four drugs, cetuximab, Bexxar, clofarabine and nelarabine, will be summarized by sponsors following this presentation.

The five longest periods between accelerated approval and completed trials verifying benefit

have ranged from 7.4 to 12.6 years, with the respective associated drugs listed on this slide.

While there is no regulatory definition for due diligence relating to the completion of post-marketing clinical trial requirements, most would agree that over seven years of marketing an unproven drug with at least some level of toxicity is suboptimal.

Recognizing the difficulties presented by the heterogeneity of disease with respect to incidence and natural history, as well as unforeseen circumstances, such as changes in available therapies, competing trials, and changes in science, we must continue to concentrate on decreasing the time between accelerated approval and verification of benefit.

As mentioned previously, of the 49 oncology indications granted accelerated approval, there are five that have failed to confirm a clinical benefit. The table on this slide presents the five drugs and their indications, with the date of accelerated approval on the left and the years on

the market on the right.

The four indications bolded on this slide have completed post-market trials which failed to confirm benefit. And as stated prior, celecoxib is going to be voluntarily withdrawn for inability to accrue in over 11 years.

Note that the time from accelerated approval to voluntary withdrawal, restricted access or activation of the withdrawal proceedings for the five indications ranged from 2.1 to 11 years, and, as you can see, most of the withdrawals here were done voluntarily by the sponsor.

When a product fails to confirm the original clinical benefit for which it gained accelerated approval, the indication may be voluntarily withdrawn by the applicant. However, as mentioned before, an indication may be withdrawn involuntarily by the FDA if either post-marketing trials failed to confirm a benefit or there is a failure to perform post-marketing requirements with due diligence.

As seen in the prior slide, until recently,

most of the removals have been voluntary by the sponsor. However, after a near unanimous July 2010 ODAC decision to withdraw bevacizumab for first-line HER-2 negative metastatic breast cancer, on December 16th, 2010, the FDA announced a proposal to withdraw marketing approval of this indication. This represents the first time the FDA has initiated the withdrawal process for an oncology indication under accelerated approval.

As of December 31st, 2010, the indication for bevacizumab in a first-line HER-2 negative metastatic breast cancer has been on the market for only 2.9 years, and with the exception of gefitinib, as you can see, this is a relatively shorter period on the market.

Notably, both of the post-marketing trials for this indication, AVADO and RIBBON-1, were ongoing at the time of accelerated approval, which, in part, explains the relatively short time from accelerated approval to the withdrawal proceedings. This highlights the important time saving seen with multiple confirmatory trials and having

confirmatory trials that are already underway.

As we have seen, when approving a product under accelerated approval, we accept a degree of uncertainty. And while the accelerated approval process has been effective in providing oncology patients earlier access to clinically beneficial treatments, the marketing of ineffective therapies is a natural is to the accelerated approval program.

The proportion of indications, approximately 10 percent failing to confirm a benefit, is now slightly higher than that seen in the 2005 ODAC. And while the FDA is pleased with the success of the accelerated approval program and providing more access to oncology drugs, the importance of decreasing the time that potentially ineffective therapies are marketed cannot be overstated, further highlighting the importance of due diligence and careful and timely confirmatory trial development.

I'd like to end the presentation with a few conclusions, followed by our agenda for the

remainder of the ODAC.

The FDA remains committed to the accelerated approval program and feels that there is beginning to be an improved understanding in the drug development community regarding both the benefits and responsibilities of its use. Since its inception, accelerated approval has led to the approval of 49 oncology indications in total, and the accelerated approval pathway continues to be utilized at an average rate of 3.3 approved indications in oncology per year.

Accelerated approval has provided early access to clinically beneficial cancer therapies. There have been a total of 27 oncology indications that have confirmed benefit through completed post-marketing trials. These drugs were made available to the public a median of 3.6 years prior to the verification of their clinical benefit, representing a substantial time savings in earlier availability to patients.

However, while accelerated approval allows for earlier marketing of promising drugs, it does

come at the expense of increased uncertainty. And while 10 percent of oncology indications approved under accelerated approval were unable to confirm a benefit, this should not be thought of as a failure of the accelerated approval program. Rather, it highlights the important reality that by granting accelerated approvals based on a surrogate endpoint reasonably likely to predict clinical benefit, we expect a small percentage of products to fail to confirm that benefit; again, the trade-off for earlier availability of promising agents for severe and life-threatening diseases.

This fact, again, just simply highlights that not only due diligence, but early integration of post-marketing trial design into a comprehensive drug development plan is critically important to a successful accelerated approval application.

Finally, a comment by Thomas Fleming I think made at the 2003 ODAC sums up the heart of the matter, and he said, "Given that there seems to be a sense of urgency in completing the trial upon which accelerated approval is granted, is it fair

to assume that we would have the same sense of urgency for the confirmation of benefit? In the first case, we're in danger of keeping dying patients away from potentially effective therapies. However, there is an equal danger that we are exposing patients to the toxicity of therapy without certainty of benefit. In both cases, it's incumbent upon those in drug development to decrease these time periods."

I'll now proceed with the ODAC agenda. The selection of drugs to be presented for this ODAC was based on indications granted accelerated approval prior to 2009, with outstanding post-marketing requirements that are not under active FDA review.

The following six indications have met these criteria and include cetuximab used in combination with irinotecan for EGFR-expressing metastatic colorectal cancer in patients who are refractory to irinotecan-based therapy; tositumomab 131 for treatment of patient with relapsed or refractory low grade follicular or transformed CD20-positive

non-Hodgkin's lymphoma who have not received rituximab; clofarabine for the treatment of pediatric patients with relapsed or refractory acute lymphoblastic leukemia after two prior regimens; nelarabine for the treatment of patients with T cell acute lymphoblastic leukemia and T cell lymphoblastic lymphoma whose disease has not responded to at least two chemotherapies; panitumumab for the treatment of EGFR-expressing metastatic colorectal cancer with disease progression on or following fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy regimens; and, finally, imatinib for the adjuvant treatment of adult patients following complete gross resection of CD117-positive gastrointestinal stromal tumors.

Each sponsor for the listed oncology drug indications will present a brief overview of the accelerated approval of their product, followed by a review of the current status of their post-marketing commitments.

Following the update, sponsors have been

asked to identify any barriers or challenges to completing their post-marketing commitments with due diligence using the following questions as a guide: For ongoing confirmatory studies, has accrual been satisfactory; and, if not, what strategies would you suggest to address this? And for planned trials, have changing circumstances impeded the conduct of such trials; if so, describe them and indicate what alternative design should be contemplated.

I'd like to thank the committee members and the sponsors for their time today. And we'll now hear from Jeff Murray from the Division of Antiviral Products regarding the use of accelerated approval in the development of HIV drugs.

Thank you.

FDA Presentation - Jeff Murray

DR. MURRAY: Good morning. I'm Jeff Murray from the Division of Antiviral Products, and I'd like to thank the Office of Oncology Products for the chance to review the accelerated approval experience for antiretroviral drugs, HIV drugs.

So in this presentation, I will summarize the history of antiretroviral accelerated approval; talk a little bit about the validation process of viral load, it's a surrogate that we've used for accelerated approval and regular approvals; talk about the record for accelerated approvals in terms of the time to confirming benefit or the time to regular approval; and, conclude.

So the regulations for accelerated approval were codified in 1992 in response to the HIV/AIDS epidemic and Videx, didanosine, was the first drug approved using this type of process even before the regs were codified in 1991. Hivid, zalcitabine, was technically the first drug approved under accelerated approval regs.

The HIV drug approval history has really two distinct periods for accelerated approval. The first period is 1987 through '96, and the second period is 1997 to present, and I'll explain.

The surrogate endpoints used evolved over time. We looked at CD4 cell counts and other things, and, eventually, HIV RNA, which we call

viral load, was a co-endpoint, and then it became the primary endpoint really for everything.

So according to the regs, after accelerated approval, the applicant must verify and describe the drug's clinical benefit -- and this is an important part of the regs for us -- where there is uncertainty as to the relationship of the surrogate endpoint to the clinical benefit, and we've done some exploration of that certainty of the relationship.

Prior to 1997, the first period of approvals, clinical endpoint studies were required after accelerated approval, and the clinical endpoint was the CDC criteria for AIDS, and it consisted of about 20 AIDS-defining events and death. After 1997, we considered viral load, HIV RNA, a validated endpoint.

So our clinical endpoint was complex and difficult and, as I said, it was originally used for epidemiologic purposes. You needed a datum committee to adjudicate 20 different conditions, ranging from infections, syndromes, malignancies,

infections that were easily treatable to those that were devastating. So it really wasn't a very friendly endpoint to use.

Around 1996, it became apparent that there was going to be great difficulties in conducting clinical endpoint studies. And why? The reason was because real-time viral load monitoring became standard of care and, at that time, physicians and study participants were really unwilling to stay on randomized treatment after they saw viral rebound and then wait for clinical progression or even wait for their CD4 cell counts to decline.

Also, another reason was because HAART, highly active antiretroviral treatment, greatly reduced the incidence of clinical events. Clinical endpoint studies would have required very large numbers or had to be carried out for a long duration of time, or would likely be confounded by the treatment switches that were occurring once viral load rebounded and the drugs were determined to be failing.

So what did we do? We embarked on a

collaborative approach. In 1996, there was a group called the Surrogate Marker Working Group, made of industry, academia and government. So sponsors, FDA and NIH, analyzed data to assess correlations between HIV RNA, viral load, and clinical outcome and also look at correlations between short-term viral load suppression and a durable viral load suppression. And then in July of 1997, much as you're doing today, we held an advisory committee to talk about these analyses and meta-analyses.

So, briefly, the conclusions of the analyses were that viral load decreases of about a half a log were associated with low risk of disease progression across a wide range of baseline characteristics. Greater reductions were associated with lower and lower risks. More sustained reductions were associated with lower risks, and suppression of viral load below assay quantification was associated with longer duration of virologic suppression and less emergence of resistance. So, at this time, the goal really became complete and durable viral load suppression,

both clinically and for our clinical trials.

So the 1997 advisory committee conclusions were that viral load was a suitable endpoint for both accelerated approval and regular approval. Accelerated approval was based on short-term viral load changes at 24 weeks, with confirmation of a durable viral load suppression at 48 weeks, and we looked for concordance with other markers, as well.

So the typical accelerated approval study design, really post this validation process and pre, has been a randomized, placebo-controlled, usually two-armed study, sometimes more if there's multiple doses studied, in patients who have failed multiple drug regimens but usually have maybe one or two drugs left.

So arm one would consist of a new regimen of optimized therapy with approved drugs, and arm two is optimized therapy plus the investigational drug. And if viral suppression does not occur or occurs and rebounds, then the patient is considered a virologic non-responder, and they can exit the trial.

So the patients liked this, clinicians liked it, statisticians liked it, everybody was happy. So that once a virologic failure was documented, they could go on to other therapies, and we've captured our endpoint and didn't really mess up the trials.

So here is kind of the record. Here is the first period where accelerated approvals were based on surrogates and then confirmed with that large composite clinical endpoint that I told you about. And in this time period, regular approval came as early as 10 months after the initial accelerated approval, but sometimes, in that case, it took as long as 69 months or almost six years.

Here are the drugs approved in the second period, where both accelerated and the regular approval was based on a viral load endpoint of some sort, and it ranged from around 15 months, again, up to 64 months.

So, really, in summary, all HIV drugs that received accelerated approval eventually received a regular approval. The longest time was 69 months,

or about five years, until submission of the NDA. Three drugs received regular approval at initial approval, and a couple drugs had a split approval at initial approval.

Thirteen drugs were approved on 24 weeks of viral load changes and confirmed by durable viral load changes at 48 weeks. And the typical packages were usually two trials and a trial size of somewhere between three and 600 patients per trial.

So the average time from accelerated approval until regular approval, I thought that there would have been a difference, but there wasn't for the two periods. Prior to validation of viral load, it was 29 months. After validation of viral load, average time was 30 months.

But in the last decade or so, I think when the process became very routine and sponsors were used to getting their trials in line for both accelerated and traditional using the same trials, it was about 24 months, or two years. And given a 10-month review clock, that means that sponsors submitted applications with 14 to 20 months post-

accelerated approval, which I think is really probably pretty excellent.

So some of the reasons for the longer times under accelerated approval until regular approval for HIV drugs were in three cases, initiating one or more confirmatory trials post-approval, so starting fresh with a new trial.

In one case, there was a drug that had a lot probably less activity than the other drugs in the same class, and so there was not great enthusiasm for enrolling in those trials. And in two cases, the indication was actually split between an accelerated approval and regular approval; it took longer to confirm one of the maybe treatment-naïve population than the experienced population.

So, in conclusion, the accelerated approval processes worked quite well for antiretrovirals, but drug development for HIV is very different than for oncology. I think the primary reason is the use of viral load as a surrogate. We found that it's an excellent surrogate that correlates very well and almost indisputably with disease

progression, and, also, early and late viral load changes for the second period of drug approval are also highly correlated.

In general, there was ability to enroll two trials, which often supported both approvals, 24 weeks for accelerated and 48 weeks for regular approval.

Right now, currently, we're in the process of discussing whether we really even need the accelerated approval paradigm anymore for HIV drugs. And since we're using viral load so reliably now, we're just thinking of having shorter duration viral load trials with regular approvals for treatment experienced patients and longer, more durable viral load suppression for first-line therapy.

With that, I thank you for your attention.

DR. WILSON: Thank you very much. That now concludes the presentation by FDA. Before we move on to the first sponsor, I have a statement I would like to read.

Both the Food and Drug Administration and

the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsor's nonemployee presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interests in the sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you, at the beginning of your presentation, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking. Thank you.

So with that, let me invite Eli Lilly and

Ms. Mockbee to the podium.

Eli Lilly & Company (Erbitux) - Colleen Mockbee

DR. MOCKBEE: Good morning. My name is Colleen Mockbee, and I'm head of Global Regulatory Affairs for Lilly Oncology. I would like to thank the FDA and the committee for the opportunity to discuss the accelerated approval of Erbitux in the treatment of patients with metastatic colorectal cancer and the post-marketing commitment studies required as a condition of this approval.

The accelerated approval pathway is an important regulatory mechanism that, in our experience, has enabled promising new drugs to become available to patients earlier than the traditional regulatory approval process allows. And as a result, we believe the accelerated approval process has played an important role in the rapid advances seen in the treatment of patients with metastatic colorectal cancer during a relatively short time period.

While having ongoing studies at the time of accelerated approval is important, and we did have

several studies ongoing at the time Erbitux received approval, it is important to recognize the environment is dynamic, so we also have to be prepared to respond as science evolves and treatment practices change.

Given the complexities, the ability to interact with the FDA in the planning phases to discuss accelerated approval as part of a comprehensive program, including the design of confirmatory studies, but, also, as challenges arise, so that we can effectively respond, is critical to the success of this process.

Erbitux is a chimeric monoclonal antibody that competitively binds to the epidermal growth factor receptor, resulting in subsequent signal transduction and down-regulation of EGFR.

In 2004, Erbitux received accelerated approval as a single agent and in combination with irinotecan for the treatment of patients with metastatic colorectal cancer whose disease is refractory to irinotecan.

The benefit of Erbitux as a single agent in

this population was subsequently confirmed based on improvement in overall survival and received regular approval in 2007, partially fulfilling the accelerated approval requirements. A restriction to the indication was added to the label based on emergence of data showing no benefit for patients with KRAS-activating mutations.

An additional approval for Erbitux was granted in 2006 based on demonstrating improved overall survival in the treatment of patients with head and neck cancer, representing the first major change in treatment for this population in nearly 40 years.

The pivotal study supporting the accelerated approval in metastatic colorectal cancer is known as the BOND study. You will note that the experimental drug, Erbitux, is in both arms of the study. This was a novel study design that tested the hypothesis that Erbitux could resensitize patients to irinotecan.

Consequently, patients entering the study had to have progressed while on prior irinotecan

therapy. The primary objective of this study was to assess overall response rate, and this study was not designed to evaluate overall survival.

As you can see from the BOND study results, the combination of Erbitux plus irinotecan had a response rate of 23 percent, and Erbitux also had good single-agent activity, with an 11 percent overall response rate.

The magnitude of response, together with the duration of response in the range of four to five months, was promising and considered reasonably likely to predict clinical benefit, thus meeting the requirements to support an accelerated approval.

There were two Phase 3 studies ongoing at the time Erbitux received accelerated approval that could confirm the benefit of Erbitux in the treatment of patients with metastatic colorectal cancer. Both studies were in the second line setting. The first commitment study is Erbitux in combination with irinotecan. The second commitment study is Erbitux in combination with FOLFOX.

I will first discuss post-marketing commitment study 2, also known as Study 014. This was a large Phase 3 study comparing FOLFOX with or without Erbitux. Overall survival was the primary endpoint of the study. All patients had to receive irinotecan as first-line treatment to be eligible for the study. The planned enrollment for the study was (1,100 patients.

Study 014 was initiated in March of 2003. We encountered enrollment challenges for Study 014 as a result of changes in treatment practices following the introduction of several new drugs. In 2004, FDA approved three new drugs for the treatment of metastatic colorectal cancer, Erbitux, oxaliplatin, and bevacizumab.

Multiple new drugs and combinations of these drugs resulted in substantial improvements in median overall survival during a relatively short time period. Oxaliplatin-based treatment quickly became the preferred first-line regimen. Since Study 014 required patients receive initial treatment with irinotecan, the adoption of

oxaliplatin in first-line limited the number of patients eligible for Study 014, and, as a result, enrollment was significantly slower than planned.

We met with FDA to discuss the challenges with enrollment as a result of the change in treatment practice. Based on the information reviewed with FDA, the commitment study was released in January of 2005.

Turning back to the first post-marketing commitment study, or the EPIC study, this was a large Phase 3 study comparing Erbitux with or without -- I'm sorry -- comparing irinotecan with or without Erbitux. Overall survival was the primary endpoint of the study. All patients had to receive an oxaliplatin and fluoropyrimidine-based regimen as initial treatment. The planned enrollment in this study was 1,300 patients.

The EPIC study was initiated in May 2003 and ongoing at the time of the accelerated approval. The study completed on schedule overall, with submission of the final study report in June 2007, as planned.

Here, we see the results of the EPIC study in the ITT population. Erbitux showed improved progression-free survival and overall response rate. However, Erbitux did not demonstrate an improvement in overall survival, the primary endpoint of the study.

The EPIC study results were evaluated to understand what factors may have impacted the ability to demonstrate an improvement in overall survival. One observation of note was the high percentage of patients in the irinotecan control arm who received post-study treatment of Erbitux plus irinotecan once their disease progressed.

Since the accelerated approval of Erbitux was for treatment of patients with metastatic colorectal cancer who were refractory to irinotecan, it is not surprising that investigators offered patients on their irinotecan control arm treatment with Erbitux after progression.

Given the magnitude, with 41 percent of patients on the irinotecan control arm receiving Erbitux plus irinotecan, the same regimen being

tested in the experimental arm of the EPIC study, the potential for confounding interpretation of overall survival, is plausible.

We met with FDA in December 2006 to discuss the results of EPIC, as well as other ongoing studies that could potentially support demonstrating the clinical benefit of Erbitux in metastatic colorectal cancer. FDA concluded the results of EPIC were not adequate to confirm the clinical benefit of Erbitux. A study that could demonstrate improved overall survival would be required.

We discussed two additional studies with the FDA at that time, Study 025 and CRYSTAL. Study 025 was a large Phase 3 study comparing Erbitux plus best supportive care versus best supportive care alone in third-line metastatic colorectal cancer. Overall survival was the primary endpoint of the study.

The study demonstrated improved overall survival, confirming the benefit of Erbitux as a single agent and supporting full approval of this

regimen in 2007 and partially fulfilling the accelerated approval requirements. However, FDA indicated additional studies to confirm the clinical benefit of Erbitux in combination with irinotecan would be required.

The other study discussed with FDA in December of 2006 was CRYSTAL. I will discuss the CRYSTAL study in the context of the emerging data on KRAS as a predictive biomarker. The role of KRAS in predicting which patients would respond to Erbitux emerged as a hypothesis in 2007.

Several events occurred as a result of this evolving science in 2008. KRAS data from five Erbitux studies in metastatic colorectal cancer was submitted to the FDA. The scientific results were presented at ASCO, and NCI CTEP recommended incorporating KRAS testing in clinical trials. The recommendation to use KRAS testing for patient selection were reaffirmed by guidelines published by NCCN and ASCO. FDA convened an ODAC in December 2008 to discuss how to incorporate emerging biomarker data from completed studies in the

regulatory process.

New information on biomarkers can emerge at any time in the development process as our scientific knowledge grows and new capabilities become available. The December 2008 ODAC outlined conditions that would be acceptable to incorporate new information on potential biomarkers that become known after studies have already begun or have been completed. The framework for incorporating emerging science has become known as prospective/retrospective analysis.

The conditions endorsed by the committee afforded the opportunity to work with FDA to find a path utilizing the emergent KRAS data as a predictive marker to determine the efficacy of Erbitux in a selected population.

We discussed with FDA the ability to use the CRYSTAL study to support an application for Erbitux in combination with irinotecan to confirm the benefit of Erbitux. CRYSTAL was a large Phase 3 study comparing FOLFIRI with or without Erbitux. Progression-free survival was the primary endpoint

of the study. However, the study was fully powered to assess overall survival, as well.

Samples were ascertained in 89 percent of patients, representing a total sample size of 1,063 patients. In the KRAS wild type population, Erbitux shows improved overall survival, progression-free survival, and overall response. KRAS as a predictive marker to select patients most likely to benefit from treatment with Erbitux has been replicated across multiple studies in metastatic colorectal cancer and will provide supportive data for FDA review to confirm the benefit of Erbitux in this population.

In summary, the accelerated approval of Erbitux in metastatic colorectal cancer provided patient access to Erbitux three years earlier than the traditional regulatory path would have allowed. Consistent with FDA's guidance, multiple studies were ongoing at the time of the accelerated approval, and we carried these studies out with diligence.

Several challenges were encountered in

completion of the post-marketing study commitments, including changes in treatment practices, Erbitux availability potentially confounding overall survival results in one study, and emergence of new biomarker information to better predict which patients will benefit from Erbitux.

Continued dialogue with FDA was important to address the challenges in completing the post-marketing study commitments. We have now confirmed the benefit of Erbitux as a single agent, and we have reached agreement on the submission package that will support FDA's review to confirm the benefit of Erbitux in combination with irinotecan in the KRAS selected population and complete conversion of the accelerated approval to regular approval.

Thank you.

Questions from Committee to Sponsor

DR. WILSON: Thank you. Now, we have a few minutes for questions from the committee to the sponsor. For those of you who have not attended ODAC before among the committee members, please

raise your hands. We will keep a list and then go from there.

Well, let me ask a question. Maybe I didn't quite follow this. So it was my understanding from this that your study, you have not done a confirmatory randomized study with Erbitux plus irinotecan. And I guess I'm a little bit confused. You're talking about getting regular approval, I presume, based on the follow-up study that involved, I think, the FOLFIRI regimen. I just wanted to clarify whether or not that's the Phase 3 trial in the wild type KRAS that you are moving forward on to get regular approval for the initial accelerated approval of Erbitux with irinotecan.

DR. MOCKBEE: Yes, that's correct. So the EPIC study was the initial commitment study, and since that did not demonstrate an improvement in overall survival, we met with the FDA in the CRYSTAL study, looking at the KRAS selected population in combination with irinotecan, which is in an earlier setting, the first-line setting, will serve to support confirming the benefit and

converting the accelerated approval to regular approval.

DR. WILSON: So you went back and then looked at the group that was KRAS wild type in the irinotecan study. Is that what you just said?

DR. MOCKBEE: That's correct.

DR. WILSON: Okay. Thank you.

Dr. D'Agostino?

DR. D'AGOSTINO: Are you saying that the approval will then shift to the KRAS testing in position? I'm not following you.

DR. MOCKBEE: Yes, that's correct. The KRAS --

DR. D'AGOSTINO: It will shift. So it's not what the original accelerated approval was for, but rather for a more defined group. Am I following correctly here?

DR. MOCKBEE: It's correct in that we will use KRAS selection, but the approval required demonstration of benefit of the combination of Erbitux plus irinotecan.

DR. D'AGOSTINO: Thank you.

DR. WILSON: Yes?

DR. MARTINO: I'm sorry. I still would like you to simply state what the approval request will be for this agent, just a simple one sentence will do it.

DR. MOCKBEE: The approval request will be for the approval of Erbitux in combination with irinotecan in the KRAS wild type population.

DR. MARTINO: Thank you.

DR. THOMAS: You know, not being a colon specialist, could you maybe tell us what the standard of care now is regarding irinotecan? Is it third-line or what line is it, and is it still used?

DR. MOCKBEE: Yes. I'll ask Dr. Chang to answer that question.

DR. CHANG: My name is Shao Chang. I'm from Clinical Development with Eli Lilly. In terms of irinotecan use, if you look at the NCCN guideline, it's recommended for first-line, as well as second-line and beyond. But in terms of what's mostly common used in the United States, is oxaliplatin-

based regimen for first-line, then subsequent irinotecan use gets increased.

DR. THOMAS: Yes. Dr. D'Agostino?

DR. D'AGOSTINO: Just so I understand how the accelerated approval works in terms of the confirmatory, is it all right in the confirmatory aspect to start shifting the gears in the picture in terms of what was actually originally --

DR. PAZDUR: Yes. We have allowed sponsors to look at a slightly different setting to confirm clinical benefit, and this is one of the issues that we'd like discussion on, obviously, in the afternoon. Once you approve a drug in that setting, it is going to be very difficult to do a randomized study of an indication that you've already approved.

So we have viewed this from the point of view that this will provide information of clinical benefit and actually promotes drug development in oncology by taking a look at expanded indications instead of just focusing solely on the approved indication.

DR. D'AGOSTINO: Can I ask another? Can I follow-up on that?

But in this case, are we talking about a narrowing of the approval, given the KRAS?

DR. PAZDUR: Well, the approval will be -- the new indication that will come out of this study will be in the KRAS population.

DR. D'AGOSTINO: And that will negate the previous accelerated approval?

DR. PAZDUR: That will stay on, but here, again, I think the field here has evolved to people looking at a KRAS-defined population when they use a surrogate.

DR. WILSON: Dr. Sekeres?

DR. SEKERES: Thank you, Dr. Wilson. I have two questions. The first is, as you were trying to fulfill your post-marketing obligations, how many ex-U.S. patients were enrolled on these studies or were these studies conducted within the U.S.?

The second question, and you may not have these data, is do you have any sense of how much off-label use of your drug was occurring within the

U.S.

DR. MOCKBEE: Regarding your first question regarding the two post-marketing commitment studies that we had agreed with the FDA, the EPIC study and Study 014, I don't know if I have the enrollment data based on U.S. versus ex-U.S. I don't have that data available, and I do not know how much off label use was occurring in the United States for Erbitux at the time of the approval.

DR. WILSON: Dr. Loehrer?

DR. LOEHRER: The elephant in the room for me is not so much with irinotecan, but with oxaliplatin. So with front-line therapy with FOLFOX, commonly, this drug is used off label for this. So what is the take on FOLFOX plus Erbitux in first-line therapy; and, also, will the indication be narrowed to only be used for irinotecan and not oxaliplatin?

DR. PAZDUR: Indication will be in the population that was studied.

DR. MOCKBEE: And, Dr. Loehrer, you want me to address the question on the combination with

FOLFOX in development of Erbitux in that setting. I'll ask Dr. Chang.

DR. CHANG: We have a Phase 2 study, OPUS, which is about around a 300-patient study that looked at first-line treatment with FOLFOX plus/minus Erbitux. And in that, in the KRAS wild type population, you see an increased benefit in both response rate, as well as PFS, with a p-value less than .05. In the overall survival, it was not statistically significant. But it's a Phase 2 study, so it wasn't powered to address the overall survival.

DR. WILSON: So, actually, I've got a question that I'd like the FDA to address.

I think we've seen here a very good example of how there was a rapid approval of very effective drugs after this accelerated approval and that the standard of care was changing. So my question really gets at a statement that is part of the accelerated approval, which is that it is recognized in some of these post-marketing studies that standards change and that the actual clinical

trial for post-marketing may not be exactly as the initial accelerated approval.

I'm trying to get some sense, Dr. Pazdur, as to how far that can migrate. Now, it can migrate in that it's the same drug combinations, such as in the case of irinotecan and Erbitux, but done in a different setting, versus the idea might be that Erbitux sensitizes against cytotoxics.

So let's just say, for some reason, irinotecan -- this is why I ask the question -- was no longer really considered to be a drug you would want to use. Could it migrate to the extent that Erbitux could be combined with another chemotherapy regimen to address the question of whether or not there is synergy or added effects of a monoclonal antibody?

So I'm trying to get some sense as to how far could this migrate off the original accelerated indication.

DR. PAZDUR: Well, generally, when we're taking a look at these different studies and we're looking at them in a different setting, we're

usually talking about studying a refractory population to a less refractory population. In other words, a sponsor gets the drug approved in a third-line setting and takes it to a second-line setting or a first-line setting.

Here, again, I think, in general, and I don't want to go into the specifics of this, we really would have to assess if there's, really -- are they looking at combinations in general or a specific combination, and is there a unique biology between that drug. And then if there is, then we should insist, obviously, on that combination from being -- being studied. But there is some flexibility here that we would, I think, entertain.

DR. WILSON: Okay. Thank you.

Dr. Kelly?

DR. KELLY: Thank you. It was interesting that in some of the information that we got in the package here is the -- in Europe, they looked at KRAS and Erbitux, and the European labels changed in July of 2008. But it was not until July of 2009 that we had the label change in the U.S.

Can the FDA or the company give me some insight? Why such a difference? And if we're really talking about accelerated approval, how can we actually shorten that, if that's a possibility?

DR. PAZDUR: So the question is the change of the label to the KRAS population.

DR. KELLY: Yes.

DR. PAZDUR: We've used this as a safety labeling change. In fact, if you were at that ODAC, there were issues about convenient samplings, et cetera, that focused around here.

So, basically, it was a review that was in progress of looking at that, coming to an ODAC meeting and really looking at it as safety label changes; that patients that had KRAS mutants should not be exposed to the drug. That's where we were going with the labeling.

DR. KELLY: Can I follow-up on that?

Is there a difference in how the Europeans looked at it versus us?

DR. PAZDUR: I really couldn't comment on that.

DR. WILSON: Yes, sir?

DR. D'AGOSTINO: Just to follow-up on this discussion. If you start off with an accelerated approval on a particular indication, and then the clinical endpoint trial is a very focused population, I guess I'm lost on how that very focused population necessarily supports what the accelerated approval was for. I know you gave an answer, but I'm just not digesting it.

DR. PAZDUR: Well, it's something that we have accepted. The issue here is if clinical benefit is demonstrated in a disease setting that is related, that we would interpret that benefit to be a benefit of the drug, in general.

So, here again, one of the issues here is, again, the difficulty one has in doing the trial subsequently if the drug is already approved in that indication. That becomes a very difficult case. That's why we are asking consideration of the committee for these other paradigms here, such as in HIV, where you have the randomized trial ongoing and take a look at an earlier time point, a

surrogate endpoint, for example, of a disease setting.

But the issue is one -- this is something that we have accepted, cognizant of the fact that it would be very, very difficult to start a randomized trial in an approved indication since we've already said the drug is safe and effective.

DR. WILSON: Okay. Thank you. If there are no further questions, we're going to now be switching sponsors. And while the sponsor changes, we'll take a five-minute break. If you do choose to go to the restroom, please do it rapidly. Thank you.

(Whereupon, a recess was taken.)

DR. WILSON: Okay. We're going to go ahead and get started. There have been some new FDA members that have joined, so if you could please identify yourselves, state your name into the record, and et cetera. Thank you.

DR. GIUSTI: Ruthann Giusti, Office of Oncology Drug Products.

DR. WILSON: That's it? Okay, thank you.

I would like to have Dr. Lin present for GlaxoSmithKline. Thank you.

GlaxoSmithKline (Bexxar) - Thomas Lin

DR. LIN: Good morning. My name is Thomas Lin, medical director for Bexxar. On behalf of GlaxoSmithKline, I will present an update on the status of the post-marketing commitments for the Bexxar therapeutic regimen.

In addition to the GSK participants who are listed here, Dr. Andrew Zelenetz of Memorial Sloan-Kettering, chair of the NCCN Lymphoma Committee, is attending today's meeting as an eternal expert on behalf of GSK. Dr. Oliver Press and Dr. Michael LeBlanc of the Fred Hutchinson Cancer Center are attending this meeting on behalf of the Southwest Oncology Group.

The Bexxar therapeutic regimen was developed -- I'm sorry. In the next 15 minutes, we will briefly review the Bexxar therapeutic regimen, review the regulatory history of approvals in the United States, and summarize the status of the post-marketing commitments for Bexxar.

We will discuss PMC Number 1, the study to confirm clinical benefit, which is reportable under subpart E. We will discuss the originally agreed study of Bexxar versus rituximab to confirm clinical benefit, highlight obstacles which prevented the study from being feasible, and discus an alternatives study which GSK has proposed if it failed PMC Number 1, the Southwest Oncology Group S0016 study in previously untreated follicular lymphoma.

The Bexxar therapeutic regimen was developed using tositumomab, a murine anti-CD20 monoclonal antibody which binds to both normal and malignant B lymphocytes. Tositumomab is conjugated to iodine 131, which emits both gamma and beta radiation. Dosemetric measurement of the emitted gamma radiation allows a prescriber to calculate a patient's clearance of Bexxar and thereby prescribe a patient-specific millicurie dose of I-131 in order to deliver a fixed total body radiation dose to the patient.

The Bexxar therapeutic regimen is

administered in two steps. In the first or dosemetric step, unlabeled cold tositumomab is given along with tositumomab, which is radiolabeled with 5 millicuries of iodine-131. Over the next week, a gamma camera connected to a high energy collimator is used to obtain three whole body scans, and these scans are used to determine biodistribution and the patient's clearance of Bexxar.

In the second or therapeutic step, which occurs 7 to 14 days after the first step, a calculated dose of Bexxar is given in order to deliver a fixed total body radiation dose of 65 or 75 centigray, depending on a patient's platelet count. Thyroidal protection is given to the patient from day minus one through 14 days after administration of the therapeutic dose.

Partly due to this complicated procedure, the need for the gamma camera and high energy collimator and the requirement that prescribers undergo certification training, only 200 patients receive Bexxar each year outside of clinical

trials.

Bexxar was granted orphan drug designation in 1994 and received full approval in June 2003 for the treatment of rituximab refractory, low grade and transformed non-Hodgkin's lymphoma. The division and sponsor agreed to 10 post-marketing commitments at this time. In December 2004, Bexxar received accelerated approval for expanded indication for relapsed, as well as refractory, low grade and transformed follicular lymphoma. PMC Number 1 now became reportable under subpart E for biologics.

The pivotal trials which resulted in both approvals are shown on this slide. The initial full approval was based on a 40-patient pivotal study in rituximab refractory follicular lymphoma. The subsequent expanded indication was granted based on a 60-patient pivotal study in chemotherapy refractory patients.

The overall response rates in these two studies were 68 percent and 47 percent, respectively, with a median duration of response in

excess of 12 months. The complete response rates were 33 percent and 20 percent, and the complete remissions were durable, as shown on this slide.

The division and sponsor agreed to 10 post-marketing commitments, which are depicted on this slide. Two PMCs, shown on the top row, were randomized studies to confirm clinical benefit and safety. Four PMCs, shown on the middle row, were companion PMCs which were associated with the first two PMCs. Finally, four PMCs, shown on the bottom row, were additional requirements by the division. Three PMCs, which are highlighted in white, have been fulfilled or are ongoing. These PMCs include quality assurance, BALL-1 reagent, and surveillance for myelodysplasia.

Five PMCs, outlined in red, including a randomized study of Bexxar versus Zevalin, another anti-CD20 radioimmunotherapy, which was not feasible to conduct, have been released. Among the released PMCs are four companion PMCs associated with PMC Numbers 1 and 2.

Two PMCs, outlined in yellow, are delayed.

PMC Number 3, a retreatment study of Bexxar, could not be conducted because the primary PMCs, Number 1 and Number 2, were not feasible to conduct. Therefore, PMC Number 1 confirmation of clinical benefit remains delayed.

The study, which was initially proposed to fulfill PMC Number 1 and confirm clinical benefit, was a randomized study of Bexxar versus rituximab monotherapy in 506 patients with relapsed follicular lymphoma. The primary endpoint of the study was event-free survival. However, only 15 patients were enrolled to the study over 30 months. Therefore, in October 2005, the FDA agreed that the study was not feasible to conduct, despite GSK's due diligence in trying to accomplish this PMC, and invited GSK to submit an alternative proposal.

Several obstacles led to poor accrual and made the originally proposed study of rituximab versus Bexxar unfeasible to conduct. Change in standard of care away from rituximab monotherapy to rituximab chemotherapy combination therapy made physicians reluctant to randomize patients to a

study with a rituximab-only arm. Furthermore, publication of other randomized studies showing that Zevalin radioimmunotherapy was superior to rituximab in this patient population further reduced physicians' enthusiasm for this trial.

In addition, several sites did not have access to the required gamma camera equipped with a high energy collimator, which is prescribed in the U.S. prescribing information and was required in the study.

Finally, other logistical issues regarding Bexxar administration, lack of trained personnel, and a growing number of competing trials in the relapsed follicular lymphoma patient population further reduced the number of viable study sites.

In response to the FDA's request for an alternative study to fulfill PMC Number 1, GSK proposed the Southwest Oncology Group S0016 study, a randomized Phase 3 study of CHOP rituximab versus CHOP Bexxar. This study opened in 2001, prior to the initial full approval of Bexxar, and randomized 550 patients with previously untreated follicular

lymphoma to CHOP alone, CHOP rituximab, or CHOP Bexxar.

The CHOP alone arm was closed to accrual in 2002 due to change in standard of care, and accrual continued to the other two treatment arms. The primary objective of this study is comparison of progression-free survival. Secondary endpoints include overall survival response rates and assessment of development of human anti-mouse antibodies or HAMA.

The study completed accrual in late 2008. However, due to the biology of follicular lymphoma and the long remissions which previously untreated patients enjoy in response to initial treatment, the primary endpoint analysis is not expected for the next year.

The SWOG S0016 study is an appropriate alternative study to confirm clinical benefit and fulfill PMC Number 1. Because this study combines chemotherapy with anti-CD20 monoclonal therapy, the SWOG study is more clinically relevant than the originally proposed study of Bexxar versus

rituximab monotherapy.

In addition, this study compares CHOP Bexxar to rituximab and CHOP, an accepted standard of care throughout the world and the most commonly used front-line regimen for follicular lymphoma in the U.S. and across the world. In addition, the study was ongoing with good accrual in 2005, and the study has subsequently completed accrual, with results expected to report within the next year.

Finally, it would not have been possible to conduct another study of Bexxar versus rituximab after the S0016 study was initiated due to participation of many experienced Bexxar centers in the SWOG study.

In three FDA meetings, GSK discussed this proposal to use the SWOG S0016 study to fulfill PMC Number 1 and responded to comments from the division. The division indicated that it would be willing to consider a study in previously untreated follicular lymphoma to confirm clinical benefit, and the division, furthermore, agreed that the study design of the S0016 study was acceptable in

principal. However, there were certain issues that the FDA requested regarding data validation, data monitoring, and the statistical analysis plan which have to be resolved before a final determination could be made whether this study would be acceptable for PMC Number 1.

This study shows the major remaining obstacles and outstanding issues, with GSK's proposed solutions highlighted in yellow. A primary obstacle is collection of CT scans, which the division has requested in order to perform independent review of the primary endpoint data.

In response to the FDA's comments, GSK engaged a CRO to collect the CT scans and perform the independent review. However, scan collection has not been fruitful because the study was not designed to prospectively collect CT scans. Therefore, GSK proposes that investigator-determined assessment of local radiology measurements, as is used in the study, be used to assess the primary endpoint of the study.

Secondly, the FDA recommended collection of

quantitative laboratory data in order to quantify safety assessments, such as cytopenias. In response to these comments, GSK and SWOG agreed that SWOG would collect this data and then transfer it to GSK.

Finally, this is a cooperative group study which uses data validation and monitoring standards and objectives which may be different from those used in traditional industry-sponsored trials. In response to this concern, GSK has identified critical variables, such as serious adverse events and treatment dates, to use to perform a quality check of the database which SWOG compares against the clinical report forms which were submitted to the study.

In summary, GSK pursued the originally agreed study to confirm clinical benefit and fulfill PMC Number 1, a randomized study of Bexxar versus rituximab, with due diligence. However, the study could not be accrued due to lack of feasibility, in large part, due to change in standard of care, and the study closed to accrual.

In order to fulfill PMC Number 1, which remains delayed, GSK proposes that the SWOG S0016 study, a randomized study of CHOP Bexxar versus rituximab CHOP in previously untreated follicular lymphoma patients, be used to fulfill PMC Number 1. This study is relevant to clinical care. It's relevant to the current standard of care, has completed accrual, and its results are anticipated within the next year.

The division has agreed in principal that the study design of the S0016 study is acceptable, but there are outstanding issues which need to be resolved in order for a final determination of this study's suitability for PMC Number 1.

GSK continues to work with SWOG to resolve these issues, come to agreement with the division, and fulfill PMC Number 1. Thank you very much for your attention.

Questions from Committee to Sponsor

DR. WILSON: We're now open for questions. Dr. Mortimer?

DR. MORTIMER: So in the SWOG study,

progression-free survival is the primary endpoint. Could you help me understand what the problem is getting the radiology, the CT scans?

DR. LIN: I'm going to defer that question to Dr. Press, who is the principal investigator of the SWOG study.

DR. PRESS: I'm from the Fred Hutchinson Cancer Research Center, and I'm here for SWOG.

The initial trial was designed as a typical cooperative group study. It was not initially involved with GSK. And in cooperative group studies, we do not routinely collect the physical scans.

The study was about half accrued, I believe, when we entered in a cooperative agreement to help them fulfill their post-marketing agreement. This is a long study. Some of these patients were treated in the early 2000s. At that time, most institutions did not have all their scans on CDs or disks, but had physical records of the scans.

Many of those institutions have a policy of destroying their scans after a period of five

years. So it is very likely that it will be very difficult, if not impossible, to get scans on all the patients.

DR. WILSON: Let me follow-up on that. So was GSK trying to physically obtain these scans to them have them reviewed essentially? Because I would think, with an ongoing clinical trial, that the scans need to be at each center. And was GSK not going to go out and simply send experts out to each center to QA the scans?

DR. LIN: So GSK engaged a CRO to collect the scans. SWOG augmented the study to request that their sites provide the contact information so the CRO could contact the sites and get the scans. To date, we have been unsuccessful.

DR. WILSON: Right. But wouldn't an alternative be to send radiologists out to each center to review the scans at each center?

DR. LIN: I'm going to defer that question to Dr. Press in terms of whether that would be a reasonable alternative.

DR. PRESS: Well, there are some

confidentiality issues related to how cooperative group studies are done. And so the identity, not only of the patients but also the investigators, is an issue in performing exactly that way. Furthermore, as I had mentioned, many of the institutions, because of storage space limitations, have a policy of destroying scans. And so even if you sent a radiologist to look at a scan from, say, 2001, in some cases, the scan would not be in the medical records department of the institution at that point. There are reports describing the scan, but the actual physical films, in some cases, are not available.

DR. WILSON: So SWOG does not have a standard that if there is an ongoing clinical trial that has follow-up, that they're allowed to destroy scans.

DR. PRESS: There is not funding from the NIH to perform that type of study. I don't think that cooperative groups regularly do that, unless it's known at the beginning that it's going to be part of a licensing trial. There just isn't

financial capability.

DR. WILSON: Right. I think this is a very important conversation, because one of the questions that we'll be dealing with this afternoon is the role of cooperative group trials, and I think there are limitations. And I think this has been a very helpful discussion.

Dr. Sekeres?

DR. SEKERES: Thank you, Dr. Wilson.

Tom, I'm curious, and you may not be able to speak to this directly, but maybe somebody from your company can. Why did you all decide to go with a cooperative group rather than doing this on your own? Wouldn't it have been more efficient to do it on your own?

DR. LIN: So the original sponsor, Corixa, proposed two studies to confirm clinical benefit, the Bexxar versus rituximab study, which was agreed upon, as well as the SWOG S0016 study, as far back as 2001-2002. At the time of the full approval in 2003, the division and Corixa agreed that only the Bexxar versus rituximab study would be necessary to

confirm clinical benefit.

The reason that GSK did not try to start another study in 2005 was that the experience in the Bexxar versus rituximab study made it clear what the obstacles were. The SWOG study was ongoing and accruing well, and because of the number of experienced Bexxar centers, which are limited in the U.S., participating in the SWOG study, it would have been very difficult for GSK to obtain enough centers outside of SWOG to do another study.

DR. SEKERES: But just more globally, and I'm trying to, again, frame the discussion we're going to have this afternoon, why would a company want to work with a cooperative group as opposed to doing the study on their own?

DR. LIN: I think the unique challenges of Bexxar in terms of the administration, and with a number of sites which are qualified to give Bexxar, makes cooperative group studies really the way to go in terms of performing such studies.

DR. SEKERES: But that's something that's

unique to your compound, so logistical issues may be one. Is there a cost savings? Is there something about participating with a cooperative group that looks better to a regulatory agency, another government agency, to do something like that?

DR. LIN: I would have to refer that question to the division.

DR. PAZDUR: No.

[Laughter.]

DR. WILSON: Okay. I think we have a very short answer there. I'd like to move on to Dr. D'Agostino.

DR. D'AGOSTINO: Just in terms of the radiology, are you saying it doesn't exist or is it that it's not uniform across the centers? I'm back to the question that was asked earlier about it.

DR. LIN: I think with respect to the scans, we would be able to collect some of the scans, but it would be a non-random selection of the scans. They would probably be weighted toward more recent scans because of the issues regarding the hard

copies and destruction of previous scans, which Dr. Press alluded to. Because follicular lymphoma has long duration response to initial therapy, assessment of more recent scans probably wouldn't give an adequate number of events to actually assess.

DR. D'AGOSTINO: So how do you get out of the dilemma then with having it done local here?

DR. LIN: I apologize. I didn't hear the question.

DR. D'AGOSTINO: How do you get out of the dilemma of having it done locally or having it done in the standard fashion if you just don't have the scans?

DR. LIN: One of our contentions is that there is no additional benefit to doing essential review, that the investigator-assessed responses correlate with the responses seen by independent review.

I think Dr. Will Bushnell from the statistics department at GSK has some data he would like to show.

DR. BUSHNELL: I'm Will Bushnell, head of statistics for GSK Oncology, and I'm also the co-leader of the former progression-free survival working group.

One of our objectives of the working group was actually to examine the treatment effects from both independent review and from investigator assessment to see if there's a correlation to see, in other words, what the benefit is from independent review, what that adds to the clinical trial process.

So we conducted a meta-analysis. And what you're going to see -- if you go to the next slide, please -- is a meta-analysis of 23 trials that were conducted primarily in the solid tumor setting. This is primarily breast cancer studies, colorectal studies, and renal cell carcinoma studies.

What you see here on the X-axis is the investigator assessment, the hazard ratio. On the Y-axis is the hazard ratio for independent review. And what you can see here is a fairly strong correlation between these estimates of treatment

effect. And, again, our concern was to look at what the treatment effect is. And we realize there's always discordance between individual patient level, but what is the correlation for the overall treatment effect. And you can see here very high correlation of .95.

Sorry. Let me explain the plot a little further. It's a bubble plot. The size of the circle correlates with the size of the clinical trial. So you can see there is a slight tendency for the outliers to be some of the smaller trials.

Now, if you go to the next slide, this is the same data, but what we've done is have a different symbol for open label studies versus blinded trials. Again, I think the concern in the community is you'll have a little bit more potential for bias in an open label study. I think, in this case, you don't really see that.

Again, I think some of the open label studies are confounded with also some of the smaller trials. And I think Dr. Zelenetz is going to speak to this issue in the hematology setting.

DR. ZELENETZ: I'm Andrew Zelenetz, a medical oncologist at Memorial Sloan-Kettering, and I'm here as a consultant to GSK.

In many ways of considering it, lymphoma is a solid tumor. It's assessed by CT-based criteria. That's why this retrospective meta-analysis is valid in assessing CT-based criteria.

If we look at a number of studies, including the pivotal study for Bexxar, there was an extremely high correlation between the investigator-determined responses and the mirror panel-determined responses in the pivotal Bexxar study. This has also been true in other lymphoma studies. In fact, the pralatrexate study, the difference there was actually in skin-based responses. There was an extremely high correlation between CT-based responses.

Because CT determination of response is the primary endpoint largely in these trials, this analysis I think is applicable to the lymphoma field.

DR. D'AGOSTINO: Actually, let me ask

Dr. Pazdur, because the question is what does FDA require from a regulatory point of view.

DR. PAZDUR: We have been in discussions with the company regarding this with not many sponsors. And, here again, we are considering some of these proposals, however, we would like them to be probably done prospectively, looking at this entire issue, rather than some kind of retrospective excuse of not collecting the films

I really don't want to spend a lot of time on this, because it's really a tangential issue that needs to be discussed in much greater detail, and we've had discussion on this. But I guess one of the questions that I have for the sponsor is there is a possibility here that we will not accept this study, and what are your plans? We've been emphasizing this issue of a need for multiple studies, a comprehensive plan, looking at, with a great deal of seriousness, the issue of fulfilling this requirement.

At this point, what are your plans if this study is not acceptable to the agency?

DR. LIN: I'm going to refer that question to Philip Witman from regulatory.

DR. WITMAN: I'm Phil Witman, from Global Regulatory Affairs. And to answer this question, at the time, the division has agreed that they would consider the study when the results were available, which we still plan to submit. We still believe in the scientific integrity of the study.

It will be a review issue, as you have told us, and, at the time, if the study is not acceptable, we'll need to have dialogue with the division as to next steps. But at this point, we cannot plan for that eventuality.

DR. PAZDUR: So you do not have any additional trials that have been done that could fulfill this; so you're resting on this study solely to fulfill that requirement.

DR. WITMAN: At this time.

DR. WILSON: Thank you.

Dr. Kelly?

DR. KELLY: Thank you. Two questions here. One is going back to about the treatment effect on

outcome. And there's a difference between treatment effect and progression. They're not the same.

Do you have any data showing the reliability of investigators on progression, not just treatment effect?

DR. BUSHNELL: Well, in this study, the treatment effect is progression-free survival, and the way you measure that is with a hazard ratio. So when I was saying treatment effect --if that doesn't help, then I can't answer your question.

DR. KELLY: Typically, treatment effect is you have a PRCR and you go down. But, actually, when somebody has a CR and go on to progression, what is the reliability of that to detect progression?

DR. BUSHNELL: You're talking about the reliability of just measuring the response rate in terms of PRCR.

DR. KELLY: Correct.

DR. BUSHNELL: And I can't answer that question in the context of a lymphoma study.

DR. KELLY: The second question is in the SWOG trial. Can you just describe to us the standard methods for radiologic assessment and if they were standardized across the protocol in the institutions, and if there is a standard that has been set?

DR. PRESS: Each center has data managers that work with the site-specific investigators. They measure bi-dimensional measurements from the CT scans in conjunction with the radiologist who reads the scans, and they record on case report forms, those bi-dimensional measurements for the six largest lesions. And those are submitted centrally then to the stat office of the Southwest Oncology Group. And partial and complete responses and progressions, when they occur, are then assessed as defined by Bruce Cheson and an international working group for lymphoma response criteria.

DR. KELLY: Actually, I was talking more about actually doing the actual radiograph itself. Do you have a standard? Do they have to be certain

millimeter cuts? Do they have to be with contrast? Do they have to be on the same machine? Things like that. Is that standardized across?

DR. PRESS: Well, cooperative group studies, as you may know, there may be 100 participating centers. So if one is too rigid in specifying the type of scanner that's used, it's not very practical for a cooperative group study.

So there are general rules about how the CT scans are done in terms of contrast enhancement, but we don't have fine details on that.

DR. KELLY: Thank you.

DR. WILSON: Dr. Freedman?

DR. FREEDMAN: I just wanted to go back to the point about access to source information. The confidentiality issue that was raised really shouldn't be an issue, because as long as the PHI is not written down, copied down, suitable auditors for the sponsor, for the applicant, should be able to go in there with a contract agreement with those institutions. I don't believe it violates any federal rule.

So I think that is an important issue. It's important to know what proportion of the patients do not have those historical films, because that is a serious issue, which, of course, goes beyond what we are discussing here.

DR. WILSON: Thank you.

Dr. Martino?

DR. MARTINO: It occurs to me that the administration of this agent is fairly complex, and I'm gathering that not many places tend to want to do it. So within the SWOG trial, was there broad participation from the committee or were there certain institutions that really became the leaders in this?

DR. PRESS: There was actually very good accrual to the trial. Now, having said that, there were undoubtedly some centers who had more expertise than others in the administration of the Bexxar product. So often there was a partnering where the community physicians or the community hospitals would administer the chemotherapy or the chemotherapy plus Rituxan, and then patient were

often referred, for the Bexxar administration, to a tertiary center, such as the University of Washington, University of Michigan, other places that had a lot of experience and expertise in administration of the radiopharmaceutical.

DR. WILSON: The final question will come from Dr. Logan.

DR. LOGAN: I just had a question going back to the original post-marketing commitment study that had been approved, the Bexxar versus Rituxan.

So this study was part of the original post-marketing commitment for the regular approval back in 2003, and it was included, as well, as a post-marketing commitment for the accelerated approval. I guess my question is, how much information was there about the poor accrual at that stage of the accelerated approval and whether that was looked at when that decision was made, because something we're considering here is whether a study is ongoing already at the time of accelerated approval. And I think certainly not just ongoing is important, but also ongoing as well as accruing

well.

Is there any information about how much accrual availability -- accrual information was available at the time that that was part of the post-marketing commitment for the accelerated approval?

DR. LIN: Can I have the slide with the timeline? So this slide shows the timeline for the original study of rituximab versus Bexxar. Just to refresh people's memory, the initial full approval was in June 2003. The subsequent expanded indication was granted in December of 2004.

So the sponsor, at that time, Corixa, submitted a special protocol assessment and received approval according to schedule. The SPA was accepted by the division in September 2003.

You can see that by 2004, there was a nine-month lag or delay in enrollment of the first patient. So by 2004, there was some indication that the study would be difficult to accrue. And as we mentioned previously, in October 2005, the division agreed with the sponsor that the study was

not feasible to conduct.

DR. WILSON: Thank you. I think that we will now move on to the next presentation. So we're not going to take a break. We'll just take a two or three-minute hiatus while the sponsors shift chairs.

[Pause.]

DR. WILSON: Why don't we go ahead and get started? Is Genzyme ready?

Let me start out by having the two new FDA members please state your name and affiliation into the record.

DR. COHEN: Martin Cohen, medical oncology.

DR. JOHNSON: John Johnson, clinical team leader, oncology.

DR. WILSON: Thank you.

Dr. Hayes?

Genzyme (Clolar) - Mark Hayes

DR. HAYES: Thank you, Dr. Wilson, and good morning. I'm Mark Hayes, group vice president of Regulatory Affairs at Genzyme. And we're here this morning to review the accelerated approval and

post-marketing commitments for clofarabine.

With me today to help address any questions you may have are Dr. Michael Vasconcelles, therapeutic area head for transplant oncology at Genzyme; Dr. Elly Barry, pediatric oncologist and medical director responsible for the clofarabine pediatric development program at Genzyme; as well as our colleagues who represent the leadership of the children's oncology group, focused on the optimization of treatment for pediatric acute leukemias; Dr. Stephen Hunger, current chair of the ALL committee; and Dr. Bill Carroll, former chair of this committee, who has been involved with us in the development of clofarabine for many years.

Clofarabine, marketed as Clolar in the United States, was approved for the following indication at the end of 2004: the treatment of pediatric patients 1 to 21 years old with relapsed of refractory acute lymphoblastic leukemia after at least two prior regimens.

At the time of its approval, Clolar was the first new agent approved for pediatric ALL in over

a decade. The approval was based on the results of a Phase 2 single-arm study, CLO-212, in which complete remissions were demonstrated in heavily pretreated patients with no acceptable treatment options. Additional safety data were provided by a separate trial in pediatric AML patients, CLO-222.

The primary rationale for the subpart H approval was that while in this setting, complete remissions were considered to be reasonably likely to predict clinical benefit in the relapsed refractory disease, we were unable to fully interpret the durability of many remissions due to the propensity to take most patients to transplant immediately following successful remission induction.

To provide some context for the subpart H -- around the approval and post-marketing commitments in this indication, I think it's important to briefly review the patient population and treatment paradigm for pediatric ALL today and call your attention to a few important aspects illustrated on this slide.

First, the number of newly diagnosed patients is, fortunately, quite small, less than 2,500 patients per year. And more importantly, front-line induction therapy in this disease is remarkably successful, with 98 percent of patients achieving a first complete remission, 87 percent of whom are ultimately cured of their disease.

These extraordinary outcomes reflect the success of cooperative group efforts over the years to optimize therapy for these children. However, despite this success, a small number of patients continue to require new therapeutic options. These include the relapse refractory population for whom Clolar is currently indicated, which represents less than 200 patient a year. And as I've just noted, many of these patients tend to go on to receive a transplant shortly after achieving a complete remission.

A second population that is the focus of a current COG randomized study that I will discuss in a moment consists of patients who have received front-line therapy, but remain at high risk for

relapse without further modification of current therapy.

What's clear from this paradigm is that the number of patients eligible for clinical trials is quite limited. Complicating this fact is that there are over 100 trials active in this space at any given time, according to a current review of the NIH clinical trials database, and this profoundly affects the accrual rates for any population in this disease.

Two post-marketing commitment were defined for Clolar at the time of the approval in December of 2004. The first PMC recognized that further trials in pediatric ALL would necessitate combining Clolar with other existing drugs, and, thus, we reached agreement in principle with FDA on original post-marketing commitment number 1 to identify an acceptable and useful combination that could then be taken forward into further controlled studies. However, there was a clear recognition that additional combinations might need to be explored, and, thus, the reference here to the potential need

for an alternative plan.

The second PMC pertained to the completion of the controlled study, but at the time of the approval, this PMC was not further defined. A proposal to incorporate Clolar into a planned COG trial in first relapse patients had been brought forward at the time of the approval, but FDA had expressed concerns with this original COG trial design, noting in the approval letter that this trial did not appear to have a realistic chance of showing a clinical benefit of clofarabine. Thus, FDA requested that we develop a new proposal and request a meeting to discuss this proposal as soon as possible.

I'm going to take you through the story of how the PMCs for Clolar have evolved since the approval over the course of several meetings with FDA, as well as a discussion before the pediatric subcommittee of this panel. Before doing so, I would like to reflect on two options that can be considered in demonstrating clinical benefit in this setting. The first is achievement of durable

complete remission in relapse refractory patients. This was clearly the objective of the original pivotal studies, but the interpretation of remission duration data was complicated by the high percentage of patients that went to transplant following attainment of complete remission.

The second is a more conventional randomized control trial, and as you'll see, this first requires the identification of safe and effective combinations with Clolar and the ability to isolate the effect of any new agent becomes the challenge and the very complex earlier line treatment paradigms utilized today in pediatric ALL. Even if these criteria are achieved, accrual to large randomized trials in this disease will be long.

Genzyme met with FDA, as we had committed, on April 19th, 2005, to hold what was our first of a series of substantive discussions on the PMCs for this product. At this meeting, following feedback from investigators expressing concerns about the potential toxicity of the originally proposed combination, we reached agreement with FDA on two

new options for Phase 1/2 combinations with cytarabine and etoposide plus cyclophosphamide, respectively. Having two options increased our chances of identifying a useful and tolerated combination regimen.

Regarding a controlled study, FDA maintained their concerns with the potential for long accrual, noting in particular that it is unlikely that investigators will be interested in entering patients over such a long time period and that something new is abound to arise. In the end, it was agreed that it was premature to discuss Phase 3 design in further detail at this meeting until we had further data in hand from the combination studies.

Later, in 2005, Genzyme was invited to present the Clolar clinical development plan and post-marketing commitments before the pediatric subcommittee of this panel. At that meeting, there was some discussion about how to identify optimal combinations for use in this setting, including the utility of preclinical models; a recommendation

that we focus on earlier lines of therapy for further controlled studies; that considerations be given to alternative endpoints in this population, such as complete remission rate or minimal residual disease assessment; and, finally, there was a brief discussion about the applicability of controlled clinical data from other populations in demonstrating clinical benefit, in this case, with a focus on adult AML.

This timeline illustrates the clinical development plan that evolved from these initial discussions. Specifically, note the two Phase 1/2 combination trials that I alluded to earlier from our first PMC meeting with FDA. These trials, CLO-218 and AAML-0523, have been conducted in parallel by Genzyme and COG, respectively.

CLO-218, which evaluated the etoposide-Cytoxan combination, has been completed, with 50 patients enrolled. While the AAML-0523 study was initiated later than CLO-218, it has enrolled more than 50 patients, and the ALL arm has been discontinued as it did not meet the prospectively

defined efficacy criteria.

However, the efficacy data arising from the Phase 1 part of CLO-218, a 64 percent overall remission rate, with 55 percent overall remission rate in ALL patients, were sufficiently compelling to stimulate interest by COG in incorporating this regimen into a front-line consolidation study.

The CLO-218 data have led to the incorporation of this regimen into a more complex five-drug regimen that required evaluation and a pilot combination trial, CLO-08808 conducted by Genzyme. The results of this pilot, along with CLO-218, have informed the design of the COG randomized front-line study, where this five-drug combination will be used in consolidation following remission induction in high risk pediatric ALL patients.

Thus, the useful combination regimen required in PMC Number 1 has been defined, and we discussed the COG trial with FDA in our second PMC meeting held in July of 2008.

At this PMC meeting, held on July 16th,

2008, FDA indicated that the COG trial was of interest, but expressed two primary concerns -- the timelines remained long and the design of this trial would make it difficult to isolate the effect of clofarabine.

We also revisited at this meeting the question around the potential utility of adult data, in this case, an AML, and, after some discussion, FDA suggested that we propose consideration of a PMC package that might combine data from the COG study and adult AML data, and we took that under advisement.

On January 14th, 2010, we returned to meet with FDA for a third time to discuss the PMCs for Clolar. After further discussion of the rationale for the potential utility of adult data, FDA concluded that these data were unlikely to be useful and reiterated their concerns with the timelines and design of the COG trial.

Thus, as an alternative, FDA proposed that we consider conducting a single-arm trial in relapse refractory patients post-transplant, with

durable remission as a primary endpoint. We expressed some concerns about the ability to conduct such a trial today and this trial design was not likely to resolve the issue since remission duration in post-transplant patients is still likely to be confounded by a second transplant.

So in lieu of this option, we proposed to submit for their consideration a second single-arm, single-agent trial that had already been completed in Europe by Bioenvision, whom we acquired late in 2007, and was submitted to satisfy a specific obligation for the EMA in association with the approval under exceptional circumstances of this product in Europe.

The results from this trial provided additional remission duration data and confirmed the results of our original CLO-212 pivotal study. BIOV-111 was a similar design to CLO-212 and enrolled 74 patients who were treated at the same dose and regimen that is currently approved today.

So where are we today? We've recently submitted a PMC efficacy supplement to FDA on

December 17th, 2010, which includes the final results from CLO-218, and BIOV-111. This package is currently under review by FDA to determine whether these data have the potential to support conversion to full approval.

As a matter separate from the pending PMC evaluation by the FDA, the COG Phase 3 front-line consolidation study will proceed with a modified dosing regimen based on the results of our pilot study, CLO-08808. This is now designed as a three-arm, randomized trial that will enroll 1,500 patients. And while the revised design does provide a better opportunity to isolate the effect of clofarabine, the accrual is expected to remain long at five years, with at least two additional years of follow-up required to assess the primary endpoint of disease-free survival.

I would like to take a moment to reflect our perspective on the four questions that FDA has posed to the committee today in the context of pediatric ALL drug development.

Regarding question 1, we believe that

relapse refractory pediatric ALL clearly represents a situation where a single-arm trial is appropriate for approval.

In the setting of relapse refractory acute leukemia, we believe that CRs represent the clinical benefit and offer patients the best opportunity to benefit from potentially life-saving stem cell transplant. In this context, it is important to recognize that the clinical objective in this population is the potential for cure following a stem cell transplant.

In addition, front-line therapy for pediatric ALL involves induction, consolidation and delayed intensification using many different drugs over a long period of time and is extraordinarily effective. Thus, the patients represented by our approve indication have already seen a multitude of the most proven active agents in this disease and, by definition, have no remaining satisfactory treatment options against which to randomize.

With respect to question 2 and the desire for more than one randomized trial, as discussed at

the pediatric subcommittee of this panel in 2005, randomized trials are only practical in earlier lines of therapy. But, again, the rarity of patients will make accrual timelines long for trials that are appropriately powered for the expected treatment effects; and this does not account for the additional time required to generate the preparative data that assures our ability to safely and effectively combine a new agent with existing regimens.

Regarding the concept of delaying approval until PMC trials are underway, proposed in question 3, we agree with the importance of this provision in the regulations, and this obligates early discussion of the PMC options during the review process. However, we believe that the timely approval of Clolar has not only provided access to relapse refractory patients with no acceptable treatment options, but, in fact, has played an important role in incentivizing further development toward assessing utility in front-line patients by COG.

Finally, since the vast majority of pediatric ALL patients are enrolled in COG trials, here, 70 percent or more, our collaboration with COG has been critical. Thus, we strongly support the efforts by the recently initiated NCI operational efficiency working group to identify opportunities to make the cooperative group process more efficient and would emphasize the importance of early collaboration between sponsors, FDA, CTEP, and cooperative groups.

In rare diseases, we believe encouraging optimal utility of cooperative group trials is the best use of resources versus requiring separate industry-sponsored studies that would compete for patients in these same population.

Thank you for your attention, and we'll be pleased to answer any questions the committee may have.

Questions from Committee to Sponsor

DR. WILSON: Thank you. Let me start out with this question. In your slide on perspectives on the FDA questions to ODAC regarding trials in

pretreated relapse refractory patients, what is the clinical rationale for saying there are no acceptable comparators in a pivotal patient group?

DR. HAYES: Regarding the acceptability of comparators, I'd like to ask Dr. Barry to help address this question.

DR. BARRY: Elly Barry, Clinical Development at Genzyme. So the fact is that most of these patients in front-line/second-line therapy receive over a dozen or more active agents in the treatment of their disease. So by the time that they've reached third-line, which is our current indication, they've been exposed to most of those active agents. And, therefore, randomization between clofarabine and one of those agents would be very difficult in that setting.

DR. WILSON: So you're trying to tell me that the population for this trial, if they didn't get your drug, they would be sent home to die? Because that's what you just said.

DR. BARRY: I don't think that's the case, but there is -- I think recognizing how poorly

these patients fare and their limited options, there's interest in new agents, particularly in this patient population. So randomizing against a known or existing therapy I think would be difficult.

DR. WILSON: The reason why I'm focusing on this is because I do think that this is a very important issue, and it involves both the use of transplant afterwards; and that is that randomization against best supportive care or a listing of agents is certainly a reasonable alternative. And unless you're saying that these patients would be simply sent to go home to die, I do think you could have a randomization against best care, whatever that might be.

I'm also not sure that the transplantation necessarily confounds the outcome. And the reason I say that is because in these very heavily relapsed patients -- and your own trial showed this -- if you in fact are able to induce a complete or, in some cases, a partial remission, patients may become eligible for a transplant. And

so the transplant is simply a reflection, in some ways, of the fact that they've had a good response to your therapy.

So, in fact, you could, even allowing transplant, look at progression-free survival after the transplant or even overall survival. So I guess I don't understand why clinical trial designs like that wouldn't be an ideal way to handle cases like this.

DR. BARRY: We, I think in the course of developing this drug, have had conversations with FDA and within COG as to what the right patient population was. I think in our indicated population, as we've seen, it's very small. And a number of challenges in trying to perform a randomized study and the number of patients and the time that would be involved, I think, was one consideration.

Transplants, we have believed and agree with you that transplant is a benefit in this patient population. From a regulatory standpoint, I think it has maybe the assessment of durability of

remission, an important factor that has interfered.

DR. WILSON: I don't want to do this to death, but the issue that was brought up in the original accelerated approval is that CR is recognized as a valid endpoint; however, you don't know how long it lasts. So by having a comparator group, you're able to actually get a sense of whether or not the responses to your drug, given the fact that some of those will go on to transplant, actually does translate into a benefit.

So I do think there are ways around, just assuming that a CR is necessarily a very high end marker.

So let me just stop and go on and recognize Ms. Mayer.

MS. MAYER: I wonder if you could give me a little context here about treatment of this disease. In children who have relapsed and are heavily pretreated and have undergone at least one transplant with the expectation or hope of undergoing another, what kind of short and long-term toxicities follow that and what does the

inclusion of your agent add in terms of toxicities?

DR. HAYES: I think I'd ask Dr. Barry or Dr. Vasconcelles to address that, or perhaps our colleagues from COG.

DR. CARROLL: I want to address issues that have come to the table. I'm Bill Carroll, was the past head of the Children's Oncology Group ALL committee.

Number one, you need to recognize -- and I think it's recognized by people around the table -- that these kids have a very poor survival once they relapse. Despite the good outcome in front-line therapy, we have not made any significant advance for patients who relapse, using a number of different combinations, none of whom have proved to be more beneficial than others.

We made a concerted decision in the Children's Oncology Group for first relapse is not to do randomized studies, for three reasons. Number one, we have very difficult accrual to those studies, a poor record of that. Number two, the low patient numbers and exceedingly poor remission

induction rate would make a randomized study almost impossible; that is to say, it would last six to seven years, and I don't think any of us would have the stamina to do a randomized study when many other important drugs are coming down the pipeline.

So our approach was to develop a baseline triple induction regimen onto which we've overlaid new agents; for example, epratuzumab is one study that's now open. It's a single-arm study. It's not randomized.

To address your question, there's no doubt we've tried to intensify therapy, and it's led to death rates as high as 8 to 12 percent. So we can't escalate any further. We're at the limits of benefit. So we're looking for an effective combination with clofarabine that will prove to be tolerable. We've identified this in the second relapse setting. We've made a decision to bring it into a front-line setting, what we thought would be the best setting to assess the potential benefit of clofarabine. So we think we have a combination now that will prove tolerable in this circumstance.

MS. MAYER: Can I follow up on that?

That's not actually what I asked. I asked about specific toxicities that these children are left with, if they do survive.

DR. CARROLL: Do you mean following transplant?

MS. MAYER: Well, that's part of the regimen, and I just want to have a sense of what their lives are like.

DR. CARROLL: I think that, first of all, transplant may be life-saving. There's no doubt the benefit for those children who get to it. It may be substantial. But, post-transplant, there are a limited number of long-term toxicity, everything from neurocognitive deficits to endocrine deficits to growth delays, which is just part of the transplant package.

So I wouldn't say that these -- these kids, although they have received multiple agents and may be, in many respects, not specifically able to tolerate the transplant, still, if they can get that -- the biggest problem is getting them the

transplant, because there's only 7 percent remission reinduction rate, but 10 percent will fall out of remission, even before they get the transplant, per month.

So hopefully I answered your question.

MS. MAYER: And there's no additional issue with the toxicity of your agent.

DR. CARROLL: No specific extra toxicity over what would be seen for another chemotherapeutic agent in this class.

DR. WILSON: Thank you.

Dr. Mortimer?

DR. MORTIMER: My question is actually to the agency. I remember vividly when this drug was approved, because it was a small study, very few patients, and it seemed, at that time, that it was pretty obvious that post-marketing confirmation was going to be a problem.

So how much levity -- how much variation is there in terms of the patient population for a confirmatory trial? I realize there's a consolidation trial being done in high risk, but

this drug is also being used in adults. How much deviation can you get from the initial drug approval in doing these confirmatory trials?

DR. MURGO: Dr. Pazdur indicated earlier that it's not feasible to do a study in the same setting and using the same regimen once the drug is on the market. So there is some thought that's given to how to design the post-marketing study. Such designs may include using the drug in combination in a front-line setting. And it's feasible to do a randomized, controlled trial, because if it's an add-on study, then the control arm, obviously, would be -- the backbone would be a standard regimen.

I'm not sure if that answered your question. There are other examples, as well.

DR. MORTIMER: And I presume it has to be done in pediatrics, I guess is my question, too.

DR. MURGO: Say that again.

DR. MORTIMER: It has to be done in the pediatric population, since this drug is being used in adults, as well.

DR. MURGO: Usually, it would have to be in the same age group.

Dr. Pazdur?

DR. PAZDUR: I think generally so, the indication that's granted here.

DR. WILSON: Thank you. Dr. Smith?

DR. SMITH: My first question is concerning the ALL 1131 trial that you mentioned and just to confirm that it does isolate the effect of clofarabine in a randomized way. And then the second question for you and, also, for the agency, you pointed out that a downside of that trial, in the upfront setting randomized trials, it will take five years to enroll and another couple of years to complete. But does that preclude it being used for this commitment? And from your perspective and, also, from the agency's perspective, if the contribution can be addressed as even though it takes five, six, seven years, does that preclude using that to meet the commitment?

DR. HAYES: We have a side that shows the regimens that are now being tested in 1131, and I

could ask Dr. Hunger or Dr. Carroll to talk about the design and the drugs that are being tested. There is a third arm that was added recently, as I'm sure you're aware, that does allow for that potential isolation.

Then I think we can address the second question. I think the agency is probably better apt to answer the question about the utility of a study that's going to take this long. I think that's the concern that has been raised all morning, is that this might be a great confirmatory study if it were something that we could have done in a shorter time period. But by the time the study gets done, the drug will have been on the market for many years.

DR. HUNGER: My name is Stephen Hunger. I'm here representing the Children's Oncology Group. I have accepted travel reimbursement from Genzyme and no other expenses or costs.

This trial is designed as a randomized trial in a subset of pediatric acute lymphoblastic leukemia. It is a three-arm, randomized trial in a

1:2:2 randomization between the control and two experimental arms. As alluded to earlier, a combination that we believe is quite active has been identified in the CLO-218 trial that combines clofarabine with cyclophosphamide and etoposide. So experimental arm one contains cyclophosphamide and etoposide, and experimental arm two contains those two agents plus clofarabine. The trial is designed to see if either experimental arm one or experimental arm two is better than the control arm and, also, to compare the results between experimental arm one and experimental arm two.

So we believe that this has the potential to show a direct benefit of clofarabine, if one such exists in this regimen. The study is projected to begin accrual in the third or fourth quarter of this year and will accrue for five years. So the timelines are relatively long until we will have an answer from this trial. Thank you.

DR. WILSON: I'd like to recognize Dr. D'Agostino.

DR. PAZDUR: Let me answer Malcolm's

question. It's not so much the time, and here, again, this is a judgment that one has to make. This is a rare -- a difficult situation that we're dealing with here with a small number of children with the disease.

So I think the issues that -- one of the reasons that we brought this forward is that there are unique challenges in pediatric oncology that we have to demonstrate flexibility with. That being said, I think, also, one of the issues and another reason why we brought this forward is really to have learning from our history, and that really we should have probably had these discussions right upfront before this drug was approved of what was going to be the confirmatory studies rather than discussing after the drug is approved.

Remember, this is before the FDAAA requirements, when we had penalties. So really the agency loses its authority, basically, other than taking the drug off the market, if these studies are not done with due diligence.

So I think really what this reflects, and

one of the major reasons that we brought it here, is this issue. We want to have a comprehensive drug development picture. It isn't just get the drug approved and then we'll discuss the confirmatory trials afterwards. Learning from this history as we go on over the years here, these really have to be very careful discussions of what these trials should be. They should be presented at the ODAC meeting when we discuss this drug. And perhaps if we don't have agreement, alternative ways of providing access to the drug rather than approval, such as expanded access, especially in such a population, should even be entertained.

DR. WILSON: Thank you.

Dr. D'Agostino?

DR. D'AGOSTINO: I wanted to go back to the questions that were basically around the single-arm study. I do work in the stent arena, and we don't like single-arm studies, but we do them and they come out to be very useful. But what goes on with the studies is something like you were referring to, Dr. Wilson, is that we have an idea of what the

sort of standard of care will produce.

Now, are we saying for this ALL, for example, it's been approved accelerated approval, but we weren't very comfortable with the response rates that we would expect to see and response rates that we would say would indicate effectiveness? I think it's not only do we have a comparative population that we want to randomize to, but do we have some comparison numbers that we can compare our results to, and I'd be interested to hear what Genzyme has to say about how -- when they got their results, why did they feel they were producing useful, significant results; and do they have populations out there where they can get these baseline data?

DR. HAYES: Dr. Vasconcelles?

DR. VASCONCELLES: Dr. D'Agostino, Mike Vasconcelles from Genzyme. So if I understand your question correctly, I'd make a couple of points.

The pivotal trial, if that's what you're referencing, CLO-212, was specifically designed for patients for whom there were no previously

recognized alternative therapy; and, in fact, two-thirds of those patients enrolled in the study were immediately refractory to their immediate prior induction therapy, and over a third of them had already been through a prior transplant. So that's clearly a patient population for whom treatment options are extremely limited.

If we look in the literature for a comparative population, I'd turn to Dr. Carroll or Dr. Hunger, but I don't think that we have any really contemporary comparative literature, given the multiply relapsed population and the proportion of patients who had already been through allotransplant.

DR. D'AGOSTINO: We have to worry about getting the clinical endpoint for trials, but we also have to worry very much about what's the front end; is the single-arm study feasible, and is it feasible in the sense of interpretable.

DR. WILSON: So, actually, maybe, Dr. Pazdur, you can comment. What we're hearing is that this is a group where nothing works. So you

have a drug like clofarabine that showed a 20 percent complete response rate. If it is as compelling as we hear, why is not a secondary confirmatory Phase 2 single-arm trial acceptable? And I'm asking this as a rhetorical question against a randomized study.

DR. PAZDUR: I think one of the issues that we wanted to take a look at is duration here. And if they can provide us further duration with additional patients, this may suffice for the conversion.

Here, again, we would prefer to have a randomized trial; let's face it. And I think we've had a discussion of what the limitations are in this population. I don't know if John or Marty want to comment on this, because they were the review staff on it.

DR. JOHNSON: We may just very well convert this to full regular approval based on a Phase 2 trial in, I think, about 60 patients. So we may take your advice.

DR. WILSON: Well, I just bring this up

because it's a little bit of a catch-22, because as we saw in this pivotal trial, 40 percent of them did go on to a transplant. So I think you're not going to be able to get that kind of duration in the absence of that. And so I think you either have to accept CR and say they had no alternative therapy, and they went to transplant and look at the duration there or simply do a randomized study.

Time is really drawing close here. So let me just finish with two more folks.

Dr. Martino, I believe you had a question.

DR. MARTINO: Just a general question. I treat adults, so I'm asking just a simple question so that I understand the issue here.

Now, my impression is that within this country, in pediatrics, pretty much all studies are confined to a cooperative group setting. So, first of all, I need someone to confirm that that's correct.

The second question is, is that also true in other parts of the world? One of the things that we've learned to do in adult cancers is that we

either seek patients outside of this country or we cooperate with cooperative group systems in other countries. Both of those avenues have precedence.

Are those solutions for the pediatric population?

DR. HUNGER: I'll try to answer those questions for you. We've recently done some analysis, and in 2009, 70 percent of all children and adolescents in the United States predicted to develop ALL were enrolled in a Children's Oncology Group clinical trial. So I think it's very different in the situation in adult cancers, where rates of less than 5 percent overall are common.

The same or even more so is true in Western Europe, where there is more centralized medical care. There is very high clinical trial participation, and we would be loathe to go outside North America or Western Europe in assessing cytotoxic chemotherapy in childhood leukemia, because, with a few discreet exceptions, then you start to get into much higher mortality rates from therapy due to local conditions and inability to

provide supportive care. So a treatment that might be effective might be confounded by excess mortality that you would not see in the U.S.

So I think the clinical trial participation is quite high and, in this case, the pharmaceutical company, Genzyme, has been very collaborative with the cooperative group, something I think both the FDA and the NCI have encouraged, and they have worked very closely with us in attempts to collaborate as opposed to compete for patients.

DR. WILSON: Thank you. So let me just close with a final follow-up question from Dr. Smith.

DR. SMITH: I have a question about the single-arm study that you're proposing. In the second relapse setting, the response rate to multi-agent chemotherapy isn't zero. There's an appreciable response rate with the kind of standard agents. And your report that you provided before the meeting indicated, in fact, that there was lack of enthusiasm for a single-agent study of clofarabine, and in the context of published data,

it's showing improved efficacy with clofarabine in combination.

So how do we make use of the single-agent study to demonstrate clinical benefit, when even in the second relapse setting or beyond, multi-agent chemotherapy is the way children would typically be treated at that relapse?

DR. HAYES: And I think that's why we went back to the BIOV-111 study as opposed to the consideration of doing another single-agent study. The CLO-218 data were out there. Clearly, that was a very efficacious combination, and it was going to be hard to convince people to treat with single agent.

I don't know, Dr. Vasconcelles, if you have any further comments, but I think that was the primary reason for not feeling there would be any enthusiasm for another single-agent study at this point in time, I think. But we have more data to bring forward, which I think may help to address the question around response duration.

DR. VASCONCELLES: The only thing I would

add is that I think we completely agree with you. What the BIOV-111 study provides, though, is a completely independent confirmation of clofarabine as a single agent with quite striking similar response rates and durability whether one sensors for patients in transplant or not. But, clearly, given the development that's proceeded since the approval, the utility of clofarabine in combination has moved forward.

DR. WILSON: Thank you all. Let's now move on, and, again, we're going to have a very short break, just long enough for the sponsors to switch.

[Pause.]

DR. WILSON: Why don't we go ahead and get seated so we can get started? So we are now going to be hearing again from GlaxoSmithKline on nelarabine, and we'll be haring from Dr. Russo.

GlaxoSmithKline (Arranon) - Mark Russo

DR. RUSSO: Thank you. My name is Dr. Mark Russo, and I am project physician at GlaxoSmithKline, responsible for Arranon. It is my pleasure to present to you today on behalf of

GlaxoSmithKline an update on the progress being made toward fulfilling our post-marketing commitments for Arranon.

In addition to the GSK representatives you see here, Dr. Stuart Winter, a co-PI for our post-marketing commitment study, is here today with us representing the Children's Oncology Group and will be available this morning to address questions that you may have for him.

Briefly, my presentation will consist of an overview of the accelerated approval of Arranon, the process leading to the post-marketing commitment establishment, a description of that trial, the original timelines, and now our current estimates for those timelines.

Arranon received accelerated approval in October of 2005 for the indication statement shown here and in the briefing materials. The approval was based on complete remissions.

Similar to the previous presentation, this is a very small patient population. In the United States, it's estimated that 1,600 newly diagnosed

cases of T cell ALL or T lineage lymphoblastic lymphoma will be made in each year in the combination of adults and children; and, of these, fewer than 300 would be predicted to relapse following two previous courses of therapy.

While this represents a very important patient population and one in need of improved treatment options, these small incidence numbers present substantial challenges and constraints to the conduct of clinical studies.

The accelerated approval of Arranon is based on two Phase 2 monotherapy, non-comparative studies. They were performed by the Cooperative Group Network, sponsored by the National Cancer Institute. These studies enrolled patients over many years into several strata based on prior therapy and other disease features. Only those subjects in the relevant strata contributed to the efficacy data and the prescribing information and are presented here, 39 from the pediatric study and 28 from the adult study.

In the pediatric trial, the complete

response rate was 23 percent; in the adult trial, complete response was 21 percent.

The safety profile of Arranon was established from patients participating in these two trials, as well as additional studies; 459 patients contributed data that demonstrated that Arranon has a toxicity profile similar to other cytotoxic agents used in a similar disease setting. A notable exception is that Arranon has a black box warning for neurologic toxicity.

Based on these results, Arranon received its accelerated approval on the 28th of October 2005 in both the adult and pediatric populations. The approval letter stipulated an agreed post-marketing commitment study to demonstrate the clinical benefit of Arranon. The letter specified timelines for most of the milestones and that this agreed study was to undergo a special protocol assessment prior to study initiation. The first patient was to be enrolled within six months following the approval date.

The post-approval commitment study is the

Children's Oncology Group Study AALL0434. The study is being conducted by the Children's Oncology Group under the NCI's IND. It is a two-by-two factorial design to address two important clinical questions on optimal treatment during the consolidation and maintenance phases of therapy. The first is the optimization of the methotrexate administration during this period of time; most relevant to today's discussion, the randomization to assess the clinical benefit of Arranon when added to consolidation and maintenance in the first-line treatment of T lineage ALL.

Drs. Winter and Dunsmore are co-principal investigators for this trial. Dr. Dunsmore also served as the study chair for the pilot program which established the feasibility of the current trial.

A schematic is shown here. Induction is shown on the left-hand side. And I should point that this complex trial was demonstrated here in a very brief format, showing only those details most important for our discussions today on the

demonstration of clinical benefit of Arranon.

Following that induction, there's a risk assignment. Following risk assignment, then, groups are randomized, as depicted here. The intermediate and high risk patients are eligible for randomization to the arms addressing the benefit of Arranon, as well as the methotrexate optimization.

Low risk patients, at the bottom center, are randomized only to the methotrexate optimization arms; and, the induction failure patients, at the top in the center, are non-randomly assigned to Arranon and high dose methotrexate treatment.

During the initial safety portions of the study, the intermediate risk patients were treated similarly to the low risk patients. Now, in the efficacy phase of the study, those intermediate risk patients are treated similarly to the high risk. The primary endpoint is event-free survival at four years, together with establishment of a safety profile of the various regimens.

The study is designed to overall enroll

1,380 patients, with 1,206 randomized to the methotrexate optimization portion, and, of those, 615 will also contribute to the randomized assessment of the clinical benefit of Arranon. It is open to all Children's Oncology Group sites. It is a first priority study in T lineage ALL. It is enrolling now at 168 centers across six countries.

Current status is shown here. We have completed the safety phase. The data was reviewed by the Data Safety Monitoring Board of the Children's Oncology Group, and those data were presented by Dr. Winter at this December's ASH.

The efficacy phase is currently enrolling, and as of last week, there were 565 of the total subjects enrolled, of which 116 have been randomized to the Arranon assessment groups.

Shown here are the timelines originally agreed, in the center column, along with the milestones, the achieved milestones, and our current projections when the remaining milestones will be achieved.

Following our approval, we were to have the

first patient enrolled in April of 2006. However, the finalization of the protocol did not occur as quickly as originally projected, and the actual date of the first patient enrolled was January of '07. In addition, there was a brief interruption in enrollment as an important safety amendment was made to many of the leukemia studies of the Children's Oncology Group related to the induction phases of therapy.

Other than these two brief delays, this program is progressing according to the agreed timelines. The actual enrollment rate is remarkably similar to the initially projected enrollment rate shown on this plot. One can see the brief interruption, again, of the enrollment due to the safety amendment.

This trial is being executed very successfully by the Children's Oncology Group, despite the fact that we are studying a very low incident pediatric population, and the required patient numbers to assess clinical benefit are relatively large. This speaks to the unique

capabilities of the Children's Oncology Group. We are honored to continue to partner with COG and work to advance pediatric cancer care.

Overall, our current expectation is that the results of this study will be available approximately 12 months from originally agreed timelines. We are progressing as originally planned and no further delays are anticipated.

Thanks for your attention.

Questions from Committee to Sponsor

DR. WILSON: Thank you. While we're waiting for questions, let me ask something. This is a very complicated seven-arm trial, and I guess I'm trying to understand what type of statistical power this would have. And it seems to me that to have power, you are combining the high dose and standard dose MTX arms, plus or minus your drug; is that correct?

DR. RUSSO: The primary assessment of clinical benefit from this trial will be the four-year event-free survival for those patients randomized to Arranon-containing arms versus those

not.

DR. WILSON: So there's an assumption here that, for example, if the high dose optimization is a more effective regimen, could that not obviate the benefit of adding this agent; and, therefore, aren't there some assumptions going on here that may not turn out to be correct?

DR. RUSSO: I think a key assumption is that the treatment effect of Arranon will not be dependent upon the methotrexate that it's co-administered with. So, indeed, both could be successful at the end of the day.

DR. WILSON: Right. Well, certainly, I think we know from other -- I just think it just points out one of the difficulties here. I think we know from other disease settings that both risk and platforms can, in fact, modulate other agents. The risk is that that won't be the case. So if that isn't the case, I guess you would then have to go and analyze it within each of these methotrexate groups, and the power then becomes very low.

DR. RUSSO: I think I'd like to address the

follow-up question to Dr. Stuart Winter from the Children's Oncology Group.

DR. WINTER: Hello. I'm Stuart Winter. I'm here representing the Children's Oncology Group. My travel expenses were covered by GlaxoSmithKline, but other than that, I have no other financial relationships to disclose.

I think that's an excellent question, your question about asking about randomization and whether the methotrexate question would contribute to either confounding the nelarabine question or not.

Recently, the study was just reviewed by the Data Safety Monitoring Committee, and there seemed to be no compelling differences between the high dose methotrexate effects versus the escalating methotrexate effect. And so the study continues on asking that methotrexate question.

I thought you brought up another great point, and that is, it is a complicated study, but when you look at the numbers of patients who are contributing to the methotrexate question and to

the nelarabine question, it's about 80 percent of enrollments. So that's about 80 percent of almost 1,400 kids. So we're pretty confident that when the study is finished, we'll be able to address whether or not nelarabine really contributed to efficacy.

DR. WILSON: Thank you.

Dr. Sekeres?

DR. SEKERES: Thanks, Dr. Wilson. I have a couple questions. The first is, I think, more mundane than the second. And that is, do you have any stopping points for futility for this study or are you pressing on and enrolling 1,380 patients?

DR. RUSSO: I'd like Dr. Winter to answer that.

DR. WINTER: Yes, another great question. Yes, we have a couple of futility endpoints built into the study that the Data Safety Monitoring Committee looks at twice a year. And so if we cross a futility endpoint, then, of course, we'd have to discuss that and what impact that it would have on the study. So over a six-year enrollment

period, that question will be asked 12 times.

DR. SEKERES: So the first time period when will hit that?

DR. WINTER: I'm sorry?

DR. SEKERES: The first time when you will hit that futility assessment is when?

DR. WINTER: We have been getting that assessment already with each time that the Data Safety Monitoring Committee looks at the study. So that has not come up as being an issue so far.

DR. SEKERES: Is that a formal statistical look or is it a gestalt?

DR. WINTER: Can you repeat the question?

DR. SEKERES: Is it a formal statistical look for futility or is it a gestalt?

DR. WINTER: I believe so. I believe so.

DR. RUSSO: If you would prefer, I could step in.

DR. SEKERES: Sure. Go ahead.

DR. RUSSO: As Dr. Winter points out, the Data Safety Monitoring Board reviews the data twice a year and on an ad hoc basis as needed, and they

have private deliberations. There is preplanned four interim efficacy analyses at 20, 40, 60 and 80 percent of anticipated events, and the alpha spend, of course, is heavily weighted towards the final analysis.

DR. SEKERES: The second question I have is, why did you -- I'm kind of repeating the question I asked a little bit earlier about the motivation for participating in a cooperative group. For example, I could envision a study where you looked at a similar population to your accelerated approval and compared it to, for example, clofarabine. So why not pursue something like that where you could do it outside of a cooperative group with adults and/or kids versus working with the cooperative group?

DR. RUSSO: There are many ways to address that question.

Dr. Winter, would you like to start?

DR. WINTER: Sure. So if I heard you correctly, it was why work with a cooperative group to ask this question. Is that the essence of it?

DR. SEKERES: Well, as Dr. Wilson just said, this is a pretty complicated design.

DR. WINTER: Right.

DR. SEKERES: So if you're thinking of an easier design where you could have a randomized study, you might, for example, come up with a design where you randomize people who failed -- people with T cell ALL who failed a couple of previous regimens to nelarabine versus clofarabine, right? Same indication within the T cell population.

So why go through a cooperative group, with the delays that are more than just occasionally inherent in working with a cooperative group, rather than doing the study outside of a cooperative group for this?

DR. WINTER: So you've brought up a couple of points I'd like to address. And first of all, I think why not look at a nelarabine-clofarabine question is because nelarabine has biological properties that appear to make it more efficacious in children with T-ALL. And then in working with

the Children's Oncology Group, we have a little bit of a paradigm shift here where we are trying to randomize giving nelarabine or not to patients with certain risk features. So it's a risk adaptive strategy based on response to therapy and induction MRD.

So I think there are some important scientific considerations as to which patients are exposed to this drug to answer the question, which I think is an important aspect of this.

Then as you heard from Dr. Hunger earlier today, the standard of care at least for children in the United States is to enter onto cooperative groups with the Children's Oncology Group. And I think that plus the fact that the Children's Oncology Group has its own auditing process and its own scientific agenda, I think, can extend some of the value of this question.

DR. WILSON: Thank you.

Dr. Martino?

DR. MARTINO: Could you add a few more details to the neurological problems with this

agent and perhaps speculate on mechanism?

DR. RUSSO: I will address the second part. The mechanism would only be speculation, and I would prefer not to speculate.

The toxicity is well described in the clinical trial database of the original application. It appears to be a multifactorial type of neurologic toxicity. The neurologic toxicity is often grade 1 or 2, but occasionally much more severe. It is usually reversible, but not always reversible. It can involve just peripheral neural toxicity. It can involve mental status changes. There are 13 cases in our files of a Guillain-Barre-like syndrome out of over 1,000 treated patients.

I would like Dr. Winter to expand on that.

DR. WINTER: One thing I just wanted to point out to the committee, that a lot of these neurological side effects were seen in heavily pretreated patients who had failed two or more previous regimens. What we're currently seeing on the study seems to be less neurotoxicity in a

patient population that seems to be less heavily pretreated. So, again, it's hard to know what the mechanism is, but there may be some sort of lasting neurotoxicities from prior regimens that were interacting with nelarabine, as previously reported for those other studies.

DR. WILSON: Thank you.

Dr. D'Agostino?

DR. D'AGOSTINO: I don't really have anything profound to say. But in terms of the study design, I was taking it, as they were doing it, that it was, basically, the risk assessment was a filter and that they really end up having a couple of studies going on here and the power within those particular sub-studies. The high and intermediate risk will be one study, the low risk another study, and they can control alpha fairly well in that.

Is that not the case? This is sort of a cooperative arrangement, so that they can get their pool of subjects, but they really have sub-studies going on here. And our money is all in that high

to intermediate risk group. Is that correct?

DR. RUSSO: That is a correct observation, yes. This trial needs to encompass all presenting T cell ALL patients.

DR. D'AGOSTINO: Its complication is basically in the risk assessment, but I don't think in the final analysis, it would be broken down by this sub-studies, I think.

DR. WILSON: Right. Well, that's the question I was asking, whether they were going to be pulling people from the standard and the high dose MTX. And they probably will, because otherwise the groups are very small and the power would be very small.

DR. D'AGOSTINO: They have 615 subjects, I guess, in the group that we would be interested in here.

DR. WILSON: Right. By combining both the high dose and standard dose MTX groups. Right.

Dr. Balis?

DR. BALIS: The numbers you present on this slide show that you've accrued about 40 percent of

the patients to the study, yet there are only less than 20 percent accrued to the randomization of interest here. I presume part of that is because of the safety study initially based on the fact that there's very few intermediate risk patients. But could you comment on the fraction or the percentage of eligible patients who are being randomized on the study currently?

DR. RUSSO: The first part of the answer is, yes, that is the reason why only 20 percent of the Arranon patients have been enrolled. As for a percentage of eligible patients enrolled into the program, Dr. Winter, would you like to tackle that?

DR. WINTER: Sure. So in terms of patients who are now eligible for the treatment studies, on this treatment randomization on the study, as I was saying before, we were thinking that about 80 percent of the patients that are being accrued onto the study as of September of 2010 are contributing fully to the questions of the study. So we're now into the part of the study where we intend to get the most information about the

nelarabine question.

DR. WILSON: Dr. Smith?

DR. SMITH: I would mostly like to comment on some of the points made in terms of the design of the study.

As you've pointed out, it has been done in the context of the COG and in collaboration with COG. And so there's a history in the COG ALL committee of doing factorial designs, because you can ask two questions in the same patient population. It's perhaps not what you would have chosen if you were going for a primary indication, but it's the context of the COG research program is to use factorial designs, and it's been a very successful strategy

So I guess one point, in terms of post-marketing commitments, when working with a research group like the pediatric oncology research community is balancing the regulatory optimum with what is kind of the optimum of that research community. And the other part of it is relating to relapse versus upfront setting. I think a study in

the relapse setting could have been of potential interest, but I think the interest was in preventing relapse rather than trying to treat relapse once it has occurred is the primary research focus.

So, again, perhaps a regulatory focused approach would have been to go for a relapse setting. But I think the research community felt that the primary goal would be to try to prevent relapses and to focus on that type of study.

So I think it's a tension here when we're talking about post-marketing commitments in the pediatric setting, is the research agenda to kind of optimize treatment for a population, may not be exactly in synchrony with what the optimal regulatory pathway might be to clearly demonstrating something. I think it's just an issue to be cognizant of as we have discussions this afternoon.

DR. WILSON: I think that that was very well said. I think that is actually one of the discussion issues we're actually going to be

dealing with is the tension that goes on and the reality, especially in the pediatric setting. As we've already heard and know, that, essentially, if you don't go through the cooperative groups, you're not going to get your trial done.

DR. PAZDUR: I really think the pediatric area is a much different area than adult.

DR. WILSON: Very different area, yes, very different, very different. I agree.

Okay. If there are no more compelling issues, we still have two more. So let's go ahead and do musical chairs and get started as soon as we can.

[Pause.]

DR. WILSON: Why don't we go ahead and get seated so we can move forward with the next sponsor? We are now going to hear from Amgen. It will be a presentation on panitumumab, and I'd like to welcome Dr. Eisenberg.

Amgen, Inc (Vectibix) - Paul Eisenberg

DR. EISENBERG: Thank you, Dr. Wilson, members of the committee. My name is Paul

Eisenberg. I'm responsible for Amgen's global regulatory affairs and safety organization.

It's a pleasure this morning to be here on behalf of Amgen to discuss our experience with the accelerated approval pathway that was utilized in approving panitumumab, or Vectibix, for patients with refractory metastatic colorectal cancer.

I'll be providing an overview of the regulatory history and the clinical studies that were performed for the accelerated approval pathway, as well as the confirmatory study that was recently submitted as part of an SBLA to FDA.

Following my presentation, I'm going to ask Dr. David Chang, an oncologist who leads the Amgen oncology therapeutic area, to join me here at the podium. Other members of the Amgen team involved in supporting the Vectibix studies are also available, as noted on this slide.

I think it's important and Amgen would like to highlight the critical unmet medical need that remains in colorectal cancer, which was the basis for use of the accelerated pathway. In 2010, it

was estimated that over 140,000 patients in the U.S. will be diagnosed with colorectal cancer. The important point is that approximately 50 percent of all patients develop metastatic disease, and five-year survival remains quite poor.

Despite the approval of chemotherapeutic agents that remain the backbone of treatment for colorectal cancer, as shown here, patients progress and there remains a critical unmet medical need that's still only partially satisfied by the recently approved biologic agents. Currently, Erbitux and Vectibix are the only approved treatments for chemo refractory metastatic colorectal cancer.

Briefly, Vectibix is a fully human IgG2 monoclonal antibody which is directed against the epidermal growth factor receptor. Accelerated approval for panitumumab was received in September of 2006 based on the pivotal registration trial, which I'll review in a moment.

Vectibix offers an important treatment option for patients with chemo refractory

metastatic colorectal cancer and is indicated, as shown here, in patients with disease progression on or following fluoropyrimidine, oxaliplatin, or irinotecan-containing chemotherapy regimens. This remains the only FDA-approved indication for Vectibix.

At the time of accelerated approval, there was an ongoing Phase 3 trial with panitumumab in patients being treated with FOLFIRI for metastatic colorectal cancer in the second-line setting, and it was agreed with FDA that this study could serve as the confirmatory trial for demonstrating clinical benefit. Overall survival was a co-primary endpoint in this study.

Following approval by FDA, Vectibix was approved in 37 countries globally. A significant difference in the indication -- I'll be discussing this in more detail and we've discussed it some this morning in relation to the Erbitux file -- is that outside the U.S., the indication is restricted to patients without activating mutations of Kirsten-RAS, which is usually referred to as wild

type KRAS.

Shown here is the timeline for meeting the commitment for the confirmatory study to support the accelerated approval for third-line metastatic colorectal cancer. The confirmatory study, which I'll refer to as the 181 study, was started in 2006, prior to approval of Vectibix. The study protocol was reviewed with FDA under a special protocol assessment process. As I noted, the study endpoints were progression-free survival and a co-primary endpoint of overall survival.

The study statistical analysis plan was amended in 2007 to address the emerging science around the negative predictive value of activating mutations of KRAS. I will discuss the KRAS data further in a few minutes, but it's important to note that the primary analysis was changed to specifically test PFS and overall survival in patients with tumors that were identified to have wild type KRAS.

The statistical analysis plan was submitted to FDA before the last patient was enrolled in

2008. The study was completed with due diligence and in a timeline that was consistent with that committed to with FDA. The final study report was submitted as part of a supplemental BLA in October of last year.

I'll now briefly review the pivotal study, that is, the 408 study, which was the basis for accelerated approval. This study enrolled patients with chemo refractory metastatic colorectal cancer and randomized them to either panitumumab with best supportive care or best supportive care alone.

The primary endpoint for this study was progression-free survival. If patients progressed, they could be treated with either panitumumab in a long-term extension study or, in some instances, patients were treated clinically with cetuximab outside of the study, as Erbitux had been approved.

A key feature of this in all trials of anti-EGFR antibodies is that the studies cannot be blinded because there's a characteristic skin rash that occurs with treatment. As a consequence, investigators are aware, as are probably patients,

when they progress, that they have not received active therapy. Of course, this also raises the need to ensure effective and unbiased ascertainment of progression, which is an important design consideration in this and other studies.

This study demonstrated, as shown on the slide, an improvement in progression-free survival as determined by central radiologic laboratory assessments. Overall survival, which was a secondary endpoint, was not statistically significant between the two groups.

The extent to which this may have been confounded by allowing treatment on disease progression with anti-EGFR agents is impossible to ascertain, although it is worth noting that the only trial that has demonstrated overall survival in the third-line setting was with cetuximab, the study described this morning, in which post-progression anti-EGFR therapy was very limited.

Now, the emergence of KRAS as a predictive biomarker, as discussed earlier, highlights one of the challenges in designing and completing

confirmatory trials when there is new emerging scientific information.

In the case of KRAS, preclinical data suggested that activating mutations of KRAS would abrogate the response to anti-EGFR agents in inhibiting tumor growth. In colorectal cancer, such mutations of KRAS are common. They occur in about 50 percent of patients. Retrospective analysis of Phase 2 studies were consistent with the preclinical data and suggested that KRAS mutations were a negative predictor of response.

Amgen was involved in defining the importance of KRAS mutations that mediate in the response to anti-EGFR antibodies, and, in fact, Amgen has had a longstanding interest in the importance of somatic mutations, in general, in determining response of tumors to targeted anti-neoplastic therapies.

As a consequence, Amgen prospectively instituted a program to collect tumor samples across all of our oncology clinical trials. There was a unique opportunity as it related to

panitumumab, since samples were available in over 90 percent of patients who had participated in the 408 trial.

In addition, this trial offered the unique opportunity to ascertain whether activating KRAS mutations were a negative predictive biomarker for response to panitumumab in a randomized, controlled trial. As subsequently published in JCO and discussed at ODAC two years ago, indeed, this was the case, and the lack of response of patients with tumors with mutant KRAS to panitumumab was remarkable.

Similar data were developed for cetuximab, the other approved anti-EGFR antibody, and this led to an FDA label change warning against poor response in such patients. These data changed the clinical treatment guidelines for the use of anti-EGFR antibodies in patients with chemo refractory metastatic colorectal cancer.

Shown here is the design of the study that was proposed as the confirmatory trial, that is, the 181 study. This was a randomized, open label

study in second-line metastatic colorectal cancer, in which panitumumab was combined with FOLFIRI and compared to treatment with FOLFIRI alone. This was a global study performed at 190 sites in 25 countries and enrolled 1,187 patients. The stratification factors are shown on the slide. I've already commented, overall survival was the co-primary endpoint with progression-free survival.

As a consequence of the emerging information on the negative predictive value of KRAS, the statistical analysis plan was modified after the trial had been started, as I've described, to analyze based on KRAS status.

Now, what I've shown here is the summary of the results of the three randomized clinical trials performed by Amgen in patients with metastatic colorectal cancer across all lines of treatment in which the response to panitumumab was analyzed based on KRAS status. On this slide, the results are those in patient with wild type KRAS. In the briefing materials, we provided all of the data, including that in patients with activating

mutations, are provided.

With respect to progression-free survival, there is evidence of statistically significant improvements with panitumumab, as initially demonstrated, first, in the retrospective analysis of the third-line 408 study, shown in the first column, and more recently in the second-line 181 study, in the middle column.

In addition, Amgen reported, as a post-marketing commitment subsequent to approval to FDA, the results of a first-line study in which the response to panitumumab with or without FOLFOX WAS assessed. The results of this study were similar to those of the 181 study with respect to the hazard ratio for PFS. And there was a strong trend towards improvement in overall survival in patients that did not have activating mutations of KRAS.

However, this differed from the other studies in that as opposed to no response with panitumumab in patients with mutations of KRAS, there was an adverse effect in these patients when panitumumab was combined with FOLFOX. These data

are presented in greater detail in the briefing book.

Amgen believes the emerging science around somatic mutation of KRAS and, in fact, other signal transducers has changed the clinical approach to treatment of patients with colorectal cancer with anti-EGFR antibodies, and, in fact, is a paradigm of the potential to improve patient selection for targeted therapies. However, there are challenges in incorporating new information into the designs of clinical studies after initial pivotal studies are performed, and in the case of accelerated approval, this may impact the confirmatory studies.

Biomarkers also represent a regulatory challenge when there is not an FDA-approved diagnostic kit, as has been the case for detection of KRAS mutations. The committee discussed some of this earlier. This impacted the development program, since approval based on KRAS status, and that is an FDA-approved indication, requires a combination diagnostic and drug approval pathway.

Accordingly, Amgen has worked diligently

with the manufacturer of a suitable test kit for several years to support their FDA application for approval. We are pleased that this will be submitted to FDA shortly. In addition, all of the panitumumab studies in which KRAS assessment was done were tested with this specific kit.

Finally, a challenge particularly in the third-line setting is the ability to perform a confirmatory study with overall survival as the primary endpoint, when clinical practice has accepted the therapy of anti-EGFR antibodies as the standard of care in refractory patients. Since it's not possible to blind assignment with anti-EGFR therapy, patients who progress may be aware that they're being denied potentially beneficial treatment.

Although this can be overcome by performing trials in countries where anti-EGFR therapy is not the standard of care, this does raise potential concerns regarding the applicability of the results to patients in the U.S.

The consistency and reproducibility of the

response of patients with metastatic colorectal cancer to panitumumab in patients with tumors that have wild type KRAS is consistent with the clinical benefit; nonetheless, Amgen recognizes that additional studies are appropriate to confirm this benefit in terms of overall survival.

Accordingly, we've planned a trial in the third-line setting with overall survival as the primary endpoint in patients with wild type KRAS. This protocol has been reviewed with FDA and the trial is being initiated.

Amgen believes that the results of this trial will meet the requirements for confirming overall survival required for full FDA approval of Vectibix in the third-line setting. In addition, this trial will allow for testing of other potentially predictive biomarkers of response.

In addition, as a specific obligation for conditional approval in the EU, and you'll hear more of this again later, regarding the requirements, Amgen is conducting a third-line study comparing panitumumab to cetuximab in a non-

inferiority design in patients with wild type KRAS.

In summary, Vectibix was approved based on the accelerated approval pathway after demonstrating unequivocal improvements in progression-free survival in patients with metastatic colorectal cancer who had progressed after first and second-line chemotherapy. The third-like monotherapy indication is currently the only FDA-approved indication for Vectibix.

A confirmatory study in second-line treatment of metastatic colorectal cancer that was ongoing at the time of approval was completed in the timeframe that was committed to with FDA and has been submitted as part of an SBLA in October of last year.

While this study confirmed a benefit in progression-free survival in patients with wild type KRAS, the trend towards benefit in overall survival was not statistically significant. Therefore, Amgen is initiating a trial with overall survival as the endpoint in the third-line setting.

Amgen's clinical trials have added

substantial information to the appropriate use of anti-EGFR antibodies in patients with activating mutations of KRAS. This has had an impact on the clinical applications of these agents globally.

Amgen remains committed to confirming the improvement in overall survival prospectively in patients with refractory metastatic colorectal cancer not harboring activating KRAS mutations, as required by FDA to support the conversion of the accelerated approval to full approval. As discussed earlier, we would anticipate a full approval would be restricted to patients with wild type KRAS.

In addition, Amgen continues to explore the role of other somatic mutations in colorectal cancer in mediating the response to panitumumab. Amgen believes that the availability of Vectibix through the accelerated pathway has benefitted patients with chemo refractory metastatic colorectal cancer.

We thank you for your time and look forward to your questions.

Dr. Chang, perhaps you can join me.

Questions from Committee to Sponsor

DR. WILSON: Thank you. Maybe I'm just not following this, and I certainly think it's great you're doing this study. But given the results of the previous studies, you're hoping that this is going to show an overall survival advantage? I'm not sure why you would think that and whether or not that's going to be required to get full approval.

DR. EISENBERG: I'll answer the question, as I understand it, in two parts. Dr. Chang can help me with the clinical component, as an oncologist and well aware of our data.

So first, I'll take the last part of what I believe your question was; is this required for full approval? To date, our discussion with FDA is that, yes, a study demonstrating improvement in overall survival is required for full approval. So the Study 181 does not satisfy that criterion, and so we have discussed this as the appropriate study.

Dr. Chang perhaps can comment on the

clinical aspects.

DR. D. CHANG: With respect to the feasibility of demonstrating the overall survival in a study that compares the panitumumab against best supportive care in a refractory setting, there are two lines of evidence.

One, when we review the data, and I think the sponsors of cetuximab came to a very similar conclusion, the use of post-progression EGF receptor therapy impacts the ability to detect a survival signal, and that was inconsistent in our study, as well as in earlier lines of Study 181 and the 203 study that was just presented.

One study was carried out by cetuximab where post-progression EGF receptor usage was controlled by conducting studies at places where EGF receptor antibodies was not a routine clinical care at the time of the conduct of the study, and that study demonstrated a clear benefit in overall survival.

Given that the mechanism of action of panitumumab and cetuximab as an anti-EGF receptor monoclonal antibody are similar, we believe that

the study as we have proposed will demonstrate survival.

DR. WILSON: So I think you hit my point right on the head, and that is the ability to do these post-marketing trials as the standards of care switch. So it's my understanding that now that these anti-EGFR antibodies are out there, if you were to do this in the U.S., not only will most, if not all, the people coming on this trial have already seen them, but they might see them in the control arm, as well.

So your plan is to do this in countries where these drugs are not available; is that what I'm hearing? Because that seems like that that would be the only way you could actually show this.

DR. D. CHANG: I think you're exactly pointing out the challenges of conducting studies when the drug becomes available. And you're correct, we plan to do the studies where EGF receptor currently is not the standard of care.

DR. WILSON: Okay. Thank you. That's where my confusion lay.

Questions? Yes, Dr. Logan?

DR. LOGAN: I had a question on the 2005 0181 study. When you modified the analysis plan to look at the wild type group, was the study then adequately powered for overall survival in that subset?

DR. EISENBERG: Sure. It's a good question. I'll ask Steve Snapinn, the head of our biostatistics department, to respond.

DR. SNAPINN: So we did take a look at the power of the study. Of course, the study was nearly accrued at that time, and we didn't have the opportunity to change the sample size when we're looking at a subset. But we did take a look at the power, and we had adequate power to detect about a 28 percent reduction in risk for the overall survival endpoint.

I can make just a couple other quick comments about that. One is that, in theory, if the treatment effect -- if a study is powered in an overall population for a certain treatment effect and that effect is manifest only in one subset,

that analysis of just that subset actually has greater power than the analysis for the overall population.

DR. WILSON: Dr. Loehrer?

DR. LOEHRER: One of the, I guess, purposes of doing these trials in advanced disease is to look at this in earlier stage disease. It's unlikely that any of these trials are going to show more than a few months' improvement in survival, and for the average patient, this has very little impact.

The results in the adjuvant setting looking at EGFR antibodies have been disappointing, at best. Can you explain a little bit about what's going on in the adjuvant setting as opposed to the metastatic setting?

DR. EISENBERG: I think probably better for an oncologist to respond.

DR. S. CHANG: There have been adjuvant studies with a biologic adjuvant in the adjuvant setting in colorectal cancer, and, as many of you are aware, the results of those studies have been

somewhat disappointing.

I think one has to realize that with the improvement of the adjuvant treatment that is based on the chemotherapy, it is really hard to detect improvement when the benefit is really high to begin with. That can be one of the reasons, and other possibilities include selection of the patients, as well as the fact that the drugs may not be working that well in earlier stages.

DR. WILSON: So one of the issues that I think we all face is what is the definition of clinical benefit, and I think that it's been, I think, stated, and I think it's reasonable that if we see an advance in overall survival, that that is a clinical benefit.

Having said that, if that advance is one month and these curves don't have a tail on them, I think reasonable people could argue as to whether or not that was an advantage.

I'm just wondering, is the endpoint of this trial simply that we get a statistically positive hazard ratio for overall survival, and that alone

is all we need here?

DR. D. CHANG: The statistical design is based on the hazard ratio, and depending on the shape of the Kaplan-Meier curve, the median numbers can vary. But based on the statistical assumptions that is pivoted against the available data on cetuximab, the study, as currently powered, will demonstrate a median of a more than two month improvement in overall survival.

DR. EISENBERG: But I think the other question is are there other elements. So, certainly, it's our view, as we commented, to look -- in addition to other predictive biomarkers, maybe we can identify patients who would respond to an even greater extent. And we have looked consistently at quality of life, other measures, to see, since these are toxic therapies, are there detriments to patients or are these tolerated.

So, clearly, all of those are factors to try and show. We're not simply going to try to demonstrate we can add one month in overall survival to satisfy the requirement.

DR. WILSON: I think it's very good, and, certainly, Amgen has had a history, as you point out, of looking at biomarkers.

Dr. Sekeres?

DR. SEKERES: I have a question for the FDA. So one of the things we're asked to consider this afternoon is the number of confirmatory trials.

There are two studies here that you could potentially consider confirmatory, one in the second-line setting and one in the first-line, neither of which shows a statistically significant overall survival advantage. And, certainly, the median overall survival advantage is two months in the second-line setting, four months in the first-line setting.

So what was the FDA's thought in talking to the company about saying, gee, go ahead with one more study to see if you can find a difference? And is it that you felt that it was underpowered, the two studies, because of the KRAS story?

DR. PAZDUR: Here, again, this application is under review, so I think that we have not

reached a conclusion and final discussion on this application.

I think you bring up a very cogent point that needs discussion as to how many bites of the apple do you get to take after you fail your studies, and that's the real issue that needs to be addressed here.

DR. WILSON: Dr. Freedman?

DR. FREEDMAN: I think everyone is interested in having a biomarker that one can identify in a very positive mode and it doesn't -- and that the behavior of the tumor doesn't change over time with the same marker. And, certainly, I think the sponsor should be commended on doing the KRAS assessment in such a large proportion of patients.

I was just wondering, looking at the response rates here in the chemo refractory group, the second line FOLFIRI group and the first-line group, especially in the first-line group, did you see any difference in the response rates in the mutation versus the non-mutation?

DR. EISENBERG: I'm not sure I understood the question completely. Yes, we did see -- with FOLFOX and oxaliplatin-containing regimens, there does seem to be a signal, whether it's restricted to the mutant or because you see greater benefit in wild type; it's not as apparent in the wild type. We do see a negative interaction, and we've focused a fair amount of basic research, as have other groups, to try to understand mechanisms for that interaction. There are some thoughts in that regard. We've included a little in the briefing material. But there is clearly a negative interaction.

DR. FREEDMAN: So if you look at the three studies --

DR. EISENBERG: Yes.

DR. FREEDMAN: -- what were the proportions of mutation in those three studies?

DR. EISENBERG: It's pretty much as I highlight in my presentation. It's about half in each study. So about half the patients have the mutation and half are wild type.

DR. FREEDMAN: And did you see a lower response rate in each?

DR. EISENBERG: We see no difference at all with irinotecan-containing regimens, essentially no response from the mutant patients in our 181 study, and, in our 408 study, as published, we saw no response.

The difference is in that first-line study with the oxaliplatin-containing regimen, the FOLFOX, in that one, the mutants actually have a worse outcome. And so we've paid a lot of attention to try and understand the mechanism. And the wild types and particularly some groups of the wild type actually appear to have quite a robust outcome, including improvements in survival.

So it's an interesting question with oxaliplatin-containing regimens and anti-EGFRs. There are some mechanisms potentially that might account for that, but it's a little different in that population.

DR. WILSON: Yes, Ms. Mayer?

MS. MAYER: I'm just trying to get a handle

on -- I'm looking at this chart and it looks to me -- and the heading on the chart says that it demonstrates consistent progression-free survival benefit in these wild type KRAS patients.

Is it your contention that this benefit is clinically meaningful --

DR. EISENBERG: We believe it is, yes.

MS. MAYER: -- 1.1 months to two months?

DR. EISENBERG: Again, it's within each line of treatment that one has to look at the context for that, and we believe, relative to other effective therapies, if you were to compare this, and we provided some comparisons, to the other treatments, some of which are approved in those lines of therapies, that those are consistent with what has been observed in clinical trials. So, yes, we do believe it's meaningful.

MS. MAYER: And is there quality of life data available?

DR. EISENBERG: Yes, there is. We could review that. I think you may what to comment briefly.

DR. SNAPINN: Maybe I can just comment on that briefly. The quality of life measures have been measured in all three studies, and in the refractory setting, both in terms of statistical significance as well as meaningful clinical difference, there was an improvement in quality of life in patients who received panitumumab versus patients who were randomized to best supportive care.

In the second and front-line settings, the baseline quality of life of these patient populations are much higher, as expected. And when we did a similar analysis, what we saw was that there was no worsening of the quality of life. There was no statistical significance, either positive or negative, and, certainly, there wasn't any meaningful clinical difference in that context.

DR. WILSON: Okay. With that, we've had a very long morning. We've got one more, so let's take three minutes to shift, and then we'll have the last sponsor. Thank you.

[Pause.]

DR. WILSON: Why don't we go ahead and get started, if we could? So the final sponsor will be Novartis, and we'll be hearing about Gleevec. And I'd like to invite Dr. Letvak to give the presentation.

DR. LETVAK: I guess we're waiting for the slides.

DR. WILSON: Okay.

Novartis Pharmaceuticals (Gleevec) - Laurie Letvak

DR. LETVAK: My name is Laurie Letvak, and I'm the global program head for Gleevec and Tasigna at Novartis Oncology, and it's my pleasure to be here today to update you on the status of the post-marketing commitments for the indication of Gleevec in adjuvant GIST.

I will just wait to see if we can get the slides up.

[Pause.]

DR. LETVAK: In my presentation this morning, I'd like to review the history of the Gleevec approvals and commitments, as well as the approval history of Gleevec in adjuvant GIST. I'll

briefly review the results from the ACOSOG Z9001 pivotal study. Then I will review the Gleevec adjuvant GIST subpart H commitments. These consist of additional follow-up from the pivotal study, as well as results from the second cooperative group trial, the Scandinavian sarcoma group-German working group study. I will also briefly review some of the challenges we faced in delivering commitments.

Gleevec is approved for 10 indications. The five indications that are noted in bold have been approved under subpart H. The other indications that were approved in 2006 are five rare diseases for the treatment of adult patients.

For these 10 indications, we have a total of 33 commitments. For the regular approval of five indications, we have six post-marketing commitments. Three have been released and three are remaining, and these three deal with the requirement for diagnostic test kits in three of the rare indications.

For the five indications under subpart H, we

have 14 accelerated approval commitments, as well as 13 post-marketing commitments. These are shown in more detail in this slide. For each of these indications, we see the date of the subpart H approval, the date of the full approval, and the status of the post-marketing commitments.

For the original CML indication approved in 2001, full approval was granted in December of 2003. For the newly diagnosed CML indication, which was based on the randomized study of Gleevec versus interferon Ara-C, the so-called IRIS trial, we were asked by FDA to provide six yearly updates following the initial results. So only after we had provided the data on seven years' total follow-up were we granted the full approval in May 2009.

In pediatric CML, the original approval was granted in May of 2003 and full approval occurred in June of 2006. For the newly diagnosed pediatric patients, approval was in 2006. Data is currently under review at the FDA and we have been informed of an April 2nd action date.

For metastatic GIST, the initial approval

was in 2002 and full approval was granted in 2008, after we provided data on the original Novartis trial, as well as on data from several additional trials, including two cooperative group trials. The adjuvant GIST indication, with its four accelerated approval commitments, is the subject of the discussion today.

I would like to provide just a very brief background on gastrointestinal stromal tumors. They are mesenchymal neoplasms of the GI tract, and about 10 to 20 cases per million population are diagnosed annually in the U.S. Surgery is the standard treatment for local disease, but recurrence following surgery is very common, with a median time to recurrence of about two years.

Overall survival in patients with advanced metastatic GIST has been relatively poor historically, with a median of about 10 months prior to Gleevec availability. Evolving data from a number of different trials currently estimates the overall survival to be about five years with Gleevec therapy.

The Study ACOSOG Z9001 is a study that was conducted by ACOSOG under a cooperative research and development agreement signed between the NCI and Novartis. Part of the objective of the CRADA is to facilitate extension of labeling for a drug. The study was done by ACOSOG in collaboration with NCI of Canada, CALGB, and SWOG.

Patients could enter the trial if they had GIST tumors expressed in kit, if the tumors were greater than or equal to three centimeters, and they could have had no postoperative chemotherapy or radiation therapy.

The primary endpoint of the trial was recurrence-free survival and the secondary endpoint was overall survival. The first patient was entered into the trial in July of 2002, and 713 patients were entered when the last patient entered in April 2007. Eligible patients were randomized 1 to 1 to receive either Gleevec 400 milligrams daily or a matching placebo, and patients were to be followed for up to 10 years.

This slide shows the results of the key

analyses resulting in approval. The primary endpoint, as I mentioned, was recurrence-free survival, and Gleevec prolonged recurrence-free survival compared to placebo, with a hazard ratio of 0.398 and the p-value was highly significant at 0.0001.

With 14 months of median follow-up, 30 events had recurred on the Gleevec-treated patients, while 70 had occurred on the placebo arm. Thirteen deaths had occurred at the time of that analysis and there was no statistically significant difference between the arms. In terms of safety, the drug was well tolerated, and there were no unexpected or new adverse events reported.

This slide illustrates the Kaplan-Meier estimate of recurrence-free survival. And it's interesting to note the powerful effect of treatment occurring during the first one year, where there were only three events on the Gleevec arm and 50 events on the placebo arm.

In discussion with the FDA prior to approval, the FDA requested that Novartis provide

follow-up data on ACOSOG Z9001 in terms of recurrence-free survival and survival, and we agreed to provide that data, as requested.

The FDA also requested that we initiate a new study to assess the optimal length of adjuvant Gleevec treatment; for example, one year versus two years. At that time, we proposed that we be allowed to use an ongoing Scandinavian sarcoma group trial comparing 12 versus 36 months of adjuvant Gleevec treatment in a randomized, prospective study, which was done in patients at high risk. At the time of the discussions, the trial had completed its full enrollment. Agreement was reached with the FDA that this could serve to satisfy the requirement.

Before going into the post-marketing commitment for ACOSOG, it's probably useful to review some of the activities surrounding the original submission. Novartis provided ongoing support and collaboration from the time of study inception.

In anticipation of potentially using this

trial for registration, we had an end of Phase 2 meeting with the FDA in April 2003. At that time, agreement was reached that recurrence-free survival was an acceptable registration endpoint.

Significant treatment effect was seen at one of the early planned interim analyses, and as per the recommendation of the data monitoring committee, the trial results were announced via an NCI alert in April of 2007. At that time, further approval to the trial was stopped, and patients who were already continuing on placebo were offered the chance to switch to Gleevec.

Novartis immediately began to prepare for the health authority submission, in collaboration with ACOSOG; also, with the Mayo Clinic, which is the official statistical unit of ACOSOG and gave input to the analysis plan. The Duke Clinical Research Institute, or DCRI, served as a CRO and provided project coordination, in-house monitoring, and statistics and data management.

A number of key activities were undertaken, and that included collection of outstanding data,

implementation of an independent blinded review of scan reports; and, here, the reports were documenting that patients who previously had no evidence of disease following surgery now seemed to have documentation of a recurrence. There needed to be extensive cleaning of the database, recoding of adverse events, and finalization of a registration statistical analysis plan. Novartis ensured the data quality requirements were met.

The FDA submission occurred in June 2008, a full 14 months after announcement of the initial trial results. This really speaks to the extensive amount of work and collaboration that needed to be done before the submission could happen. FDA approval occurred in December of 2008.

Immediately following that approval, Novartis began working with ACOSOG to fulfill the post-marketing commitments. ACOSOG, at that time, directed Novartis to work only with Mayo. DCRI was no longer involved. A scope of work to meet the commitments was fully defined and agreed upon in April 2009, including newly defined roles and

responsibilities, accounting for the fact that DCRI was no longer involved in the work.

A total of three contract amendments were required and were executed between ACOSOG and Novartis during 2001, and a contract between ACOSAG and Mayo was executed in late 2010.

Mayo is currently actively working to clean and complete the database in preparation for statistical outputs, and we're in regular contact with them, and we anticipate receiving the initial draft data outputs in the coming weeks.

When we think back about some of the challenges we've had in working this through, one thing that we hadn't really anticipated was the need for the multiple contracts and amendments with several legal entities on how long this would take.

Also, execution of the terms of the complex contracts can be quite challenging. For example, timely transfer of funds between the third parties could be rate limiting. And then, again, we are also dealing with third parties who have a lot of other studies and other obligations. So sometimes

it's challenging to keep our commitment at the top of the list.

The SSG study started when a number of investigators were talking about what to do with high risk patients with adjuvant GIST. They did not feel it was appropriate to put these patients on a no treatment control. So, for them, the idea of a duration trial was the perfect trial for this population.

This schemata shows the trial design where patients were defined as having high risk of recurrence by the criteria listed on the top of the slide. The patients were randomized 1 to 1 between either 12 months or 36 months of Gleevec therapy. Four hundred patients were randomized between February 2004 and September of 2008. The primary endpoint of the trial was recurrence-free survival; and, the secondary endpoint, overall survival.

The final analysis was to be completed when all randomized patients had completed their first visit following the one-year treatment. In other

words, all patients on the 12-month treatment arm would have completed their therapy, while patients were still ongoing on the 36-month arm. Also, in order to do the final analysis, 110 events would need to have occurred. Follow-up overall survival analysis is planned for five years after the final analysis.

Novartis has been working collaboratively with the SSG for quite some time, and a statistical analysis plan has been finalized. Data collection and monitoring is being prospectively supported, and Novartis will ensure that all data quality requirements will be met. We have been informed by the SSG that the data cutoff for the final analysis has occurred on December 31st, 2010. The database is being prepared by the SSG, and the data collection is being completed, and the data cleaning is ongoing.

This slide summarizes the status of the four post-approval commitments for adjuvant GIST. The first commitment is the four-year follow-up, which is currently being worked on. Novartis commits to

provide the FDA the clinical study report within 10 weeks of final data receipt from ACOSOG. We then have a further commitment for a five-year follow-up on overall survival and recurrence-free survival.

The SSG data, final study report, and datasets will be submitted, we anticipate, on time by November 30th of this year.

In summary, Novartis has already fulfilled 25 post-marketing and subpart H commitments for Gleevec. We are working with due diligence to deliver on all remaining commitments, and we continue to work diligently to influence and address the complexities encountered in working with cooperative groups for regulatory filings.

Thank you, and I'd be happy to address your questions.

Questions from Committee to Sponsor

DR. WILSON: Thank you.

Dr. Martino?

DR. MARTINO: Just a question to the FDA. It's not clear to me why the European trial was part of a commitment where they're comparing 12

months versus 36. That strikes me as really a secondary, tertiary kind of question. So help me to understand; was that, in fact, part of a requirement to them and why?

DR. COHEN: Well, if you look at the relapse-free survival curve that was shown for 12 months of Gleevec, it appeared that relapses were occurring relatively soon after Gleevec was stopped. So the question was whether, if you gave Gleevec for a longer period of time, there would be fewer recurrences.

DR. MARTINO: I understand the general question, and I actually like the general question. It's one we ask with other things, for Herceptin in breast cancer, for example. It's not clear to me why it would be part of this fulfillment. It's a different question all together, to me.

DR. PAZDUR: Perhaps the issue here is what is the -- it's a dose and duration question, and that's what we were after, how to optimally use this. And here, again, it's not like we're going to multiple applications for this indication. So

it was thought to be logical to ask them to answer that question, since this trial was also ongoing, and I think we knew of it, to get the data into the label.

DR. WILSON: Let me follow-up on that. To what extent did that play a role in looking at this trial for accelerated versus full approval?

This recurrence rate is hugely different. Of course, one could argue that you're simply delaying recurrence, that you add this drug at the time of recurrence and people may do just as well. However, it does seem as though you were impressed with this.

So I'm just trying to get an understanding. How did the thought go? Why was this given accelerated versus full approval?

DR. COHEN: You have to realize that the median follow-up of this study was only 14 months, and we considered that too soon to make a final judgment of the worth of the therapy.

DR. WILSON: So help me, from a regulatory point of view. If that's true and you wanted to

get the drug approved sooner, why couldn't you wait longer for follow-up on the study, and if it still looked really good, then give it final approval based on that?

I'm trying to integrate what the thoughts were here. I think the question about whether or not 12 months is adequate is a very good one, because it does look at though everything was fine and then suddenly it just kind of dropped off a cliff. So it was because it was a very short-follow-up?

DR. COHEN: Yes.

DR. WILSON: Dr. Freedman, you had a question?

DR. FREEDMAN: In this situation, the sponsor is actually dealing with different groups, pediatric groups and adult groups, and there seems to have been an issue with the previous presentations. We noticed that, in some cases, there was not the same cohesion as you got with others.

So I was wondering, since Novartis has had

the experience of dealing with a number of different groups, can they separate the different issues that they have identified between those groups that could have affected the conduct of the trial and the speed in which the trials have been completed?

DR. LETVAK: Could I ask you to repeat the last part of your question? I understand you mentioned we work with a number of different groups, but what was the exact question?

DR. FREEDMAN: I think it's perhaps building up to a discussion later today, where we're going to be looking at the contribution of groups to the post-marketing studies.

You have had the opportunity to work with different groups, including pediatric and non-pediatric. It seems that there could be differences, that different issues, different problems perhaps have arisen. And perhaps these problems are addressable, but we need to know what they are.

DR. LETVAK: There are a number of different

issues. One category of issue relates to the administrative issues and contracts and things like that, which can be a bit frustrating, and sometimes I'm not sure what the answer is in order to facilitate.

Some of the other drug development related questions I think could be helped if you work very early on in collaboration and make very clear what will be expected in case the data will be used for registration. And the sooner that you can be sure to align the expectations and get some resources in place, I think the better off we would be in terms of speedy fulfillment of the commitments.

I think some of the challenges that other sponsors have faced really are around the accrual issues, and we didn't really face that in these trials. But, again, that's an issue that needs to be taken into account.

DR. WILSON: Thank you.

Dr. Loehrer?

DR. LOEHRER: A couple thoughts come to mind, but one in the ACOSOG trial, and I think this

was alluded to earlier, whether or not Gleevec is a cidal drug or a static drug. And if it is static, then one would expect, whether you give it to them now or give it to them later, then it really is not going to make a difference in the life expectancy of the patient. And you see the progression-free survival curves flatten out at about 70 percent for those groups.

The logical question then is do you treat 10 patients to help three, and what studies should be done to help identify those seven patients who don't need treatment. I say that as a purview of following-up on Dr. Martino's question in terms of follow-up studies by the FDA. I guess this goes to Dr. Pazdur and everybody else over there.

There is an opportunity and responsibility, I guess, that comes up with follow-up studies. And I actually love the study of one versus three years, although it hits Dr. Martino's point. It's not really pertinent to whether or not this drug is useful. But I think many times we have these lost opportunities with new drugs that we don't know how

long they should be given or at what dosage. Capecitabine comes to mind as one situation.

So I guess along with it, I guess most of this is a comment, but also a question, is what does Novartis have planned for deciding -- and I know this is laughable, I'm sorry -- but what does Novartis have planned for those who you decide who shouldn't be getting treatment; what opportunities?

We heard a previous -- we had the KRAS mutants that show that you shouldn't be treating those with cetuximab and panitumumab. But what opportunities are available right now for looking at who should not be receiving Gleevec, particularly in a drug that's static and it may be treating for years with this agent?

DR. LETVAK: Well, a number of people would say that the patients who have an extremely low risk of recurrence should not be treated; now, people define that in different ways.

For some of the other questions you asked, I think, on one hand, the delay of recurrence for patients actually is very important, because the

life of a patient on adjuvant therapy or not on any therapy at all is much different than the life of a patient who has had a recurrence and then needs to be treated and followed very regularly for metastatic disease.

When the disease recurs, it often occurs as a bulky symptomatic tumor, and there can be a lot of morbidity. So, actually, delay in recurrence, we believe, and investigators believe, and patients believe, is very significant.

In terms of one of the questions you asked at the beginning, whether we're just delaying the need for treatment and whether it's better to treat later or not, there are additional analyses ongoing from this trial, the ACOSOG trial, as well as from the EROTC trial, to look at whether adjuvant therapy with Gleevec has any impact on the response of treatment to Gleevec later on.

So some of these questions will be answered with additional follow-up. But we believe that the strong treatment effect and the high risk of recurrence in patients with GIST, which, in fact,

is much higher than the recurrence in breast cancer -- and we readily treat patients with adjuvant therapy for breast cancer, with a much lower risk of relapse. So I think when you look at it in that context, it's an extremely effective and useful therapy.

DR. WILSON: Dr. Kelly?

DR. KELLY: You sort of hit on the question. In the ACOSOG trial, those patients who actually relapsed and you actually retreat them, what was the proportion of patients that actually showed a response in each of the arms? Do you have that data?

DR. LETVAK: We are trying to collect the data. We have some preliminary data actually coming from some of the European trials and also the anecdotal data given to us by multiple investigators, which clearly says that most patients who relapse after the completion of their adjuvant Gleevec will respond to Gleevec; and, qualitatively, the investigators report that the response is the same as they would expect to see in

a patient who had not received adjuvant therapy. The data is being formally collected and we hope will be published.

DR. WILSON: Dr. Richardson?

DR. RICHARDSON: I was just curious about some of the mechanics of the old ACOSOG study. Was there central radiology review in that?

DR. LETVAK: There was not central radiology review. And we attempted, as I mentioned, to do some kind of surrogate for that by at least having a central independent radiologist review the reports so that they could clearly see that a patient had been documented to be clear of disease following surgery and that there was a recurrence afterward.

DR. RICHARDSON: Having seen CT scans on this type of patient, these are very difficult to interpret. And I think it probably accounts for the fact that some of these folks, when they do relapse, they relapse with bulky disease that was probably missed earlier on by somebody who might not have had the same experience as somebody that

might have been a little more suspicious.

DR. LETVAK: Generally, I think the reading of the scans in patients with advanced disease is extremely complex, and although you still have to deal with the fact that these are patients who have had surgery, I think it's a little more straightforward to look for a new lesion in patients who have no disease following surgery.

DR. WILSON: Thank you.

Dr. Curt?

DR. CURT: From your presentation, it sounded as though you resourced your interaction with the cooperative group, which is maybe not the way most sponsors work with NCI cooperative groups. At one point, you said that the academic institution acted as a CRO, and you did this in anticipation of a regulatory filing.

I'm wondering, what kind of resourcing, what kind of information did you gather in this process that might not have been gathered with a drug-only interaction with a cooperative group, where a sponsor would only supply drug?

DR. LETVAK: In fact, for the ACOSOG trial, we really didn't get a DCRI involved until after the interim analysis results. And here, we had thought about and started to have discussions with ACOSOG about trying to get some things going in order to prepare for the eventuality of a submission. But because the positive results came at an unanticipated very early interim analysis, we were caught a little bit unawares, and then had to really rush very quickly to put everything into action. But, clearly, that's something that would have helped, and I think the fact that we're doing a lot of this work already with the SSG is going to make things a lot easier when the data becomes available shortly.

DR. WILSON: Thank you.

Dr. D'Agostino?

DR. D'AGOSTINO: I'm curious, with the 12 months versus 36 months, the SSG, what you're going to be able to say about overall survival. The idea here is that the survival rate is pretty good. So the RFS somehow or other becomes the

primary outcome. And then what will happen when they do have a recurrence? Will they go back on the treatment or are they just going to be off; it's going to be 12 months versus 36 months? Giving the discussion about maybe the length of treatment is useful?

DR. LETVAK: I'm sorry. I'm having trouble hearing the end of your question.

DR. D'AGOSTINO: I'm sorry. I'm not concerned. I'm interested in knowing what you're saying about overall survival. It sounds like the way we're talking about is the RFS, the recurrence-free survival, is the primary outcome.

DR. LETVAK: Yes.

DR. D'AGOSTINO: And there's a low rate of mortality here in comparison to other things we might look at, and I'm wondering, how is that overall survival? Are we going to get meaningful data on the overall survival? Is something going to happen when there's a recurrence that will follow up our ability to make statements about the overall survival, putting them on other treatments

or putting them back on this treatment?

DR. LETVAK: Well, as you've mentioned, the recurrence-free survival is the primary endpoint, and the overall survival will be driven by the available therapies at the time of the patients' recurrences.

We know already that patients who recur -- or at least we have the anecdotal evidence that patients who recur off Gleevec adjuvant therapy do at least initially have responses. But, again, they will recur. It's not a disease like CML, which can be kept under control for many, many years. The median progression-free survival on Gleevec is in the range of two years. And these patients are high risk patients, so they may recur even earlier.

So we're going to have to wait. And I think knowing that there were treatments available for recurrence was probably the driving motivation at least for the survival analysis to be not until five years after the recurrence-free survival analysis.

DR. D'AGOSTINO: But you wouldn't necessarily be surprised if the survival doesn't look different because of, as you say, the therapies that they'll get once they have a recurrence.

DR. LETVAK: That's possible, yes. It's possible they will not be significantly different, at least not at the five-year point.

DR. D'AGOSTINO: And that's all right for the FDA to -- because we keep talking about how important overall survival is.

DR. PAZDUR: We kind of take a look at this as an adjuvant study, in a sense. So we have taken disease-free survival in adjuvant settings as a primary endpoint for approval.

DR. WILSON: So this is a very -- at least for me, in preparation for thinking about some of the questions this afternoon and the nature of these post-marketing studies, this is a very different setting, because this can be a negative study, and yet your primary study was very positive. And just because three years isn't

better than one year doesn't obviate the fact that one year is better than no year.

So it's just a very interesting post-marketing study. I think it's very nice, but it gets back to my original question of this study doesn't -- this study, if it's positive or negative -- I think it's going to be positive, but even if it was negative, it doesn't obviate the first one. And, therefore, would you go on and give full approval based on this study, whether it's positive or negative? And, if so, I still don't understand why the 14 months was a problem when the relapse-free was huge.

DR. PAZDUR: I think we were looking for more data on this, obviously, and further follow-up of the first study. Here, again, we were looking for this to be additional data on labeling. It's not that if the second study regarding the duration doesn't answer that longer duration is better than shorter duration, that we would take the approval away; it's just to give us further information.

But there are two issues here, one of

further follow-up of patients -- remember, even on the Gleevec studies for CML, we generally give an accelerated approval on the basis of an endpoint with a need for further follow-up, and that further follow-up is what converts the indication to full approval.

So there are two issues here, one being wanting further follow-up of the existing study, and then additional -- well, you have this other trial going on; let's get this information into the labeling.

DR. WILSON: So, actually, that's a very good point, and I have to say it's one that I did not realize that it may not be that you need a confirmatory trial; it may get accelerated approval because you need further follow-up. And then the trials may be confirmatory or they may be additional data. So it's a little broader than I had thought. So that was very helpful.

Any other questions?

Yes, Dr. Kelly?

DR. KELLY: Just one question to the agency.

When you have post-marketing commitments, do all those commitments have to be done before you get approval? For example, here, they still have the diagnostic test kits. Would that have to be fleshed out, or just a good plan in place?

DR. PAZDUR: Well, it depends, in the approval letter, which ones are stipulated as, for example, post-market requirements versus post-market commitments. And there are many things that we may list as commitments that we're interested in seeing, that it would be, for lack of a better word, nice to know versus those that are required.

DR. MURGO: Just to add to that, is that some are required to meet subpart H commitments or subpart E commitments, and some are post-marketing requirements that are outside of that context. So the full approval can be given when the company has met all of their subpart H or subpart E commitments. The others are still required.

DR. PAZDUR: So they're specifically indicated as this is an indication for subpart E.

DR. WILSON: Well, it's 12:30. It's been a

very long but productive morning, and we will adjourn until 1:30.

May I remind the members, please do not discuss this ODAC outside of the regular meeting. Thank you.

(Whereupon, at 12:33 p.m., a lunch recess was taken.)

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

(1:28 p.m.)

DR. WILSON: We're going to go ahead and get started. So this afternoon we will be, first, hearing from Ms. Hilde Boone from the EMA, who will be going over how EMA deals with conditional approvals. We will not be having a open public hearing, and then we will go directly to questions to ODAC and discussion.

So may I ask Ms. Boone to please come up and start?

Speaker Presentation - Hilde Boone

MS. BOONE: Good afternoon, Chairman, distinguished committee members, colleagues, ladies and gentlemen. My name is Hilde Boone. I am the European Medicines Agency liaison, based here in White Oak with FDA. And as you may know, FDA and EMA have been collaborating for many years under our confidentiality arrangements, and the dialogue between both agencies has been particularly active and efficient in the oncology area. So I'm, therefore, delighted and honored to be here with

you today to briefly talk to you about the conditional marketing authorization framework in Europe, which is similar to FDA's accelerated approval.

So, in my presentation, I will give you, first, an overview of the regulatory background and the key features of the conditional approval process, followed by some general feedback on EMA's first experiences with this early access tool in the oncology area.

So following a major review of the pharmaceutical legislation in Europe in March 2004, a new provision was introduced in one of our key regulations, which sets out the principle of a conditional marketing authorization. It says that following consultation with the applicant, an authorization may be granted, subject to certain specific obligations, to be reviewed annually by the agency; and, such authorization shall be valid for one year, instead of the normal five, on a renewable basis.

One of the preambles of the regulation

explains the motivation behind this new provision; namely, in order to meet, in particular, the legitimate expectations of patients and to take account of the increasingly rapid progression of science and therapies. This new provision could only be implemented after the adoption of a further implementing regulation on conditional market authorization, and this was finalized and published in March 2006.

This implementing regulation and further guidance from our Committee for Human Medicinal Products, the CHMP, further defines the scope and the requirements that must be met for the granting of a conditional marketing authorization. So it applies to medicinal products that are submitted and reviewed by EMA and which aim at treating or preventing seriously debilitating or life-threatening diseases, or which are to be used in emergency situations in response to certain public health threats, as recognized by the European Commission, or which are orphan medicinal products. It further specifies that a conditional marketing

authorization may be granted when, although comprehensive clinical data have not yet been provided, all of the following requirements are met.

So, first, the available data must show that benefit-risk is positive. And because approval will be based on less comprehensive evidence than is normally expected for a normal full approval, the applicant is then expected to be able to provide additional clinical data to confirm the benefit-risk, the so-called specific obligations. And a conditional marketing authorization will only be given to products which will fulfill a high unmet medical need. And this is either because there is no satisfactory treatment available in Europe, or when there is, the new product is expected to provide a major therapeutic advantage. So that, finally, the benefit to public health of the immediate availability of the new medicine will outweigh the risk inherent to the fact that certain data are still awaited.

So in order to obtain these additional data,

a conditional marketing authorization will be subject to specific obligations, which require the company to either complete ongoing studies or to conduct new studies, with a view to confirming the positive benefit-risk balance. And it will be up to the applicant to explain and provide reassurance on the feasibility, the timelines, and the quality of these additional studies that need to be performed.

The guidance also specifies that if CHMP is of the opinion that timely completion of those additional studies required for the confirmation of the benefit-risk cannot be expected, then this may lead to a negative opinion on the granting of a conditional marketing authorization.

In addition, in case of noncompliance with the specific obligations, financial penalties may be imposed on the company by the European Commission at the request of the EMA. And the regulation also emphasizes the need for transparency and for clear information to be given to patients and health care professionals about the

conditional nature of the approval. And, also, the list of what data we still expect and in which timeframes is publicly available on EMA's website.

Finally, the guideline also clarifies that the conditional marketing authorization can only be granted in the context of an initial marketing authorization application, since the current legal framework for conditional approval does not apply to new indications that are applied for as a variation; so what is called a supplement here. But an important feature of our conditional marketing authorization is, indeed, that it's only valid for one year. But it can be renewed on a yearly basis upon application by the company.

The aim of the renewal is really to allow CHMP, our committee, to review and confirm the benefit-risk of the product on the basis of all available data and to provide for an annual review of the status of the specific obligations.

So six months before expiry of the marketing authorization, the company should submit the following application as part of their renewal

application; so, first, a chronological listing of all the data submitted since the granting of the initial conditional marketing authorization and the status or the outcome of the assessment, together with any study data or latest safety information data, when these were due to be provided at renewal.

In addition, companies have to give an interim report on the status of all specific obligations. Now, the structure and the content of that report will vary, depending on the type of study and its status, but, in general, we expect the applicant to provide a short synopsis and a description of the study, to give us an update on accrual and baseline characteristics by treatment group, describe any important adverse events that occurred, describe expected timing of primary endpoint analyses, and the outcome of possibly planned interim analyses; also, give us an update on treatment compliance, any important protocol amendments, or any other issues that may impact on the feasibility or the timing of the study.

Our committee then will have 90 days to assess this renewal application in order to confirm the benefit-risk balance or to recommend an appropriate regulatory action. At that stage, CHMP may also modify the prescribing information, the label, as well as the specific obligations and their timeframes in view of the information that they received at renewal. But upon fulfillment eventually of all specific obligations, this conditional marketing authorization will convert to a normal full marketing authorization.

So these were the key features, the key elements of a conditional marketing authorization. And in this slide, I just wanted to present to you also another approval early access tool that we have available in Europe, since, in fact, the beginning from EMA's review procedures in '95. And this provides for the granting of a marketing authorization under exceptional circumstances.

This has now been partially overtaken and replaced by conditional marketing authorization. But it applies specifically to products for which

it is not expected that we will ever get to the full comprehensive clinical data package since the studies cannot be performed, either because of the rarity of the disease, or the present state of scientific knowledge, or because of ethical constraints.

Such a marketing authorization will be, again, subject to specific obligations, specific procedures. But with the introduction of the conditional marketing authorization tool in the legislation, the focus of these will now be more on safety and risk management rather than on efficacy, and it is also morally not expected that such a marketing authorization will eventually convert to a normal marketing authorization. This type of marketing authorization will, again, be valid for the normal five years, but there will be an annual monitoring and reassessment of benefit-risk by the CHMP.

Looking then at EMA's experience with the use of these early access tools, since the conditional marketing authorization is really still

a very recent new legal provision, I thought it could be interesting to first show you how exceptional circumstances was used in the period before 2006, so when conditional approval became possible, because this was, at the time, the only tool that we had available to allow safe and effective medicines on the market for which certain clinical data were not yet available, but for which there was a high public health interest.

So in the 10-year period before 2006, approximately 18 percent of all products approved by EMA obtained the marketing authorization under exceptional circumstances. And, in particular, indeed, the first HIV products were granted using this provision on the basis of surrogate endpoints, as we also heard this morning from the FDA speaker. But then looking specifically at oncology products, this even accounted for 27 percent of all the oncology products that were authorized in that period. And the eight products concerned are listed in the slide. And with the current distinction that we have between exceptional and

conditional marketing authorizations, several of these would probably now meet the criteria for the conditional rather than an exceptional approval.

So, therefore, it could be interesting perhaps to look at the time that was needed to provide the additional clinical data that were requested at the time of those initial exceptional circumstances approvals before they converted to normal MA, which is, again, more associated with the conditional approval.

Of the eight oncology products concerned, two so far have not yet converted to normal MA, but for the other six products, the time needed to provide additional data and to convert to a normal MA ranged from just over two years to eight-and-a-half years.

So looking then at the period between 2006 and 2010, this slide presents the ratio of normal full approvals versus exceptional circumstances and conditional approval, and this excludes generics, bio-similars and duplicates.

Whereas a conditional approval was granted

for about 7 percent of all new product approvals by EMA, in the oncology area, this represented 20 percent of all new approvals. And as you can see from the tabulated overview of recent oncology approvals, approximately two products per year are using one of our early access tools, some of which, indeed, are still requiring an approval under exceptional circumstances mainly due to the very small size of the target patient population, which makes it unlikely that the full comprehensive clinical data package is ever going to be provided.

For the five oncology products that have received conditional approval so far, efficacy evidence at the time of approval mainly resulted from a Phase 2 single-arm trial with objective response rate as the endpoint or from a single, randomized, controlled Phase 3 trial, with time to progression or progression-free survival as the endpoint, but with promising first results.

The confirmatory efficacy data that were required as a post-approval specific obligation were either updated overall survival analysis of

the pivotal trial; results from ongoing Phase 3 randomized, controlled trials with PFS or overall survival as an endpoint; or it required the sponsor to conduct a brand new randomized, controlled trial, including some even with a non-inferiority design; or to perform a Phase 4 observational study in the approved indication. And for Vectibix, the sponsor was also required to collect the data on compliance of physicians with KRAS testing and on the performance and quality of the tests used in clinical practice.

In fact, in all five of these cases, due to either the unconventional trial design, but with significant results, or the sometimes small but promising signs of clinical benefit, but all for indications for which there was a high unmet medical need, these were usually quite difficult discussions at the level of our committee. And it led CHMP, for each of these cases, to also seek advice of our external scientific advisory group for oncology.

Of the five oncology conditional approvals,

one product so far has converted to normal marketing authorization, already after six months even, and this was sunitinib for renal cell carcinoma, following the submission of data of an ongoing Phase 3 trial in first-line setting. For the other four products, additional clinical data are still awaited, but this is not unexpected in view of their rather recent conditional approval.

Finally, we think it's important for companies to consider a possible conditional approval at an early stage during development, and EMA is available to give input in the development plan of a company -- of a product which may be suitable for a conditional approval. And in that case, companies are strongly recommended to request early scientific advice from EMA. And, in fact, since 2006, many companies have taken advantage of this possibility, and they pay a user fee for this. There have been 91 scientific advice procedures on conditional marketing authorization, 37 concerned oncology products; questions related to general eligibility for conditional approval, questions on

the adequacy of efficacy data or of the safety database at time of submission, and then, of course, questions also on the design of the proposed specific obligation studies. There is also the option for companies to request scientific advice in parallel from both FDA and EMA, which is something we strongly recommend to optimize global clinical trial resources.

So, to conclude and to summarize, we have the legislative framework in place in Europe for the granting of conditional marketing authorizations, and it came into effect in April 2006. It applies to drugs and biologics for life-threatening of rare diseases and which may have been studies in trials with a different design and different endpoints than we would usually expect, but which are expected to fulfill a high unmet medical need.

In any case, the preliminary data coming from those trials have to demonstrate a positive benefit-risk balance. Data from new studies will be requested by CHMP as a post-approval specific

obligation in order to confirm that the benefit-risk is and remains positive in the approved indication. And then the yearly renewal of such conditional marketing authorizations, we believe, is an effective tool to ensure close monitoring of compliance with post-authorization data requirements.

The early access tools, both conditional and exceptional circumstances, are applied to approximately two oncology products per year. And in view of the many methodological and scientific issues to be considered for the design and the analysis of clinical trials that will support an initial conditional marketing authorization or for the post-approval confirmation of the benefit, applicants are strongly encouraged to seek European scientific advice from EMA at an early stage during development.

Finally, I would like to thank colleagues both at the EMA and FDA side for their helpful advice for this presentation, and thank you all very much for your attention.

Questions from Committee to Guest Speaker

DR. WILSON: Thank you. We've got a few extra minutes, so I thought maybe we could ask you a few questions.

Is it possible to outline how the EMA regards cooperative group trials from the European groups and whether or not the challenges with those cooperative group trials are similar to some of the ones that we are encountering here in the U.S.?

MS. BOONE: I will only be able to address that at a general level, but, indeed, we also have experience with trials that are conducted by such collaborative groups. But it's my personal understanding that these are still to be done under the responsibility of the company, and the company should closely monitor and work with the groups to make sure that the trial is conducted and finalized as per their objectives.

DR. WILSON: Dr. Pazdur?

DR. PAZDUR: I just wanted to kind of emphasize, from Hilde's talk, several important points. First of all, this issue of yearly

renewal, and I think that that is very unique and different from the accelerated approval provisions that we have here in the United States. And here, again, I think this is one of the reasons that we wanted to have, on a continuing and more frequent basis, this type of meeting. Although we're not renewing the authorization, obviously, at this meeting of any of these applications, we are bringing it into somewhat of a public focus and we do plan on continuing that.

The other issue that I think is very important that Hilde mentioned is that the supplements are not covered under accelerated approval. These are for new molecular entities only, and this is also a difference from the U.S. accelerated approvals, and also the wording of the legislation.

If you notice, they use the word "preliminary evidence of a benefit-risk." Nowhere is this issue of surrogacy, a surrogate reasonably like to predict. And I think that when one takes a look at the time and energy that we spend here in

the United States debating, well, is this effect on PFS going to reasonable predict a value, an improvement in overall survival, that kind of lexicon doesn't necessarily go on in the EU, because that issue is not there. It's a risk-benefit relationship. And here, again, in dealing with them and in our discussions with them, they have had significant issues also with single-arm trials, because of the issue of the lack of clarity and ability to really evaluate a risk-benefit decision in a single-arm trial. Obviously, you don't have a comparator, and, hence, if you have an 80 percent AE, adverse event, you have to assume that it's due to the drug. You don't have a control arm really to compare it to.

So these present a lot of issues, and although some of them are different, there are some fundamental issues in the way the legislation is written that deserves at least comment here. I'm not quite sure, in the day-to-day application of the legislation or the regulations, how much it really effects discrepancies, but there is a

different fundamental basis. We're taking a look at a surrogacy issue here. That is not in their legislation.

DR. WILSON: I think you said it, and that is that maybe functionally, it's not as different as the language, but they're talking about preliminary evidence that could be applied to a surrogacy, as well.

DR. PAZDUR: Correct.

DR. WILSON: So maybe you can comment Is there a -- I don't want to use the word "higher bar," but is there a bar that is above a surrogate marker that is more commonly applied in these applications to the EMA versus here. I would gather not, because I think a lot of the same studies are used for both FDA and EMA. But perhaps you could comment with regard to the points that Dr. Pazdur made.

MS. BOONE: I fully agree with the comments from Dr. Pazdur that, indeed, our framework speaks about an initial positive benefit-risk and it doesn't specifically refer to the use of surrogate

endpoints. It's one of the tools that we have available and that we will use, but it's not exclusively based on the use of surrogate endpoints, as such.

DR. WILSON: Dr. Pazdur, though, wouldn't it be reasonable to say that we always -- in evaluating drugs here, we always look at the risk, as well, and the risk is always part of it.

DR. PAZDUR: I'm just bringing this out as a difference in the way that the things are written. Actual application, I'm not quite sure how differences are interpreted, and you'll see a great deal of similarity between the actions. Obviously, a lot of people like to point out differences that may exist between approvals in the EU and the United States. But if one takes a look at the number of concordant approvals and disapprovals or non-approvals, it far exceeds the few differences that we have.

DR. WILSON: One thing I noticed, and you also brought this up, Dr. Pazdur, is that these conditional approvals are renewable every year.

Functionally, do you believe that gives you a leverage that FDA may not have or is it -- if you could just comment on that.

MS. BOONE: Perhaps I will not compare the two systems as such, but I can say that at the EMA, we find as a very effective tool; perhaps the first one, that the company already has to come back after six months, is a bit of a challenge. But I think the possibility for the committee to review and receive an update from the companies and to see the latest available information and what the status of the specific obligations is, I think is very helpful. And if needed, to engage in a dialogue with the company and then see how, indeed, do we take this forward to get the data that we need.

DR. WILSON: Thank you.

Dr. Freedman?

DR. FREEDMAN: Just two questions. Is there anything like the expanded access that we have in the U.S. in the EMA?

MS. BOONE: Yes, indeed. We have a system

called compassionate use, which is also to make approved drugs or people that cannot get the drug in a trial available to patients in Europe.

DR. FREEDMAN: And is it provided in the three subgroups that we have with individual small trials, large trials?

MS. BOONE: I'm not aware of that, but I think it's on either a named patient basis or it applies to a cohort, a group of patients.

DR. FREEDMAN: And the other question that I had, to what degree does the reciprocity extend into the review process? In other words, looking at either agency, to what extent would they use the data to push a trial further or faster in the review or take any component of it into consideration in the review?

I guess it's a question for both agencies.

DR. PAZDUR: Let me address that. We do share reviews after they are completed. For example, our reviews or our action letters are available to our EMA colleagues. The issue here, though, we do have independent review processes

that are going on. We do talk. We have a monthly teleconference between the two agents and it includes Health Canada, also, in that conference, where we will go through all of the applications that are coming in, that are being reviewed, and discuss where we're at and what our preliminary issues are with those. So there is a dialogue here.

I'd like to point out, even with the parallel advice that Hilde recommended, it's not an attempt to have a uniform opinion at the end of the day. The governments are aware that there are going to be differences between, for example, recommendations that the EU may offer and what the United States may offer. It's really to have a discussion of what those differences are with the company and why we want them, but it is not an attempt to, so to speak, lock-sync the decisions together or to have uniform decisions between the two countries.

DR. WILSON: Dr. Martino?

DR. MARTINO: I have a couple of questions,

but they primarily relate to this one-year provisional concept. And, first of all, I think the word "provisional," to me, has always made so much more sense than the word "accelerated." They imply very different things.

But it does occur to me that the one year really only provides a time point where you then have to reassess where they are. It doesn't necessarily mean that anything major happens at that point. And since this has been going on for only a few years in Europe, I'm not sure what its ultimate real value is. At first, I thought it would have real value. I'm a little less confident of that now.

But it brings me to my question, which is what is our process once you give that accelerated approval? Is there a frequency with which interactions have to occur or is that purely based on judgment?

DR. PAZDUR: It's based on judgment and the division's review of the material as it comes in, and that's why we're really having these attempts

for periodic reviews and looking at this much more closely. We do not have it stipulated that you have to take a look and renew an application or do a complete review after a year, and that's why we have been paying much more attention to these as they go on.

Here, again, I think the major issue -- and this is one of the reasons why we're having this committee -- is really to discuss efforts in the front of the application to ensure that these studies are ongoing rather than try to take some punitive attempt at the end when they fail or something, because it's, I think, very hard in either of the systems, either in the EU or in the United States, to remove an indication, especially if the company does not agree with it.

Fortunately, with many of the accelerated approvals, the five that were listed, many times, the companies, because of poor accrual to the studies or just blatantly negative studies, have agreed to remove these indications. But it is very difficult to remove an indication, and, therefore,

I think we have to really focus our attention to the upfront studies, what they are, before the drugs are approved rather than trying to negotiate this at the very end.

We all realize that there's a great deal of enthusiasm when a drug is going to be approved and people want that drug, et cetera, but unless these studies are really thought out, we really get into predicaments that we've been discussing either at this ODAC or at previous ODACs, where the studies have not been really well thought out of what we're going to do if they fail, what are alternative studies, what the impact is going to be once the drug is approved; so multiple issues here; that probably our efforts should be better thought out in the very beginning.

I often have stated this, that I think the American public realizes, when there is a new safety issue, that a drug should be withdrawn from the marketplace, et cetera, but I think many people have a difficulty in understanding that, well, the drug was effective a year ago and now you're

telling me that it's not effective.

That, I think, is a very nuanced endpoint and nuanced issue for the public to understand. So I think really our efforts here, again, need to be focused on this upfront attention to the details of these studies.

We really have been emphasizing this in the last couple of years in our end of Phase 2 meetings, in our SPA, our special protocol assessments, trying to clarify where the studies are going to be accelerated approvals, in our filing meetings with the companies, et cetera. And there are companies that, I really want to emphasize, have done a very good job in getting studies done and paying attention to this, doing several randomized studies, looking upfront and addressing this issue. But as with anything, one deals with the very best and then people that want to take a look at what's the minimal they could get away with.

DR. MARTINO: So it occurs to me that you now have the ability to levy a tax, shall we say,

to a company at some point in its interactions. Am I allowed -- are we allowed to know what is the nature of that tax?

DR. PAZDUR: It is a fine. I don't have the dollar amount in front of me. But here, again, the issue is we have post-marketing requirements that are stipulated in the approval letters; and, therefore, if a company or a firm does not meet their study obligation on that date, then we can attach a fine to it. And that came out of the initial FDA Amendments Act. We have not done that to date; and, therefore, this would be kind of new breaking ground that we have. But I will say that we would have an intention of using that tool that is available to us.

DR. MARTINO: I think what I'm trying to get a sense of, if you're able to give it to us, is it $5 or is it meant to be, in some way, shall we say, motivating?

DR. PAZDUR: It's meant to be motivating. I don't have the dollar amount.

Do you know, John?

DR. JOHNSON: It can be up to $10 million. It wouldn't usually be that much, but it can be if there are multiple failures.

DR. WILSON: Thank you.

Dr. Loehrer?

DR. LOEHRER: It was a nice presentation, appreciate it. But just to help me wrap my arms around the differences and similarities between Europe and the United States, do you have any data on the number of drugs that have been approved in the United States versus EU, the time to approval for that? And then, finally, the last one would be withdrawal of indications, in Europe, how many drugs have had indications withdrawn or the drugs disapproved?

MS. BOONE: I believe that, indeed, an analysis has been done a couple of years ago comparing, indeed, the outcome on both sides. I don't have that information available. We can certainly provide it because I believe it's in the public domain. I don't think we have done a further analysis of looking for the issues that you

mentioned, but it is perhaps something that we could do as a follow-up.

DR. PAZDUR: We could get numbers to people.

MS. BOONE: Exactly.

DR. WILSON: Thank you.

Ms. Mason?

MS. MASON: Does cost play a role in the EMA approval?

MS. BOONE: No. It's purely quality, safety, and efficacy.

MS. MASON: Thank you.

DR. WILSON: Dr. Curt?

DR. CURT: Thank you. Is there any special safety surveillance for products that are used clinically when they're approved under this mechanism?

MS. BOONE: Not specifically linked to the mechanism, as such, but every product, indeed, will be evaluated to see whether there are specific risk minimization measures that may be needed. And that will, again, also be specified in the decision which grants the marketing authorization or whether

any specific tools, such as control distribution, patient registries, et cetera, would be necessary, but that would be on a case-by-case basis.

DR. WILSON: Dr. Sekeres?

DR. SEKERES: Thank you. Just a couple quick questions. You brought up a lot of potential punitive actions that could occur if a company doesn't meet its obligations. Have you ever actually invoked financial penalties or decided to not approve a conditional MA after one year?

MS. BOONE: The answer to both questions is no. And for the financial penalties, well, it's also, for Europe, quite a relatively new piece of legislation, since July 2007. So the discussions on how to implement this practically are still ongoing, but it hasn't been necessary yet to apply this.

DR. SEKERES: And have you not invoked those because you didn't feel they were necessary or is it for some other reason?

MS. BOONE: Well, it hasn't been necessary to invoke the formal penalties in an infringement

procedure. But, of course, with every suspected case of noncompliance, EMA will always address this very promptly with the company and use an appropriate tool, be it meetings with the company, sending formal letters, doing an inspection, if needed, and then, indeed, consider whether there's a need to initiate an infringement procedure or not.

DR. WILSON: As a follow-up to that, this is tangential, but I think relevant. Does EMA have an outside advisory group, or are these decisions made internally with EMA employees?

MS. BOONE: So the scientific review at the level of the EMA is done by our Committee for Human Medicinal Products, the CHMP. That has experts nominated by all of the European member states. So that is an internal committee of experts.

Now, in some cases, it may be that that committee decides that it would like to have specific input from an external expert group, very similar to this group, which we call a scientific advisory group, and that consists of, indeed,

approximately 12 experts coming from academia, hospitals, universities, and that will also have an advisory role towards our scientific committee on very product-specific assessment questions.

DR. PAZDUR: But those meetings are closed, correct?

MS. BOONE: They are closed, but the company concerned by the discussions is invited to present to the SAG and will be briefed on the outcome of the discussions.

DR. PAZDUR: But they are not public meetings.

MS. BOONE: But they are not public meetings, indeed.

DR. WILSON: Any other questions on this topic?

[No response.]

Questions to the ODAC and ODAC Discussion

DR. WILSON: Thank you very much.

So I think that we will now move on to the questions at hand. Dr. Kluetz will be giving an overview of each question and as a framework.

Also, because these are not voting questions, after the question is posed, we'll have a discussion. And then what I would like is I would like each of you to think about how you yourself may want to address it, because I will then go around the room and I will ask each of you to answer the question so that FDA has a more specific discussion from each individual. I think they would find this helpful in trying to obtain as much guidance as they can.

So, Paul?

DR. KLUETZ: Thank you. So we're going to talk about four nonvoting questions to be posed to the committee members. Again, these are designed to facilitate discussion on ways to improve the accelerated approval process. And, to remind everyone, discussion of specific drug indications should only be made in order to make a broader point in the accelerated approval process.

So for the first question, with respect to single-arm trials to gain accelerated approval, single-arm trials have formed the basis of 29 out

of 49, or over half, of our accelerated approvals for oncology to date. And while they often require less resources and time to complete, they provide limited data on clinical benefit and safety.

Single-arm trials for accelerated approval have usually been performed on refractory populations where no available therapy exists. But as a greater number of drugs are approved, identification and documentation of the refractory population is becoming increasingly problematic.

In addition, marginal response rates observed in single-arm trials in a refractory setting make it difficult to determine whether the findings are reasonably likely to predict clinical benefit.

Some alternatives to single-arm trials in a refractory population include randomized trials in a less refractory population against an active control using a surrogate endpoint analyzed at an earlier time point or a randomized trial on a refractory population comparing the investigational agent to either best supportive care or a dealer's

choice of various agents selected by investigators. Randomized trials provide the opportunity to look at a wider variety of endpoints and allow for an improved characterization of safety.

So the committee members are asked, given the problems with single-arm trials, discuss scenarios where randomized studies should be required for accelerated approval. Alternatively, please discuss situations where single-arm trials may be appropriate to support an accelerated approval.

DR. PAZDUR: If I could just mention a few things here that perhaps we did not mention on the slide, and that is really the need to really define the population very well in a single-arm trial.

Remember, by law, these have to be controlled trials, adequate and controlled trials that lead to an approval of a drug. And in a single-arm trial, what we're looking at is really a situation where no other therapy exists, so the response rate in the control arm, this make believe control arm, is basically zero, because there's

other effective therapy for this disease.

Let me give you an example of this. One of our very early uses of a single-arm trial was in irinotecan or CPT-11 for colon cancer, when only there was 5-FU for that disease. So it would make sense that a single-arm trial of X percent, I think it was about 15 percent in that situation, would be a situation where one might consider an accelerated approval, the control being there is no control. There is no other active drug in this disease, so if one did a randomized study, one would expect to see a zero percent response rate.

Some of the problems that you get into, especially with more and more drugs being approved in other disease settings, is that it might not be that cut-and-dry, especially for some of the hematological malignancies, lymphomas, Hodgkin's disease, myeloma, et cetera, leukemias, where you might get response rates even by retreating patients with drugs that they've had in the past or drugs that are on the market that may not have a specific indication but are widely used in

oncology.

Here, again, the other issue that I think people have to understand is that we're probably one of the very few therapeutic areas that takes single-arm trials for drug approvals. Most other therapeutic agencies, the agencies go right away to randomized studies. And this use of a large single-arm trial of 100 to 120 patients really is a manifestation of the accelerated approval process.

One could say an alternative would be, right after the Phase 1 study, if you see some really interesting level of activity, high level of activity, maybe you want to start a randomized study very early on rather than basically just accruing large numbers of patients to a single-arm trial.

Sometimes when you get to some of the single-arm trials that have two single-arm trials with 150 patients, you're well on your way already of randomized study, and you might have been better off by just doing a randomized study relatively early on. And that's some of the issues that we

really wanted to discuss.

As with everything, we feel that there is a role for single-arm studies, particularly in unique diseases or where one has very, very high response rates. But as with everything in medicine and advice that we give, water tends to seek its lowest level and we frequently find sponsors coming in saying, "Dr. Pazdur, what's the fewest number of patients and the lowest response rate that you'll take?" Okay, that's problematic for us, and that's where we're going with this question.

DR. WILSON: So I do think that one can always make an argument in settings that a single-arm trial is okay. I think one of the difficulties you've already pointed out is the fact that in numerous settings where it is said that nothing else works, that is actually not correct.

Actually, in kind of a follow-up to that, you all mentioned that 29 of the accelerated approvals were based on single-arm trials.

What percent of the follow-up trials were randomized? Let me restate it. What percent of

the follow-up trials did you require a randomized study at perhaps an earlier stage?

DR. JOHNSON: Twenty-four of 27.

DR. WILSON: I'm sorry?

DR. JOHNSON: Twenty-four of 27 that were converted were converted based on randomized trials; almost all.

DR. WILSON: So if I hear right, 29 got accelerated approval on single-arm, and of 27 that were converted, 24 of those required randomized studies.

I think this really brings to bear the very thing you said, Dr. Pazdur, which is that should small, single-arm trials be what gets you accelerated approval or should you wait for the randomized studies, because as we all know, and it's been brought up here, it's not that these drugs are not available. They can be obtained through compassionate use. There's a variety of different mechanisms that they can be made available.

Dr. D'Agostino?

DR. D'AGOSTINO: In terms of this, we were told that they can't be randomized, yet most of them at the later endpoint were, in fact, randomized. So there's sort of something contradictory here. But let me go back to the notion of the single-arm study.

In this single-arm study, is the endpoint a surrogate endpoint or is it the actual clinical endpoint?

DR. PAZDUR: It really depends on the disease setting, but most of the time, in solid tumors, we're talking about this to be a surrogate endpoint reasonably likely to predict clinical benefit. And that's where the real problem becomes, because the issue, especially when one is dealing with a low magnitude of benefit, if somebody is coming in with a 10 percent response rate here, in a solid tumor, how does one really make that jump and leap of faith here, so to speak.

DR. D'AGOSTINO: Given if it's a small population, like maybe some of the things we heard today, that you have a very small population or an

offering drug situation, you could see the notion of a surrogate endpoint trying to move things along. But, again, I find the fact that later on, you can do a randomized trial and it materializes, that most of them are randomized trials that somehow or other undermines the notion. So I guess the notion that you need the single-arm -- so I guess the single-arm trial is basically to entice the company to move on with the drug; get the single-arm trial going, they get accelerated approval; then they have incentive to put more substantial controlled clinical trial together. And I don't see why they can't package that all at once to get it right on the table; this is what we're going to do. And you can handle both of these issues.

DR. PAZDUR: I really want to make this point very clear. The accelerated approval program is a patient-centric program aimed at getting drugs to the patient. It is not an incentive program, financial incentive program to the industry. And that's why I think it's very important that we pay

attention -- this is why we keep on using that word over and over and over again in our presentation.

DR. D'AGOSTINO: Well, no. What I meant by that is that there's an incentive with an indication that they can enlarge the indication and so forth by doing it, and the single-arm study entices them into a way of getting it. But I think one of the questions, put them all together. And I think they should move from the single-arm study to the clinical study, and that should be laid out, and that should be how the approval is based.

DR. PAZDUR: And remember, nobody has to start a development program in the most refractory population. They could introduce the drug into a less refractory study and do a randomized study.

Here, again, we did point out other potential alternatives to single-arm trials, very similar to the AIDS scenario, where one has randomized study where one would take a look at a surrogate endpoint in the middle of a study or near completion of the trial, base accelerated approval on that, and then look at survival at the end.

DR. D'AGOSTINO: Can I make one more comment?

Moving to a different population, I see where you're coming from; you've got a bigger population and what have you. But there's sort of a danger in that that you're moving away from the target that you wanted and the balance of, say, you can't do a single-arm study, do a randomized trial on a different population. Then you're scratching your head at the end, is it really applicable.

So the single trial, with some kind of indication of how do you judge effectiveness, even at the accelerated level, followed by or in conjunction with the follow-through with the randomized trial seems to me like, from what you're saying, it should be possible, especially given 24 did go on to do the randomized trial.

DR. WILSON: Dr. Sekeres?

DR. SEKERES: Thank you, Dr. Wilson.

Dr. Pazdur, something that you said about the justification for single-arm studies is exactly what went through my head at the same time, and

that is that it's a rare disease and that there's some type of benefit that's impressive right off the bat.

In my world, I'm a leukemia doctor, that's arsenic. Right? You have arsenic trioxide given to people with relapsed acute promyelocytic leukemia, which is an extraordinarily small population; so small that you can't justify opening a study in your center because it's not cost-effective, and you have a big magnitude benefit.

But I think the third piece to it -- and, Ralph, this gets a little bit at what you were saying -- is the either real or perceived imperative to getting a medicine out there to market, and that's a real tough balance to strike.

So then if you take that to the next level, what kind of randomized study could you propose and what would your population be, it seems to me -- and the examples we had presented to us today were great, because you saw very small patient populations where it would be difficult to do a randomized study right off the bat to get approval,

and you saw relatively small, but not that small, where randomized studies were enrolled too efficiently, and that example was with GIST, which, by the numbers presented to us, looks like it affects between three and 4,000 people a year in the U.S. Chronic phase CML is very similar, about five to 6,000. Yet, they were able to accrue quickly to a randomized study.

It seems to me that if you have a patient population that's somewhere around a thousand, that becomes difficult. And maybe the type of study you have to design to encourage accrual within the U.S. gets a little vague in the comparator group, and that may be dealer's choice by the physician; because I think in the U.S., it's hard to convince somebody to not get the latest and greatest or to be randomized to a placebo when it's a very small patient population who happens to be very vocal.

DR. PAZDUR: And we have advocated that to several sponsors who said they couldn't -- there wasn't agreement on a comparator arm or there is none, and that has been used in drug approvals.

DR. SEKERES: And do you have roughly -- I know you can't give a number, but is there some sort of rough patient population where, in your own mind, you think, gee, they could probably do a randomized study; it might not be easy, but they could do it versus it ain't going to happen?

DR. PAZDUR: It's hard to say because it also depends on the treatment effect that you're seeing. If you have a very effective therapy, you can see a big effect in a very small number of patients.

I'll give you an example. Who would ever think you could do a randomized study in paroxysmal nocturnal hemoglobinuria? They did it, and it was highly successful, because they had a very, very effective drug. I've never seen a case so -- they did a randomized study on that. So it really depends on the effect size that you're talking about here.

Here, again, I think there are some issues, for example, in some of the GIST supplements that we approved on single-arm studies and gave them

just a regular approval, because we knew it wasn't going to be possible to even do a randomized study, like in eosinophilic leukemias, et cetera, and other very rare tumors. It's going to be very difficult to do.

DR. SEKERES: You know, the PNH example is a great one. So there's something that that company did with a very vocal and active patient group, where they were able to accrue to that sort of study. And the same thing happened with imatinib for just our first CML. And there's probably a lesson that other companies can take out of those that did that successfully.

DR. PAZDUR: And one would hope, as we get more targeted therapies that have greater efficacy in a subpopulation, one could go more rapidly to a randomized study rather than doing this cookie-cutter approach of let's do now 150 patients on a Phase 1 study.

If you have done an expanded Phase 1 cohort in 20-30 patients and see a 70-80 percent response rate, why not just jump into a randomized study,

and with an effect size that truly is what you think it's going to be, not aiming at the garden variety two-month improvement in overall survival, but really a big effect on overall survival. So one would have to deal with a small -- or one could deal with only a small trial here.

DR. WILSON: Maybe you can give us some guidance here. And I'm really caught up on the fact that 29 accelerated approvals were single-arm, of which 24 of 27 that were converted were on randomized study.

So really this is how rapidly the FDA -- I mean, this really is under your control. And if the FDA wants to, as Dr. Sekeres said, move a drug forward quickly, then you might be willing to accept a single-arm trial. But it sounds like in the vast majority of settings, randomized studies were done; they were positive, presumably, et cetera.

So I'm trying to get a sense of what you're looking for from us, because at the end of the day, the FDA can say, "Listen guys, yes, you've got a

strong signal here, but don't come forward with this, because you can do a randomized study."

DR. PAZDUR: Well, you've heard our arguments, and we've used these arguments and had, over the past 10 years, discussions with companies on this. Nevertheless, I think it's important for us to have this discussion so people hear it again in public, so to speak. So it's not just the FDA saying it, but there is some recommendation by the advisory committee of where you feel these should also be going.

I want to say, and I want to make it real clear to everybody here, we're not saying we will never accept a single-arm study. There are situations where we think it's appropriate, in homeruns, when somebody comes in and it really is a drug that we really want to get out from a public health perspective. But here, again, many times, what we have seen here is people coming in with a very small response rate, with ill-planned if no confirmatory studies, saying there's nothing else for these patients; please approve this drug.

They also may be doing themselves a disfavor, because many -- we've had circumstances where the true benefit of the drug was realized in a randomized study on the basis of survival, where the response rate was miniscule. The example that I gave to you of irinotecan, we approved that drug at 15 percent response rates. The Europeans demanded a randomized trial. It showed a survival advantage, which really put that drug in the context of how it should be used, and that was only a year after the accelerated approval, roughly, of that drug.

DR. WILSON: Ms. Mason?

MS. MASON: Thank you. I wanted to go back to your comment about the ability of patients to access medication prior to approval through expanded access or compassionate use programs. And while it's wonderful that that mechanism is in place, unfortunately, it doesn't seem to be working like it might, simply because the industry does not want to take the risk or, for whatever reason, it's not out there for patients, and that's been a real

issue.

DR. WILSON: Would FDA like to comment on that?

DR. PAZDUR: Well, we're very much in favor of an expanded access program, where it makes sense, especially in these situations where there is evidence of activity of the drug or the drug provides a benefit while we're developing the drug. Here, again, we cannot make a pharmaceutical company give a drug either to a single patient, to an expanded cohort, intermediate size or large size of large patient population.

So here, again, I think before the pent-up demand is realized, what we're really encouraging people to do is think randomization early rather than doing these large single-arm trials here.

DR. WILSON: Dr. Freedman?

DR. FREEDMAN: I agree with the point that you made. It seems that the default position has already been established. The standard is to do the randomized trial. But there's always going to be the exception, where you have a clear-cut

response that's durable and it's associated with specific symptoms that you can direct. Take esophogeal cancer; the patient can either swallow or they can't swallow. That's the way I see it. It's going to be a minority of trials where you could consider that; but, otherwise, the usual route is going to be the randomized trial.

DR. WILSON: So far it's been 58 percent, so it's not a minority.

Dr. Logan?

DR. LOGAN: I guess I certainly agree with all the concerns that have been raised about single-arm trials in terms of the difficulty interpreting these marginal response rates that we're seeing, difficulties in assessing toxicity.

I would also just raise a concern that I think it oftentimes makes it difficult to do those follow-up randomized trials, certainly, in the same relapse refractory setting. It makes it difficult because of the accelerated approval. But I think it also -- as we've seen in several of the presentations today, it may make it difficult to do

that follow-up randomized trial in a less refractory population because of the potential for crossover to the agent being studied.

The other point that I wanted to make was in terms of doing an upfront randomized trial. I think it's been alluded to in terms of setting up an upfront randomized trial where a surrogate endpoint is the primary endpoint for accelerated approval, with additional follow-up for survival.

Certainly, that's a reasonable approach. You just want to make sure that -- make sure of a couple things; first, that you're adequately powered for survival. Second of all, you want to be careful about the duration of the follow-up in terms of when are you presenting the results on the surrogate endpoint; is that done at the end of accrual so that you're not presenting results before accrual is completed.

DR. WILSON: Dr. Martino?

DR. MARTINO: I think I'm getting old and crabby and probably that's the sum of everything I want to say to you. But I'm very disappointed in

the fact that this process of approval has really become a screening process.

I'll just remind you of Dr. Pazdur's recent comments. Everyone is interested in what is the least that we have to offer. And I think that this committee and the FDA and others have allowed that to become the mood of science within the field of oncology during at least my lifetime, where we are willing to accept drugs with the most minimal evidence that they do anything at all, and move them forward.

I actually wonder whether we're having the right discussion here. I appreciate all of these procedural issues, but I'm starting to find them somewhat irrelevant. I think we have moved the whole field in absolutely the wrong direction. And the reason why a single-arm trial is so inadequate is because we're dealing with drugs that barely have any activity. And it isn't just a drug that falls into that category; it is most of our drugs. The exceptions are the ones that have more than a whiff of activity. And at some point, we have to

start to take responsibility for that.

To the simple question of is a single-arm trial adequate, there's almost no circumstance where it should be adequate for approval for human beings, which is who we're dealing with. So, again, I'm wondering whether this is the right discussion to be having.

DR. WILSON: So let me try to put this into perspective, and maybe you can give us some numbers. Twenty-four accelerated applications or accelerated approvals were converted to full approval based on randomized studies.

What is the median and range between the accelerated approval and the full approval based on randomized study? And this going to be the worst case, because if these companies were told they had to have randomized studies early on, this whole thing would have been quicker, because the whole idea here is to move drugs -- is to make drugs -- as Dr. Pazdur said, it has to be patient-friendly; it's to make the drugs available.

I'm no advocate of single-arm trials either,

but I think the other statistic is that only four drugs have been not confirmed that have reached the point of confirmatory trials, and that was 10 percent.

So the system seems to be working. Again, so the question is it's just a matter of a balance between how quick versus do we even know how to use these drugs in a proper manner.

But what is the median time for those 24 drugs?

DR. KLUETZ: If you're talking about the median time between the accelerated approval based on a single-arm trial and the verification of benefit based on the randomized trials, of all 27 indications --

DR. WILSON: Twenty-four that required --

DR. KLUETZ: I can't take out the 24.

DR. WILSON: Okay. Well, 27 is fine.

DR. KLUETZ: It's 3.6 years, and the range is 0.8 to 12.6. And if you take the tails, which is what happened with the longest trials and what happened with the shortest trials, it's off the

topic of whether it's a single-arm trial or not, but what it looks like is a lot of the very long time for very long trials have a couple of things in common.

Number one, only one confirmatory trial was undertaken. And what we'll talk about later is if you lose on that, then it's scramble time. Do you do another trial? If you don't withdraw it, you do another trial, that's a long time before that drug is up.

Another thing that's happened that we've already seen is that there are certain populations where there's a very small amount of patients that can also take a long time. And another thing that can take a long time is if you're not looking early on in drug development and you want to do your confirmatory trial as a combination trial, moving the drug up front, and you don't have a Phase 1 trial yet, that's a big problem, too. That adds years onto the development.

DR. PAZDUR: This is why we're trying to emphasize planning, planning, planning. It's not

coming to us with a single-arm trial and then let's discuss after the drug is approved. There's no reason why somebody can't -- and here, again, I think the numbers will bear this out. The successful drugs have had trials ongoing. If there needed to be a Phase 1 study, okay, you're studying the drug in a refractory setting. The other disease settings that you're going to be comparing this drug to involves combination therapies. Why not start developing those Phase 1 studies early on while you're getting the registration trial in place?

Here, again, it's this planning issue here that needs to be emphasized to the companies, and that's why we're asking the series of subsequent questions about the timing, implications of not having the trials well thought out, the number of trials, et cetera, who you're going to be using for these trials.

DR. WILSON: So the numbers are median -- you're shaving 3.5 years off availability on the median. If these things were preplanned to

be randomized upfront or even preplanned to be approved on single-arm, but randomized is already starting, you might be able to move this up even more.

So I think that Dr. Martino makes a very good point that things have probably slid way far over to not planning, to allowing single-arm trials too often, and there's got to be some middle ground moving this back.

Dr. Loehrer?

DR. LOEHRER: I wasn't going to initially comment, but I agree with Dr. Martino on this. There was a journal years ago that Rick knows about cancer treatment reports. If it was zero for 14, it was a negative trial, and if it was one for 25, it was a negative trial.

DR. PAZDUR: The Gehan rule.

DR. LOEHRER: Yes. And now one for 25 is promising results.

DR. PAZDUR: No; it's a drug approval.

DR. LOEHRER: Right. And move for approval, right.

A couple points I wanted to make. One has to do with the second point, situations in which a single-arm might be appropriate.

So an example from our institution that hasn't been raised is in refractory testes cancer. When a patient is cisplatin refractory, when I was a boy, there was no drug that had activity until etoposide came around, and then that, again, moved into a randomized trial and was approved that way.

The next generation drug was ifosfamide, and ifosfamide got approved by the FDA not based on a randomized trial, but because in third-line therapy in patients who were refractory, there was a 15 percent long-term survival and a cure rate for that patient population; impossible to do a randomized trial on that. There's probably two or 300 patients in the country. But yet it was a population in which you could clearly show people were alive that wouldn't have been alive, and so there are situations in which this occurs.

The next bullet point, to follow-up with Mikkael, is that if you look at the website for the

Office of Rare Diseases by the NIH, it's defined as a disease that is less than 200,000 people, which encompasses colon cancer. And I think logic would dictate that we could probably define some diseases in which there are less than a thousand patients that are, really, very rare diseases, and some of the examples were brought today, in which the bar in terms of doing a randomized trial may not necessarily have to be there, but the endpoint needs to be solid.

If you have clear historical data that there is a zero percent one-year survival and now you have a 20 percent one-year survival, something like that, I think you could do it. But the progression-free survival is a very soft endpoint, I think, and some of the trials in which we have a two-month improvement or 1.5-month improvement is a little shaky.

Then the final bullet point has to do with something I think we all have to wrestle with is this era of personalized medicine, and that with the genomics and pharmacogenomics and all the other

aspects of the cancers, we have to think of a different way than the randomized trial. If I get colon cancer and Kevin gets colon cancer, just because we're different people, it's going to have different responses.

Now, the randomized trial is supposed to correct for that, but I think ultimately we need to correct for the randomized trial by coming up with better genetic markers. And so the point would be in KRAS mutant patients, for example, in which we know that EGFR antibodies don't work, great, we've got this unique population. If we had an EGFR antibody that suddenly had a 30 percent response rate, that would be meaningful; probably not enough to be approved, but it certainly would be meaningful. And I think down the road, in rare diseases, we're going to have to use these kind of genetic markers to help us.

DR. WILSON: Dr. D'Agostino?

DR. D'AGOSTINO: The comment I was trying to make, I was going to make it earlier, I think it has been answered. But back to the 24 randomized

trials that follow the single-arm, were the 24 on expanded populations or were they the same population?

DR. JOHNSON: Nine of the 24 had a randomized trial at a higher stage, lesser resistant. Think about it. You were talking about randomized trials and they couldn't do randomized trials in refractory patients. And if you can't do it initially, just think, after the FDA has given it accelerated approval, it's likely to be better than anything that's available, and then you're going to approach a patient and say, "How would you like to be randomized?"

DR. D'AGOSTINO: I think that's the dilemma that some of us are facing is that once you give accelerated approval, why would anybody go into a randomized trial. And so you have to do something to entice them, and one of the things is to broaden the population so you get a different group of individuals where it's not proven.

So it makes a lot of sense, but it does impact on what the single-arm trial looks like and

then how you expand. It's not basically solely the same population. When you present to the FDA, when you're designing, as Dr. Logan was saying, you have to worry about the fact that you're going to have a maybe single arm which you're working, but then you're going to go into a randomized on probably a broader population. So there are, obviously, lots of things to think about that are not necessarily typical in putting a randomized trial together.

DR. PAZDUR: But here, again, I think that's why the regulation clearly states that these trials should be underway at the time of approval. And here, again, you saw the AIDS paradigm, where the trials, two trials, large trials, are underway looking at a surrogate endpoint and then verifying clinical benefit in the identical trial here. So there's not this issue of let's start a new trial after the drug is approved.

DR. D'AGOSTINO: And it's not the issue with saying, well, the indication we're looking for in the single-arm is we can put a randomized trial together. Maybe you really can't, but then you can

move to a broader population in the context of a research program.

DR. WILSON: Dr. Curt?

DR. CURT: If a sponsor goes to the agency and asks whether a single-arm trial will lead to approval, you'll be told it's a review issue, which is the right answer. But I would just like to add that I agree that in rare diseases or large areas of unmet medical need, there may be, in some cases, a need for a single-arm trial. I agree entirely with Dr. Pazdur that planning beyond that is a must.

But the one question I had for the agency is, in some way, do you think that your decisions were flawed in approving drugs with single-arm trials? Because most of them went on to randomized trials, and most of them went on to prove their worth. So is the message that we shouldn't be doing that or that you regret having approved 29 out of 49 by single-arm trials?

DR. PAZDUR: No. I don't think we want to go into that, that we have regrets about the

approvals. We're looking at ways to improve the program here and not go backwards, so to speak, and learn from lessons, because here, again, remember, there are outliers here of 10 years of doing randomized trials and us finding out that the drug didn't work, and even one of these is a painful experience.

So, yes, and we've stated this repeatedly. We really believe this is a successful program, but we're interested in improving the program. And, yes, if one takes a look at the medians, it looks good, relatively, three years. Could that be improved? Yes. Do we want to avoid the outliers? You better believe we want to avoid the outliers. And how can we do that is by looking at how to optimize the program.

DR. WILSON: Dr. Sekeres?

DR. SEKERES: If you take kind of a broad look of this program and, again, fold into one of the things that has to be considered, is either the imperative or perceived imperative of getting a drug to patients, to say 90 percent of the time

that the initial decision was proven in a well designed follow-up study, I think, is, frankly, a success for getting drugs to people who have a terrible disease, which is cancer.

I wanted to play off of something Dr. Loehrer said, also, focusing on the personalized medicine. I think as we start to define cancer on a progressively more molecular level, we're going to start to cut into smaller and smaller patient populations who then will claim to be a true rare disease and, therefore, would qualify for a single-arm study.

So maybe an approach to that would be if it's truly this astounding size effect and truly a rare disease, it might be appropriate to approve on a single-arm study; prior to that approval, negotiating a much bigger study that even could include patients with and without that molecular defined lesion and kind of have a long-term follow-up of those patients and a validation of the initial, while having a well designed study that could maybe identify other patient groups who could

benefit from that drug.

DR. WILSON: Ms. Mayer?

MS. MAYER: I want to go back for a moment to Dr. Martino's eloquent, not crabby at all, statement and talk about the issue of patient benefit and how we look at that, particularly as advocates, or at least how some of us look at it.

It's not only about getting access at the earliest possible moment to the newest drugs. It's about making sure that the treatments that are approved make a really significant difference in the disease, and those are not necessarily the same things. And I think we've seen a number of instances where they are not the same.

So I'm really concerned that we don't get into the business of lowering the bar in the name of compassion, in the name of thinking that that is something that benefits patients, when there are many, many more other patients who will be diagnosed in the future or who don't have access to treatments early on, who actually may be harmed by an influx of drugs that have very, very minor

effects. I think that sends a message to the industry at large that you don't have to work very hard to make a difference and to help us, and that's not a message I, as an advocate, would ever want to send.

But getting to the question, I think single-arm trials should be really reserved for circumstances where there are so few patients and such an unusual -- I like the phrase that was used in the EMA presentation about exceptional circumstances. I think they should be reserved for exceptional circumstances. And I think it's possible to almost come up with an algorithm of the factors that might make those circumstances exceptional, and then require -- since we don't get now a way beyond comparing groups to require randomized trials pretty much across the board outside of those circumstances.

Not to be rigid about it, but, again, it's really important not to lower our standards and create a sort of de facto, low level route to approval, which we've had at least up to FDAAA, in

place, because there has been no action taken to withdraw indications.

Anyway, that's my statement.

DR. WILSON: Thank you.

Dr. Balis?

DR. BALIS: I think other people have said this, but what's apparent is that this process of accelerated approval has an impact on the drug's subsequent development. And so just subtracting the time from accelerated approval to when it's finally approved may not be an accurate reflection of what would have happened if that had never occurred at the beginning.

Clearly, it can impede subsequent randomized trials, and if a drug has a very narrow spectrum of activity, it may actually prevent its final approval, if you can't accrue to those studies. And I think that's something that needs to be -- I don't know how you would measure it, but needs to be somehow evaluated in evaluating this program overall; in some way get at what impact it's having on the drug development process.

The other point I wanted to make in response to the issue about where our bar is currently set is that, at least from the perspective of somebody who is a pediatric oncologist, it is becoming more and more difficult to detect any drug effect in patients who have gone through standard therapies and second-line therapies, because we have so many drugs that are currently available.

So although the bar may seem lower, I think it's different now giving drugs to patients that have come off intensive front-line therapy and expecting to see an effective and new drug that may actually be quite active if it's given in a front-line setting. So I think we have to be careful not to also set the bar too high in some circumstances when you consider the population of patients that are being looked at in these initial studies.

So I guess the other point I wanted to make, actually, was I agree that these single-arm studies, because of the potential impact of these approvals, must be restricted to a very narrow clinical setting.

DR. WILSON: Dr. Mortimer?

DR. MORTIMER: I think inherent in doing a single-arm study is a presumption that there is good over doing nothing. And I just want to point out that there have been five randomized trials of best supportive care compared to therapy, largely in non-small cell lung cancer, where the best supportive care arm had a survival advantage.

So I think doing studies with best supportive care versus an investigational agent is a really good way of doing a study.

DR. WILSON: Dr. Lyman?

DR. LYMAN: I'm basically saying the same thing I think we're all saying, and that is randomized, controlled trials should be the default position for approval of any type, including accelerated approval, recognizing that there has to be some flexibility in terms of exceptions.

As Ms. Mayer said, I think we could come up with some very explicit criteria, including the rarity of the disease, the magnitude of treatment effect, some evidence of low toxicity or safety,

and there are probably others. But I think if industry understands that it's only under those exceptional circumstances that they'd be able to come forward and expect accelerated approval, I think that helps them just in terms of the reality and what they're going to need to do in advance.

Also, as Dr. Balis said, I think we also could be doing some harm with more rapid approval based on limited evidence, because it clearly does impact on completing the definitive trials and the validation study. So I think we're not necessarily doing anybody any service by using single-arm studies when clearly randomized trials with some type of control can be done.

DR. WILSON: So maybe the agency could comment. I've sat on this committee through some drugs that were focused on regulatorily defined unmet medical needs, and they were single-arm trials. And I think that's another slippery slope, because sometimes these things are simply defined by what's been previously approved and may not really be the best thing from a clinical point of

view.

But how do you view unmet medical needs that are the kind that fit within a regulatory definition based on what's been previously approved for that sector?

DR. PAZDUR: It's really kind of a -- what you're really getting at is the definition of available therapy, where there's no available therapy, and we have a guidance on available therapy.

Generally, it focuses on approved therapies and there's an asterisk with an exception for oncology drugs, and it said where there's standard oncology treatments. And that comes to a definition of kind of interpretation -- or interpretation rather than a strict definition.

In general, when we've tried to clarify that, it's been stated, "Well, the level in the literature, for example, should meet the criteria for drug approval or an NDA." So in other words, there should be multiple trials here.

So that is kind of the regulatory stance on

what available therapy is. It doesn't necessarily have to be approved therapy, but the body of evidence in the literature, in the scientific literature, should meet some expectation where there are multiple trials that one could come into for approval of the drug; so it's not one trial that shows a 10 percent response rate.

DR. WILSON: Dr. Richardson?

DR. RICHARDSON: I was taken by Gary's comment on randomized trials being kind of the default position. And particularly when it comes down to the issue of best supportive care, the field has changed so much over the years, when you think back on the old 5-FU leucovorin studies in colon cancer, when the comparative arm was, in fact, observation, those things would be, I think, difficult to do in today's environment.

I honestly find myself in a real quandary trying to take care of some patients where best supportive care is one of the randomizations, and you're trying to discuss that with a patient who is desperate for some kind of treatment, trying to put

that patient on that type of observation arm gets to be a pretty difficult discussion.

I can give you a good example of kind of a similar situation that we were presented with not long ago, a study that was offered to us looking at an investigational drug in patients who had failed in treatment of their prostate cancer and they had to have failed dosetaxel and prednisone, and the control arm, in fact, was continuing the prednisone. It's a difficult sell in that circumstance when you've got a patient who is looking for something other than what isn't working.

I wonder whether, in fact, we'll end up going back to the old Tom Fleming two-stage stopping rules, where ultimately you end up putting a group of patients on a particular study and, as you say, if you go 3 for 15, it's of interest. If you're 1 for 15, forget it. Maybe that's what we need to go back to.

DR. WILSON: Dr. Smith?

DR. SMITH: Speaking to the pediatric

setting, the interpretation of single-arm studies is as problematic in that setting as it is in the adult setting, and so randomized trials should be the default in the pediatric setting, as well.

A couple of exceptions. The arsenic trioxide is the obvious one that you would think of as saying, obviously, you don't need to randomize when you have something as active as that.

There is one more in the pediatrics arena that I would call attention to, and that's brainstem glioma in the pediatric setting, where in the setting of a national clinical trials group, where there's recent historical experience, the opportunity for patient selection bias is minimal, because most patients will enroll in one of the national group studies; and where the outcome is so reproducibly poor over decades, that would be one case where I think the pediatric oncology community would put forward that a substantial treatment effect could be reliably detected in the absence of the single-arm trial. But there you do have a national group, and you've taken away much

selection bias.

I think in terms of the pediatric setting, a couple of adaptations, and we do randomize trials all the time in the newly diagnosed setting with patient populations that are in the 200-300 nationwide per year, diagnosed per year. And so it's possible to do it with small numbers.

In the relapse setting, it gets even more challenging, though, as was discussed in the morning presentations. And there, I think adaptation, such as reducing the type one error in a randomized trial would -- you need to think about adaptations like that.

A challenge in the pediatric leukemia setting and the relapse setting, again, as discussed this morning, is patients are going to transplant, and so you have to factor in that that's going to happen, as well. And so how are you going to account for that.

There's a case where the intermediate endpoints may be useful to corroborate survival or progression-free survival endpoint after

transplant. But something like minimal residual disease before transplant as a measure of treatment effect could help corroborate outcome after transplant and give more confidence that the treatment that was being investigated was appropriate. But, in general, randomized studies should be to the default in the pediatric setting, as well.

DR. LEWIS: Malcolm, I just wanted to follow-up on that, because we just heard about nelarabine and clofarabine, and we've heard from the COGs that they don't feel they can do randomized studies in these third-line. And then, of course, some of them are following up as transplant.

I can't help but feel that this is kind of the way they do business as opposed to the fact that randomized studies couldn't be done in settings like that. It just seems like if they're not upfront in the pediatric setting, all of the eggs are really being held by the COGs, and FDA has to go along with whatever they say.

DR. SMITH: Right. And I think that makes another point I did want to make, is that in the pediatric setting, whatever plan goes forward, if it's going to be a randomized trial or even a large single-arm trial, it's going to really take most of the patients that are diagnosed over as a several year period. And so it needs to be with the full support of the pediatric research community and that community at the table from the get-go of discussing the research project.

I think large randomized trials with conventional levels of significance that night take five or six years in the relapse setting, I agree with the comments this morning that those may not be something that would be desirable from the pediatric community, but smaller trials, perhaps, again with reduced type I error that could be done more quickly, perhaps could be done.

Relapse trials have been done in solid tumors in the first relapse setting, like neuroblastoma and rabdomiosarcoma. So there is a history of being able to do it, but it does need to

be with the input and buy-in of the pediatric research community, whether it's in the U.S. or Europe or elsewhere.

DR. WILSON: Dr. Mortimer?

DR. MORTIMER: I just wanted to address the comment about best supportive care. Best supportive care is not ignoring somebody or observing them. Best supportive care is providing the psychosocial support, controlling people's symptoms. It is not inactivity. There is activity associated with it, and perhaps this is why those patients live longer, because they have more peace, comfort, and so forth at home rather than being addressed and onslaughted with new agents.

So I think the best supportive care study really is a great option in the randomized trial.

DR. WILSON: Dr. Loehrer?

DR. LOEHRER: Actually, I have two questions. The first one is, are we going to go question number 2?

[Laughter.]

DR. LOEHRER: But before we do, actually,

just to echo what you're saying. I was thinking of a friend of mine who died of breast cancer years ago who needed to get on -- she felt she had to get a bone marrow transplant for her breast cancer, and finally got an attorney to sue to get this to happened. And I think we all felt it was ethical, in fact, morally responsible to get her treated with bone marrow transplant at the time, and, obviously, we were wrong on that.

The point that was brought up earlier about the difference between accelerated approval and provisional approval I think opens up a door that's not asked by all these questions. But when a drug has accelerated approval, it's now many times used off label for many other indications, and there's a lost opportunity to study drugs in a different way. And I brought up the capecitabine as one example. It may be dose and duration. And this expanded access I think gives us the opportunity to -- instead of opening it up for everyone with provisional approval, these are the studies that absolutely need to be done before it is just widely

used.

The difference between the Children's Oncology Group and the adults is that 70 percent of their patients go on clinical trials and 95 percent of the adults don't. And if the drugs were limited to be available for these trials before it got full approval, then it might give us the opportunity to answer these questions and minimize some of the delays in terms of helping other people.

DR. WILSON: So I did want to tell Dr. Loehrer that there is a little rhyme and reason to this first question taking so long, because it really has direct application to 2 and 3. So the longer we spend on 1, the less you have to spend on 2 and 3. So don't despair.

Dr. Kelly?

DR. KELLY: I just want a clarification. In the EMA, do I understand it correctly they only prove, under accelerated approval, only new agents that have not been proved before?

DR. PAZDUR: For new molecular entities.

DR. KELLY: New molecular entities. In the

29 that were approved, how many were new molecular entities versus those that had prior approvals?

DR. PAZDUR: Mr. Number?

DR. MURGO: I do know that there are certain applications that have had multiple indications. So imatinib is one, had four or five; pemetrexed had a couple. So off the top of my head, I would say that the majority are new molecular entities, but there's certainly cases where there are multiple indications that we're counting as approvals in that 27 number.

Give me a moment. I actually have a spreadsheet, and I'll get you that in a second.

DR. WILSON: I also think that, as everything in science, this is going to be a moving target. I think as we do move into prospectively identifying targets, such as alc in lung cancer, that very small studies, one arm being alc positive, the other one being negative, they're not randomized but their molecularly directed studies can probably address some of these questions in a very rigorous way with a very small number of

folks.

Rick, I wanted your thoughts on that, because I do think that we're going to see -- hopefully, we're going to see more therapies that really are hitting targets. And so the nature of these - they won't be randomized studies, but they'll be molecularly directed studies.

DR. PAZDUR: Here, again, I totally agree with you. I think you know everything is effect size, and it's much different when we're talking about a response rate, somebody coming in with a response rate of 15 percent versus somebody coming in with response rate of 60 percent in a refractory disease setting or a therapy that has marginal therapies available to it.

But it's very hard to recognize that early on in the drug development scheme. And here, again, what do we really get out of doing a 200-patient single-arm trial? Would it not be better very early on to start the randomized trial, looking at a big effect size, answering a survival question, because here, again, once you deem that

as the drug in a particular disease, it's going to be very difficult to go back and do randomized studies. I'm not talking about large randomized studies; I'm talking about small studies with big effect size.

We've been -- I'll be quite honest with you -- been somewhat disappointed with some of these trials that have claimed big effect size or promoting themselves as very effective therapies, and then when the randomized trials were being done, they were looking at conventional improvements in overall survival of one or two months and be powered for such. You can't have your cake and eat it. So either you have an effective drug, and let's take a look at it and develop it appropriately.

DR. WILSON: Yes, Dr. Martino?

DR. MARTINO: Rick, it occurs to me that the one thing that I got out of the presentation from the European system is this concept of knowing that there is a very specific timeline when you are meeting with me again, and it's a year from now;

not two or three years or when we get around to you. And I wonder if that alone doesn't give one the opportunity to evaluate these issues. And maybe that's' really the key here is to have that

DR. PAZDUR: I'm glad you brought that up, Silvana.

DR. MARTINO: I'm glad you're glad.

DR. PAZDUR: That's why we plan on having this meeting on a yearly basis and to go over these trials. There's nothing like the light of day that brings people to contrition, so to speak. And we've seen several sponsors come up to the table when we announce this meeting and say, "We really don't want to attend this meeting. We're going to consider withdrawing our drug."

DR. MURGO: So it's just 21 out of 27 are new molecular entities.

DR. WILSON: So anymore discussion on this? If you raise your hand, Dr. Loehrer is going to hit you.

[Laughter]

DR. WILSON: Kidding.

Anything more?

[No response.]

DR. WILSON: Okay. So let me just kind of give my own phrasing of this question, then I'd like to have you go around the room and give us in a very tight, short statement how you would view it.

I think the issue here, obviously, is that when should single-arm trials be considered to be acceptable for accelerated approval. We've already heard that 58 percent of accelerated approvals up to this point have been based on single-arm trials. And so the implication is that perhaps we would like to see this less.

The other side of it is that if we start to require randomized studies for approval, then it's going to also take longer to get the drugs to patients. And the accelerated approval was set up in order to be, as Dr. Pazdur said, patient-friendly, so there is a balancing act here.

So I don't know. Dr. Curt, do you want to start?

DR. CURT: Yes. I think the accelerated approval process has been a success, as well, and I think the evidence says that's been an equal success for the drugs that received accelerated approval with the single-arm trials versus randomized trials. But I would agree with the committee that single-arm trials are done at your own risk and should be done either in very rare diseases or areas of significant unmet medical need.

DR. MARTINO: I think a single-arm trial, for me, would be acceptable for accelerated --

DR. WILSON: Can I stop you? Can everyone say their name first and then -- sorry.

DR. MARTINO: Silvana Martino. I think that, for me, a single-arm trial would only be acceptable for accelerated approval as an exception in circumstances where the patients are few and the activity of the drug is considerable. Unless both of those are met, for me, it would not be acceptable.

DR. RICHARDSON: Ron Richardson. I like

Dr. Martino's comment. On the other hand, I think that one can make a strong case for approval of a single-arm study even in diseases that are very common, such as, say, non-small cell lung cancer, if you demonstrate activity above a certain threshold. And how high you set that threshold I think is going to depend on your patient population, the kinds of toxicities that these kinds of treatments entail, as well.

Looking at the issue, again, of randomized using the comparator arm, I think that remains a problem, and that also gets back to the patient population that you're looking at. If you're looking at patients with refractory disease, I would agree that -- in spite of my comments, I think there still is a role for best supportive care in that population.

DR. MORTIMER: Joanne Mortimer. I think the only indication I would have for a single-arm study is an agent that has incredibly high efficacy.

DR. LYMAN: Gary Lyman. I agree randomized trials should be the standard. The exception

should be limited to rare disease situations, situations where the treatment effect is quite pronounced and/or the balance of risk and benefit clearly suggests a beneficial effect compared to risk. I think part of that is the durability of the response, so a strong treatment effect and evidence for quite a durable response. These might prompt a single-arm study for approval.

DR. D'AGOSTINO: Ralph D'Agostino. Given the discussion, there seems to be the real possibility in a lot of these situations of running a randomized trial, and I think that should be the first item on the table in terms of putting these together. There are situations, however, where a single-arm study might be necessary and certainly warranted, things like orphan drug situations, very rare conditions.

But I think in those situations when you're doing that, you have to ask the question, how do I interpret this single-arm study and how do I link that single-arm study to the confirmatory aspect later on where I'm dealing with a real clinical

endpoint. So it's a big drug development program, I think, that has to be attached to a single-arm study. It also has to be attached even to a randomized trial, but in particular, the single-arm study, I think it just can't run by itself. You have to have it in this clinical drug development setting.

DR. LOGAN: Brent Logan. I share Dr. D'Agostino's concerns that it's crucial at the single-arm trial to be able to interpret the outcome that's being collected. So I think in many settings, that that is very difficult. So the default should often be a randomized trial, with certain exceptions that have been raised before, rare diseases, where there's substantial activity, as well as reasonable toxicity.

DR. FREEDMAN: Ralph Freedman. I guess there's less and less for me to say at this point. Clearly, there needs to be quality associated with those surrogate endpoints, and people can reasonably agree that a single-arm study is appropriate in that circumstance. But it's going

to be unusual. And I think that the track record that you have over this period, obviously, the agency has been learning since accelerated reviews were introduced, and one would expect the number of single trials to reduce with time.

DR. SEKERES: Mikkael Sekeres. I echo what that side of the table has already said. There's a role for single-arm studies in extraordinarily rare populations where there is an extraordinarily large benefit, but only when it's been negotiated that the post-marketing study is going to enroll a much larger patient population, where there will be longer-term follow-up, and that that study be completed in a timely manner.

DR. WILSON: I think we all agree that randomized studies are the way to go. I have to say that I'm a little bit conflicted by this question, because I'm thinking why is accelerated approval there, and we've heard why. We then heard the data, and we've heard that the vast majority of single-arm trials have been approved, and they've been approved with randomized studies. And many of

the single-arm studies didn't -- in some cases we've seen here, the activity wasn't that great.

So I'm not really sure of the issue. I'm not sure what the issue really is here. I myself share the concern that's been voiced here and that is that we are seeing many, many drugs with extremely marginal activity getting approved, because they prolonged survival six weeks. To me, that is a bigger issue than this.

One thing that does concern me about having the bar for single-arm trials too high and to be rigid about it is that you have small companies out there that may be developing very targeted therapies, that might have some very interesting activity, but if you start to say you need a randomized study, these drugs may simply die. And I don't know how you walk that line.

In no way would I want to open the gates or lower the bar to prevent drugs from moving forward, but at the same time, I think it's a very difficult call. And I think that one can say, yes, it's got to be a very small population. I think response

rates need to be very high, but we're seeing single-arm trials that our response rates aren't high, and they're being approved through randomized study that we don't see very much either. However, they're being approved because they prolong survival six weeks, or maybe in some cases haven't even been able to show any prolongation.

So I guess the longer you talk, the more it means you really aren't sure. But 58 percent sounds like a very high number, so I would say that they should probably shore it up.

DR. LOEHRER: Just as a point of order, there's no question mark on this statement whatsoever, so I'm not sure where the question is. So I, like the rest of you, will just ramble on.

[Laughter.]

DR. LOEHRER: So , again, obviously, we all believe in randomized trials, and I think one of the aspects of the importance of randomized trial is the safety part; how do you judge the standard care versus a new treatment. So there's the efficacy and whether or not you have a response

rate, but the other one is how toxic is it and you need to have that comparison.

I do think it behooves the FDA to come up with, if they can, a better working diagram of a rare disease and what the number of patients should be that would fit this. My fear, again, dealing with a number of different rare diseases, is that industry will abandon rare diseases and not study them because it's not going to be fruitful.

So I think if one is transparent on this process, and whether it's 500 patients, a thousand patients, whatever it is, it would be helpful to have this generally as benchmarks for what we would really call a rare disease. And for those, I do think that we need to be sensitive to doing single-arm trials.

DR. KELLY: William Kelly. Again, I think that there is a role for single-arm trials, but it has to be part of a good, well thought out drug development plan. And I think that's what the agency is really saying, what is the whole overall plan for development here so it's continuous.

I think that -- again, I agree with Pat -- it is that we have to define what rare populations are. You can redefine that in multiple ways, but I think that going forward we have to do that. But we also have to define what is a significant treatment effect. I can pick up the Wall Street Journal or New York Times and say brand new drug, fantastic results, and keep on reading; 12 percent response rate. You know? So I think that we have to be able to define what we really mean as significant treatment effect for these type trials. Thanks.

MS. MASON: Virginia Mason. I'm not sure I can add a lot to what's been said. But I do appreciate that the current system seems like it's -- we're moving even to be more dynamic and allow for flexibility, and I appreciate that, as a patient myself and representing the patient population. And I would hope that with this annual review, it will help us to move further and further toward looking at what really constitutes good evidence to move things forward.

So I agree. I still think there's a role for some single-arm trials, but clearly a randomized larger trial has real benefit to giving us more information.

MS. MAYER: Musa Mayer. I think if what we're looking for is strong, durable responses, another way of approaching that, perhaps even with the agents that we've seen so far, is through doing the biomarker research to select the responders so that we have predictive biomarkers developed with therapeutic agents. That simple thing may change the dynamic in such a way that we may need fewer randomized trials. I don't know. That's a sort of unexplored territory, but at least a possibility.

In breast cancer, which I represent, we certainly have seen a strong effect of co-development of biomarkers and drugs, and I'd like to see that happen in all cancers, and see no reason why that couldn't happen if the will is there. And I think the will could be there if we provide the incentives and restrict single-arm trials to very exceptional situations.

DR. SMITH: Malcolm Smith. Moving forward in the pediatric setting, I think the standard should be randomized trials for accelerated approval, and that the response to modest response rates in a single-arm trial isn't accelerated approval, but further research to see how the agent fits into the overall treatment paradigm for that particular childhood cancer.

I think there does need to be some accommodations in terms of study design and study endpoints to take into account the smaller patient sample sizes that will be available in some of the pediatric settings. But with that flexibility, that would be the general gold standard.

Finally, that all of this would need to be done in the context of discussions with the pediatric research community to really make sure this is a priority and the thing that would best serve a particular patient population for which it's being considered.

DR. BALIS: Frank Balis. I think that what we're really talking about, in some sense here, is

the level of evidence required for accelerated approval. And I think when we make that consideration, it needs to go, at this point, beyond just considering what demonstration of benefit to the patient there is.

For example, in addition to probably having a better idea about benefit from a randomized study, I think we can learn more about toxicity from a randomized study. When we have a control arm to compare to, we have a much better idea of what the incidence and what are real side effects of a drug compared to what we get from a single agent study, where we're obliged to report anything serious that happens, related or unrelated.

Then the other thing I brought up earlier is the impact it's going to have on the development of the drug itself, and that is potentially a negative one. But on the other side, what effect does it have on people making the decision to approve a drug knowing that it just got accelerated approval. Is that somehow impacting on the decisions that are being made at the point in time that we are

looking -- although we think we're objective, that we're looking at the definitive studies.

So I think there are a number of factors to be considered, and, because of that, I think we need to have, at this point, until we know more about this process, a pretty high bar for what we use to determine if a drug should have accelerated approval.

DR. WILSON: Thank you very much. So why don't we move on to the second question?

DR. KLUETZ: With respect to the number of confirmatory trials, the time from either successful completion of a required post-marketing study or withdrawal of the indication can be prolonged. For drug approval in most therapeutic areas outside of oncology, two well designed randomized trials are usually required.

In oncology, the FDA has frequently approved drugs on the basis of a single well conducted trial, and the FDA usually receives proposals for a single trial to be conducted post-approval to demonstrate clinical benefit for drugs that have

received accelerated approval.

In the setting of accelerated approval when only one confirmatory post-marketing trial is conducted, there is the increased risk that clinical benefit will not be demonstrated in a timely manner if that single trial fails to confirm a benefit or doesn't accrue patients as rapidly as planned, and this may lead to either withdrawal of the indication or the need to conduct a second trial, resulting in substantial delays.

So discuss whether applicants should be required to conduct at least two adequate and well controlled clinical trials as their accelerated approval commitment to verify clinical benefit.

DR. WILSON: So maybe the agency can put this into perspective for us. For full approval, it's usually two randomized studies.

DR. PAZDUR: No.

DR. WILSON: I'm just talking about new.

DR. PAZDUR: Most other therapeutic areas -- I want to make people understand this. Most other therapeutic areas in the FDA have required two

randomized trials. We in oncology, for many reasons, have accepted one randomized trial or one pivotal trial for drug approval, for full approval or accelerated approval; they're both approvals.

What we're asking here is, given the issues here of the uncertainty of confirming clinical benefit, would it be better to have two trials ongoing rather than relying simply on one.

Remember also that these can be done in a slightly different setting, and we allowed this. This could actually lead to supplemental indications for a new indication in addition to fulfilling their subpart H or subpart E commitments. So in a sense, it's a twofer. You're getting additional benefit, you're not just dotting the I and crossing the T on a regulatory issue here. You could actually be proceeding with developing your drug further.

DR. WILSON: So I want to put this into the context of what type of trial you did to gain accelerated approval. If you did a single-arm trial, that would be one context. But if you did a

randomized study, I suppose that randomized study couldn't be a knock-down, drag-out pivotal trial; otherwise, you would get full approval.

Do you distinguish between those two with regard to whether or not you would have two randomized studies in the post-marketing?

DR. PAZDUR: We could. We're taking a look at the total body of evidence. What we're trying to suggest here is rather than just negotiating a single study here, would it not be better to have an array of studies. If you have a commitment to the drug, you're obviously developing the drug in the disease, and would it not be better to have a discussion of various studies ongoing rather than just a single study?

DR. MURGO: Not to put the eggs in one basket.

DR. WILSON: No, I realize that. I'm just trying to put this in the context of full approval with one randomized study versus accelerated approval with perhaps three randomized studies. That's all.

DR. PAZDUR: Here, again, you're getting other indications potentially, too, and there is a risk here that we do not have with the full approval.

DR. WILSON: Right. Absolutely.

Yes, Dr. Martino?

DR. MARTINO: I'm reminded of several therapies in breast cancer, where there's lots of patients, as you know, around the world. Probably the drug that most comes to mind is the drug Zometa, that some of you know. It's a bisphosphonate. There have been at least five well recognized trials all in the adjuvant setting, all trying to ask the question of does a bisphosphonate either reduce bone metastases or improve survival in breast cancer, at least five good trials.

We still don't have an answer to that question. Why is that? Well, the first trial suggested that you reduced metastases to bone, you reduced metastases to everything else, and you improved survival -- German trial. You just turned the page over practically.

Another trial from, again, Europe, showing exactly the opposite, not less bone metastases, more other metastases, and a poorer survival.

Third trial from England; maybe you improved bone metastases in post-menopausal women; a survival difference only at one time point, 10 years. Confusing, isn't it?

A year or two ago, we got another wonderful trial in pre-menopausal women who were placed on hormonal therapy that suggested absolutely you improved survival in these women. Well, a few months, at San Antonio, we got another very well done trial that showed two curves, completely super-imposable.

So I'm just reminding you that sometimes even five well done, large adjuvant trials seem confusing, so wherein lies the biological truth? So, for me, to think that anything short of two would be acceptable is to be ignorant.

DR. WILSON: But one is used for full approval. That's the only thing I'm trying to get at.

DR. MARTINO: And I'm still using the word ignorant to when that has been accepted. I'm not changing my thoughts on this issue.

DR. WILSON: Dr. D'Agostino?

DR. D'AGOSTINO: It appears to me that in the discussion, that there are two issues going around here. One is, is the drug really effective and do you need more than one trial to do it. And I think of the accelerated approval, given it's on a surrogate variable and so forth, it wouldn't be hard to or inconceivable to ask for two pivotal trials, with a solid clinical endpoint and have them designed early.

But it seems like the real issue, to me, from hearing the discussions this morning, is that when you design one trial and it doesn't work, then you drag the thing out. Then you design another trial, and six years later, you don't have anything going.

So I think we have two things we're talking about. One is how much evidence do we need to believe the drug is worthy, but, also, these are

going to be hard trials to put together, and there's a good likelihood they're going to fail, and we saw that this morning, and they drag out.

So in the case of having the two pivotal trials being put forth, two clinical trials being put forth, the agency would have the flexibility of saying, "Well, this was a very hard trial, but this other trial was just overwhelming in terms of what's happening," and they'd be able to get on to a decision in a timely manner. I think the dragging out is really a serious issue with what we've seen here.

DR. WILSON: So I think Dr. Pazdur, to me, said it well, and that is it's all based on the totality of evidence. And I think that if your accelerated approval is based on a study, be it single-arm or randomized, it has a very high signal, then I think that one could, with good likelihood, assuming it was a well done trial done in a proper manner, go with the single trial.

I think the problem with the Zometa is probably -- and I don't know the breast cancer

literature, but I suspect the effects were relatively modest.

DR. MARTINO: No. They had survival advantage, Doctor, and it was actually two bisphosphonates. So, again, adding to the confusion of the whole field.

DR. WILSON: A survival advantage does not necessarily have to be a large amount. It could be -- if you had enough patients, it could be one hour.

DR. MARTINO: But it is what we accept as the standard. When you show me that there's a survival advantage, that's what we consider the highest level of proof. I'm sorry, Doctor, that's the way we look at things. I agree with you on a clinical basis.

DR. WILSON: Right.

DR. MARTINO: But on an approval basis, that's how we think.

DR. WILSON: No. But what I'm trying to say is that the level of evidence would depend on how big the signal is. Having a statistically positive

survival advantage is not necessarily a big signal, and that's all the point I'm making.

So I'm trying to get at what the FDA is asking for, and that is that should there be just a carte blanche, a guidance that we need two clinical trials, two randomized studies. I'm trying to give some nuance to this, and that is that there may be settings in which one randomized study well done may be adequate if the signals are very great.

If there is an eight-month survival advantage, I'm going to put a lot more confidence in that than if there is a four-week survival advantage, even though they both may have good hazard ratios and p-values.

Dr. Pazdur, I don't know if you want to comment on that.

DR. PAZDUR: I guess the issue, it's kind of what Ralph brought up, is this sequential look versus having a body of evidence there in a timely fashion. And here, again, you don't know what the results of the trial are going to be, the second confirmatory trial. Obviously, if it shows a

strong survival advantage, everyone would walk away happy, but you don't know that when you're negotiating these up front.

So what we're discussing here is kind of risk minimization, to have multiple trials or at least two trials that are ongoing. It's the whole concept of robustness of the clinical data package, and one of the areas of robustness is, obviously, the statistical persuasiveness, but also replication of a trial.

We see that in other therapeutic areas. And what we're asking for is, given the uncertainty of the drug approval process rather than of the accelerated approval, the inherent uncertainty, would it not be better to have two trials to lead to a robust finding at the end?

DR. WILSON: Dr. Lyman?

DR. LYMAN: And I think the key here is exactly that, that confirmatory, because in many circumstances, two trials may not be enough to grant it if there are inconsistencies or, as we had recently, an example where a pivotal trial looked

very impressive and then two additional trials came along with much more modest effects, so, in essence, not confirming the magnitude or durability of the effect.

So it's not just the fact that maybe, in most circumstances, two randomized trials should be done, but there should be consistency. But I think what Dr. Wilson was suggesting was maybe this has to be somewhat tailored to what the nature of the trial is in the accelerated approval phase. If it has been a well done randomized, controlled trial, perhaps one more trial, consistent trial, would be sufficient. If it was a single-arm study and wasn't in the exceptional categories of rarity and so forth that would prevent randomized trials, I think we'd all be much more comfortable with at least two or whole packages, as Dr. Pazdur suggests, indicating a commitment to really get to the bottom of the totality of efficacy versus safety.

DR. PAZDUR: There have been examples of very, very well developed drug development programs

that all of the trials are negative, and it provided a great deal of confidence at least that we could say at that point that there is no way to go with this drug or where to go with this drug.

The issue is one of a data package to deal with the uncertainty, and I think you're right, Wyndham, in saying what is the initial approval data package and then go from there. But if you're especially dealing with an area where there might be greater uncertainty, one could take a look at -- one should really demand multiple trials to be done here.

DR. WILSON: So that's the exact point. I think that if the data package upfront is not really robust, the uncertainty goes up. And then, absolutely, I think if you do one trial and then you may have to do another, et cetera. So exactly right.

Dr. Kelly?

DR. KELLY: I think the question is quality or quantity here. I think there are financial constraints on the companies, too. And to have a

small biotech company do two or three trials is really unrealistic. So are they better off to put more of the money into a better quality trial that's one well controlled trial with all the bells and whistles you need into it to answer all the trials versus two?

We saw some examples today where, if we had all the right things in the trial, it would have answered a lot of the questions for us. So you have to balance do you do one well conducted trial versus two, well, not so much and we'll cut some corners, and that's what you see a lot. So we have to weigh those two.

DR. PAZDUR: If I could address that issue, I really want the committee to understand. We do not have different standards for small biotech companies, large biotech companies, large pharma, et cetera. We have one uniform standard, and we don't really get into what the economic underpinnings of any company are. Remember, these could be changed in a moment by mergers, acquisitions, et cetera. And, really, if you take

a look at many of the actual presentations that were done in the morning, many of the initial sponsors were not the sponsors that were standing up in front of you.

So the fortunes of these companies can change dramatically and, really, when companies come with these arguments to us, we really have to put them aside. We have to have one uniform standard in dealing with any pharmaceutical firm, sponsor, et cetera.

DR. WILSON: Dr. Sekeres?

DR. SEKERES: I think one of the best arguments for having two studies is really the mechanistic argument that things happen that one may not accrue and another may accrue, and you want some kind of answer eventually.

You could say to a company, based on a good package, gee, you have such a great effect size, why don't you just do one study? I think that becomes challenging, though, because things can change. New markers can be discovered where they'll have to define a different population, or

now that the drug is available, people won't enroll on that study. I think you're safer with two studies.

Just speaking to the point you made, also, about all the randomized studies that have been performed on one drug that are all over the map, in science, in general, the more times you investigate something exactly the same way, your effect size will diminish. And that may be a quirk of statistics, that you're just regressing to the mean the more times you look at it, also. So validating your efficacy actually doesn't resonate with me as much as just mechanistically trying to do the confirmatory study and get it done efficiently.

DR. MARTINO: May I respond to that? I take your point and, yes, sometimes that's true, especially when you're using small samples. However, when we planned the Herceptin trials in this country, we very -- and Herceptin turned out to be a good drug, as I trust you all know -- we programmed that whole experience so that we would have more than one trial. And so we were very

thoughtful to start with in the sense that we -- NSABP did a trial, the rest of the intergroup did another trial. The Europeans were planning another trial. So we were preparing to answer the question in a serious way by having various trials look at the issue. Because that turned out to be a good drug -- the trials have been positive.

So, yes, mathematically, I do understand and I agree with your concept, but I think when you have a really good drug, the biology repeats itself over and over. The problem is when you have drugs with limited ability, where I think you're much more likely to see these opposing results, which is the problem that I have with this whole field.

DR. PAZDUR: And I think we're actually agreeing. I think that's even more justification to have two studies.

Speaking to the point that Dr. Kelly made earlier, if you're a small biotech company and you have a drug that is just fantastic, people will want to give you money to do these studies. If you have a drug with a marginal benefit, it's going to

be a lot harder to get those studies done, and maybe that, in and of itself, is a signal.

DR. WILSON: I also think we can't lose sight of the fact that there are rare disease settings where doing two large randomized studies is simply not practical. So I think we have to understand that the ideal is always to do two, three, four, five maybe, but I think that there are going to be caveats. So what I think is important for the FDA to hear is where.

Maybe rephrase the question, in what settings shouldn't two randomized studies be done? That might be more helpful to them. We all assume that it's best to do two, and the real issue then being where do we deviate from that.

Ms. Mayer?

MS. MAYER: The example that Dr. Lyman gave involved studies that were based on progression-free survival, not overall survival. And I think it's important to look at how meaningful the endpoints are regardless of subsequent confounding therapies.

The fact that there was a relatively large effect for a new drug that worked in a novel way got everybody excited, and the fact that that wasn't confirmed in subsequent studies, the magnitude of the effect, and there was no overall survival advantage, was really useful information to have, because it took out -- we had three well conducted or relatively well conducted randomized trials, and that had the effect of taking the variability out of it. You could really trust that what you were seeing was real. You can't always make sense of why that would be true. But I think it's important, also, to take into account the endpoints that are used and to make sure we're not prematurely adopting endpoints that may or may not have clinical meaning, especially in the absence of really well done quality of life studies, which are often difficult.

DR. WILSON: Dr. Balis?

DR. BALIS: I was going to say the same thing you did about not being definitive about two studies, because there are many cases where two

studies will never get done and they certainly won't get done simultaneously.

The other point I wanted to make is that I think one of the other issues to consider is the study population. When looking at the study that's being proposed, if a highly selected population is going to be studied to maximize the potential to see benefit or like a proof of principal study, that's different than a very generalizable population that you can say this drug can benefit the maximum number of patients with a disease.

So I think, from my perspective, if it was more towards the latter, it would make more sense to use a single study to confirm that rather than using a highly selected population to base the approval on.

I had one other question. I'm sorry. What I don't understand is what the outcome is of two studies and how that's used. So there may be three possible outcomes; one, they're both negative; one, they're both positive; but one where one is positive and one is negative. And so what happens

under those three circumstances?

DR. PAZDUR: What we're looking for is robustness. This is an issue of is the finding true or not. And when you have duplication or replication of a finding from a statistical point of view, you have greater confidence that you're dealing with a true finding here. So if both of them are positive, I'm happy. This is a real effect that we're seeing. It's been duplicated here. It adds to this issue of a robust statistical finding.

If both of them are negative, likewise, I think we could say lightning doesn't strike twice, so to speak. So the issue is one that I think is robustness. If they're one negative and one positive, then you're in a no man's land. It probably points to the fact that you're dealing with an iffy finding here.

DR. WILSON: Dr. Smith?

DR. SMITH: I was just going to make the point that in the pediatric setting, we can't do two randomized Phase 2 trials, and so that would be

one exception to the desire to do two randomized trials.

DR. WILSON: I do want to remind some of our colleagues here that they deal with diseases that are the most common cancers out there. Many of us deal with much more rare diseases.

Dr. Freedman?

DR. FREEDMAN: I think the basic principal is flexibility, because there are so many different situations that may apply and, obviously, you're going to look at the data that you have available. And I think the other aspect is the size of the population, which is obvious. But the other thing is what is the likelihood that the indications will be expanded for a particular disease entity. In other words, what is available for the other situations within a condition, currently available, is it practical to expand the number of trials to include those or not? And I think all of these things need to be taken into consideration.

DR. WILSON: Any other discussion on this?

[No response.]

DR. WILSON: Okay. So I think that what the FDA is asking us for is our thoughts on whether or not following a single trial for accelerated approval, whether or not the default should be two randomized studies, at least two randomized studies, and, if not, perhaps you could give some settings. And I also want to remind myself that you should identify yourself before you speak, because I didn't do that.

Let me start with Dr. -- no, let me not do that. Let me start over here with Dr. Balis.

DR. BALIS: Frank Balis. I think I would say it shouldn't be required, obviously, because of what I do. And I agree with Malcolm completely that there are many circumstances where it's not possible. And considering that two out of the three outcomes are bad when you do two studies, whereas only one out of two is bad when you do two or a single one, I think there has to be some pretty careful consideration in terms of which is best for a particular drug and how you're going to design those trials. So I think it really is drug-

specific in terms of how it's developed.

DR. SMITH: Again, in the pediatric setting, we can't do it. I think in this context of accelerated approval, the point made earlier was that if you do two studies or if you have two studies going, it avoids the we did one study and now we're starting another study, and this interminable accelerated approval purgatory process that you would be in. So that's an argument in favor for having two studies, but I think it is context-dependent.

MS. MAYER: Musa Mayer. I'll keep it short. If possible, yes.

MS. MASON: Virginia Mason. I circled the word "required" on my page just to remind me that I would not like to see the word "required" in there. But clearly, if it's necessary, you want to do whatever is required to get what's needed to provide that information for clinical benefit.

DR. KELLY: William Kelly. I like the term "robustness" that Dr. Pazdur used, and I think that's what we have to see. It's just that we have

to have robust results. And I think one well, robust randomized trial may show that, but, unfortunately, most of our drugs have really little treatment effect, and you're probably going to need confirmatory trials, probably more, but at least two, to really show that robustness.

DR. LOEHRER: This is Pat Loehrer. I like it. I think we ought to add a minimum. I think this ought to be the standard for the majority of the trials they do. I think there is the exception part, which is part of the EMA, which I like, and so for pediatric trials and rare diseases. But I think the standard for common diseases ought to be at least two.

I think, again, from my perspective, I think if we just replicated the same study again in another cooperative group, I think that's doomed to failure. But I do like the concept of using this as an opportunity for us to define dosages and schedules and patient populations, so that it would help us down the road in terms of looking at the activity of the drugs.

DR. WILSON: Wyndham Wilson. I, too, think that two studies at least ought to be done. I think that that should be the standard for diseases that are common and where we're looking at large populations. I do think there will be exceptions to that, rare diseases, perhaps some other niche areas where the primary trial is randomized with a very high positive signal, and there might be compelling reasons not to do two studies. But I think for common tumors, for all the reasons, scheduling, toxicity, et cetera, that two randomized trials at least ought to be a standard.

DR. SEKERES: Mikkael Sekeres. I agree with Dr. Wilson. Ideally, two trials should be mandatory and they should have solid endpoints, such as survival and not rely on interim endpoints that may have been used for the initial approval. The exceptions should be rare diseases or populations where it would be impossible to conduct two randomized studies.

DR. FREEDMAN: Ralph Freedman. I'd say two, if the first one is the completion of the

accelerated trial as an endpoint, such as overall survival. But going beyond that, I think the agency needs to have the flexibility with the sponsor and discuss the relative needs for that particular disease entity and what else is available.

DR. LOGAN: Brent Logan. I think not having a well thought out development program where you do one trial and another if that fails and keep going certainly can dramatically slow down the approval process, the regular approval process.

Having two well defined trials which are part of a reasonable, well thought out development program, which are designated up front, can help mitigate the risk, as has been discussed here; in particular, the risk of doing randomized trials in somewhat different populations from the original accelerated approval, as well as the difficulty that you might have in accruing and can help prevent the regular approval from being delayed.

It also, obviously, could help with the robustness of the finding. And, in particular,

that can help overcome potential concerns that there may be about the study design; for example, assessment of the outcome, lack of blinding, things like that. If you have reproducible results over multiple trial, that can help overcome those kinds of concerns.

DR. D'AGOSTINO: Ralph D'Agostino. I said a number of things earlier, and the panel has also said some things which I completely agree with.

So my focus is solely on the -- I think the two trials is a very useful idea. I think of it -- I'm driven by the fact that we want to make a decision on these drugs, and if you drag it out, one trial fails, you follow with another, you could go on for years, as we've seen, and not have a decision.

So requiring two trials or at least asking for two trials, under most circumstances, gives us the possibility of getting the data, seeing if it does, in fact, reproduce and that you do have robustness, and also putting us in a situation of making decisions in a timely manner about these

particular drugs.

DR. LYMAN: Gary Lyman. I agree. I think that two well designed, randomized trials should be the default position, with the exceptions that we've discussed, many of them the same as the single-arm study for the accelerated approval.

I think, also, again, the effect should be clinically relevant. It should be both clinically significant as well as statistically significant, and I think needs to -- the consistency between those studies applies to both the treatment effect as well as the safety profile that's observed in those drugs.

DR. MORTIMER: Joanne Mortimer. I agree with it as written, at least two adequate and well controlled trials.

DR. RICHARDSON: Ron Richardson. I agree with Dr. Lyman. I think having two trials requires consistent, reproducible demonstration of efficacy, whatever the endpoint.

DR. MARTINO: Silvana Martino. Again, I feel that two should be the minimum requirement,

with exceptions, as have been noted by the committee. And for me personally, I actually wouldn't mind of if those two well done trials were simply the same trial done in two separate groups of human beings. I would consider that good enough evidence if they both were unanimous in their conclusion.

With this, I apologize to all of you, but Dr. Mortimer and I have to leave to catch our plane. So that's that.

DR. CURT: Greg Curt. I think it really depends on the details, the target population, the magnitude of the effect, as other people have said.

I think most sponsors will undertake two or more trials of an approved agent, just as part of lifecycle management. But I'll caution that the biology of antibody monotherapy in the setting of chemo-resistant colorectal cancer may be a very different thing from chemo immunotherapy in first or second line disease or adjuvant treatment. So it really does depend on the details of the individual trials.

DR. WILSON: Thank you. I was hoping that maybe we would decide not to take a break and go through. I think that we're on the homestretch here.

So, Paul, do you want to go ahead and give us number 3?

DR. KLUETZ: With respect to the timing of confirmatory trials, accelerated approval regulations clearly state that post-marketing trials would usually be underway at the time of accelerated approval. Once a drug gains accelerated approval in a refractory disease stage, accrual to a confirmatory trial in the same setting is difficult.

Pursuing a confirmatory trial in a less refractory setting can potentially circumvent this problem. However, changes in science, accrual challenges, and other hurdles may lead to delays. The FDA believes that more timely completion of accelerated approval confirmatory trials can be enhanced if accelerated approval is granted when the confirmatory trial is ongoing.

Given the regulations state that confirmatory trials would usually be underway at the time of accelerated approval, discuss whether an approval should be delayed until such trials are ongoing, keeping in mind that access to drugs could be accomplished under expanded access programs if delay is anticipated.

DR. WILSON: So, to me, this is one of the most critical questions, and I think that it really gets at a compromise. I think that when we see accelerated approval without these trials being planned, we can sometimes run into problems with accrual, et cetera.

So, to me, accelerated approval is to be patient-friendly, but it's also not to undermine the ability to get good, clean data. So I personally feel that this should be a standard; that there should be a plan, and these randomized studies ought to be underway before accelerated approval is given, because I think otherwise we've already seen some of the issues that have been raised.

DR. PAZDUR: Well, here, again, I think this requires planning on the part of the sponsor, and we've seen cases where this planning has not been there, that they want to start discussing accelerated approval confirmation studies after the drug is approved or during the review process of the NDA or the BLA.

Frequently, also, there might be a step before you even begin this trial. For example, if you know the drug in the confirmatory trials has to be started, used in combination, you need to start doing these Phase 1 studies of the combination relatively early, before you begin the Phase 3 studies. One of the drugs that was removed this year had a Phase 1 study that was initiated after the drug was approved, and it took 10 years, basically, here to evaluate the completeness of the data package.

So what we're really asking for, again, not to harp on it, but a comprehensive drug development plan that is well thought out. It's not just a single study. I don't care if it's randomized; I

don't care if it's a single-arm trial. I'm talking about not just a single study; it's a drug development plan that has to be thought out on where you're going in which diseases in a timely fashion, and that's what, basically, we're asking for.

These studies should be discussed with the agency long before the NDA is submitted. We're emphasizing that to the sponsors now in our end of Phase 2 meetings and our special protocol assessments. And here, again, I think some sponsors are clearly hearing this message, but there are others that do not, obviously, and that's why we're in this situation.

DR. WILSON: Dr. Lyman?

DR. LYMAN: I think Dr. Pazdur just said it all. It is the whole package, a concerted effort to develop the drug and in a definitive fashion. So I think of this, again, as a default or standard approach; that the sponsor would be expected to have not only designed the trials, but have them ongoing.

I think I might make an exception if the studies are at a very advanced phase of planning, if sites are being identified, the protocol is done and been approved or going through approval. What you want to show is a commitment to move this forward in an expeditious fashion to satisfy the requirements for full approval.

DR. WILSON: I think it's hard to imagine a setting where they shouldn't have this all planned out. I mean, to me, it should be planned out and maybe if it's in the very advanced stages of getting the protocols approved, but to get a single-arm trial approved and say, oh, well, we'll discuss what we're going to do later on, I just think it is undermining the safety of the entire approval process.

Dr. Sekeres?

DR. SEKERES: I think there are two reasons to encourage companies to have post-marketing trials underway at the time of accelerated approval. The first is it will incentivize them like nothing else to actually start that post-

marketing trial and get it done quickly. The second is that it will discourage a swing for the fences approach to regulatory approval, where you just hope for the homerun and don't plan things out in a little more regular way.

DR. WILSON: Dr. D'Agostino?

DR. D'AGOSTINO: Everyone has said the same thing that I would say. The comment I want to make is the way the question is worded, should the approval be delayed until such trials are ongoing, you don't want to get to that stage. You don't want to get to that stage; you want to get to the stage when you're talking about what trials you're going to do. And the first trial, the accelerated approval trial, plus the later confirmatory trial are all put together at the same time. It's not that later on they come and you punish them for not doing that.

DR. PAZDUR: Well, the question is should the application even be filed until we have these trials.

DR. D'AGOSTINO: That I would say yes,

absolutely shouldn't be filed until the whole package is put together.

DR. WILSON: Dr. Kelly?

DR. KELLY: I agree with everybody here; they absolutely should be ongoing. The only exception I have is in the pediatric population. That might be a little more difficult because you have to negotiate with multiple groups, and that's the only exception.

DR. PAZDUR: We've heard that repeatedly, and we do have a different mechanism here really for peds, with a pediatric subcommittee of this committee, et cetera.

DR. WILSON: Dr. Smith?

DR. SMITH: I would just respond to that that, in general, though, there should be a clear pathway, even in pediatrics, that is clear what the pathway is. For example, most agents would be developed in combination regimens in pediatrics. And so going forward, you would want to see that the combination regimen that you want to move into a Phase 3 testing is, in fact, at least feasible or

tolerable. So even though you may not have the study started, there is good evidence that, in fact, the study is a plausible, feasible one that could be conducted.

DR. KELLY: One question for the agency. A lot of times you require a lot of these new agents to have studies ongoing in pediatrics or something, thinking that way.

Should they also be going, if agents are appropriate for pediatric populations?

DR. PAZDUR: You mean the pediatric -- well, the pediatric drug development program really is a separate program. And there's two issues here; one, the best pharmaceuticals for children, BPCA, which basically is an exclusivity program, and that usually occurs after the drug has been approved, because it attaches exclusivity to a marketed drug.

The other issue is kind of mandatory pediatric studies, if the disease is the same in children and adults. And, generally, that, other than lymphomas and maybe some brain tumors, is not commonly used, because most of the drugs are being

investigated in prostate cancer, colon cancer, lung cancer, where one cannot make that connection.

DR. WILSON: So it sounds like we all have a consensus here, but perhaps you can clarify. I think we all agree that a company shouldn't even file an application without a plan and the trial is either very advanced or ongoing.

But the way the question is written is that if, in fact, they don't do that and they do come in, the question is should the approval be held up. And I guess my feeling -- I don't know what kind of regulatory teeth there is behind that, but if we all think that there ought to be a plan and it ought to be pretty much set and almost if not ongoing, presumably, the answer to that is yes. Otherwise, there's no teeth behind --

DR. PAZDUR: I think it's important for sponsors to hear it from this committee, and here, again, I think it's more important the file-ability (ph) rather than reviewing a study where we know the trial is not going to be approved.

But I think what we're looking for is early

discussions, these protocols being under some type of special protocol assessment, where we've come to agreement with trials. Frequently, we hear of proposals that we really wouldn't accept for a confirmatory trial, but this is what the sponsor is proposing.

I think there has to be an agreement what these trials are, a special protocol assessment in place on these trials, some attempt to show us where these trials are going in terms of accrual, what the effect of the approval is going to be on the completion of these trials.

DR. WILSON: Everyone who has spoken, I think, is in complete agreement with that.

Does anyone disagree with that? I'm not sure we need to go around the room to restate it in this case. Does everyone agree that there's a consensus that there has to be a plan that the FDA has gone over before accelerated approval even ought to go forward? Do we have a consensus here?

[Affirmative nods.]

DR. WILSON: Okay. So I think that people

agree that the standard ought to be a plan that is regulatorily sound and clinically sound.

So why don't we go on to the fourth question?

DR. KLUETZ: With respect to the use of cooperative groups to conduct confirmatory trials, the FDA recognizes that cooperative groups both in the U.S. and Europe are critical to drug development and encourages their participation throughout the drug discovery process.

Applicants may engage a cooperative group to design and execute a confirmatory trial to fulfill their regulatory obligation; however, the ultimate responsibility of completing the confirmatory trial with due diligence rests with the applicant. This fact may hold added importance to sponsors with the introduction of the financial penalties through FDAAA for lack of timely completion of these trials at the agreed upon dates.

Discuss the use of a cooperative group to conduct trials required to demonstrate clinical benefit to fulfill their accelerated approval

obligation. If a cooperative group is used, discuss whether additional trials should be conducted under the direct supervision of the applicant to ensure adherence to completing post-marketing requirements by a specified date.

DR. PAZDUR: And let me just begin, we're not talking about pediatrics here. Okay. So let's take that off the table.

DR. WILSON: Thank you.

DR. PAZDUR: So relax, guys.

I think one of the issues that brought this forward to us is when a company realizes that a trial is not going well in terms of accrual and it's their sponsor-run trial, they can step in here and add international sites, additional sources, additional resources, et cetera.

We have been in positions where a cooperative group is running a trial, the sponsor is on the other hand, the trial isn't going well, where is the data, and everybody is pointing fingers at each other. The company is saying that they've relegated this responsibility to the

cooperative group. The cooperative group is saying that this is not their issue, they are an independent scientific organization with competing interests, and this may not be a high priority for them.

Remember, these also have now financial penalties associated. They are post-marketing requirements with specific dates that these trials have to be done with, and this is our issue here of trying to really make sure these trials are done on time, and we cannot be in a situation where a regulatory requirement is transferred to a third party, so to speak, and then it's transferred, in fact, de facto back to the government in many cases.

DR. WILSON: So being a little bit of a number cruncher here myself, if we have agreed for trials in non-rare diseases that we need two confirmatory trials, and then they're doing a cooperative group trials, are we talking now three trials?

DR. PAZDUR: No. We'd include this one. We

want at least one study that is delivered on time here to us.

DR. WILSON: So you aren't saying that they need two and --

DR. PAZDUR: No.

DR. WILSON: Okay. So let me just say that my attitude is buyer beware. It is the drug company's responsibility to get the trial done. Cooperative groups do, in fact, have a different agenda, and I don't think that it -- the onus cannot be put on the cooperative group nor can the drug company point to the cooperative group.

I think that if the cooperative group doesn't come through -- and there are many reasons why they don't, they have many different competing agendas and all kinds of things change. I think, absolutely, if there was ever a reason to have two trials, I think this would be one setting in which you would always have to have a second trial.

So that would be my feeling. But if a sponsor is trying to say it's the cooperative group's fault, I wouldn't -- personally, I wouldn't

even codify that with a response.

Actually, we have Dr. Curt here.

DR. CURT: I was just wondering, this is somewhat a tangential point. But the Institute of Medicine, in its review of the cooperative groups, actually raised concerns about the groups being able to deliver licensing trials. And as a result of that, the FDA and the NCI have apparently formed an interagency agreement to allow the cooperative groups to play more of an active role in that. And I was wondering if the agency could update us on that interagency agreement.

DR. PAZDUR: I want to really make this quite clear. This is not to be anti-cooperative groups. We in the FDA and all of the oncologists here really endorse the use of cooperative groups in the drug development programs. But there are trials that probably the cooperative groups should do, and there are trials that -- because of a requirement with a specific penalty, either there has to be very well laid out guidelines of how these trials will be done, with added resources

allocated to the groups and an excellent interworking relationship with these groups if they are going to do these trials.

But this is a specific type of trial that is a requirement. That is much different from a trial of, yes, why don't you take a look at this drug in another disease, and if it's positive, we might file this application; and if it takes three years, four years, whatever your timeline is, that's okay. That's a much different trial than a requirement with a date, with a penalty that's associated with it, with a drug out there that has unknown clinical benefit, so to speak. And that's the whole crux of the issue.

Now, we are working with the cooperative groups and with the NCI -- in fact, there was a whitepaper from PhRMA on this -- to really try to improve the submissions, and they include having all of the parties together, what data we're going to be looking at. But the emphasis is more on communication of what trials are going to come in here.

Our purpose here in asking this question is to highlight this specific type of trial, because it is a unique trial here with a date, with a penalty, with tremendous public health implications.

As I stated in the closing remarks in my opening statements, we really think that these clinical trials, these confirmatory trials, they are as important, if not more important than the actual registration trials that led to the drug approval. They really provide the missing piece of what that clinical benefit is, and they can't just be relegated to a third party.

DR. WILSON: Well, we've already heard today from one of the sponsors, one of the difficulties in just confirming, getting an outside review of responses. And, also, if there's slow accrual, they can't just snap their finger and add sites. I think that, as you've pointed out, there is a tremendous value to cooperative groups, and they've really advanced clinical therapy enormously.

But as you point out, their role and their

focus is very different from a very timeline-sensitive, QA-sensitive trials, that you require to confirm efficacy and safety on a very rigorous level.

DR. PAZDUR: But here, again, I think if there is a trial that is being done by the cooperative group, we would like to see at least an additional trial.

DR. WILSON: Absolutely. Right. So it's not like you can't use it as support, but it shouldn't be the only trial. I think this gets back to the same issue that you brought up before, which is it's ideal to have two randomized studies. And I think this is even perhaps a compromise on that, but there should be at least one randomized trial that is built to rigorously answer these questions.

Dr. Lyman?

DR. LYMAN: Just to reiterate, I think the cooperative group mechanism represents both an opportunity and, at the moment, at any rate, a real challenge. And the Institute of Medicine review

clearly laid out the many, many issues that could prove problematic for a licensing trial. But I think it's something -- with the reforms taking place, and there seems to be commitment across cooperative groups to do that as well as the FDA, this does provide a real opportunity.

For one of the trials, I agree completely there should be -- both that the company, the sponsor, even in the cooperative group study has to have the ultimate responsibility and can't defer to the cooperative group, and there should be at least one other one that they tightly control for confirmatory trials.

DR. WILSON: Dr. Sekeres?

DR. SEKERES: I think I'm just reiterating what other people have said. I've certainly conducted a study through a cooperative group, and it's both a privilege and a challenge. And it's a privilege because it's one of the highest academic levels you can reach of conducting a clinical study, and it's real world; it's sites all over the country. But at the same time, if you have a time

impetus to get a study done, it's probably not the right mechanism to go, so caveat emptor. So I think it should be required that if somebody does go through a cooperative group, they must do another study separate from that.

DR. WILSON: Dr. Loehrer?

DR. LOEHRER: I guess I'll voice the alternative viewpoint. I think this is dangerous for the cooperative groups to have the language and the discussion, to be honest with you. The purity of the cooperative groups, in general, has to do with science and academics, and I think you took the pediatric people off the table, but in reality, they're the model.

They have done trials with industry and 70 percent of their patients go on clinical trials. And, in reality, in the private sector, it will be the marketplace that will determine who goes on a trial or not rather than the science.

You already have a group of investigators that are committed to looking at disease processes, and I think it -- however we do this, I think

excluding the cooperative groups would be dangerous. I think from the other aspect, again, talking about rare or uncommon diseases, ain't going to happen in the community setting with rare diseases. We have the CTSU that is a nice network of bringing things together, but even the CTSU looks at common diseases rather than rare diseases.

So, again, I appreciate the differences between having control data, but I do think that we need to bring the cooperative groups into this and figure out a way to use the Institute of Medicine to help us become a more robust clinical research entity in the United States rather than just dismissing the cooperative groups.

DR. PAZDUR: To give you another example, one other alternative would be, since trials are usually done internationally, to have an international study or a European study or outside of the United States being conducted by the company and the cooperative group, for example, doing one here, and we've seen that example.

DR. LOEHRER: Again, one other point from an

academic point of view is promotion and tenure, and the process of developing a trial and moving it forwards gives you credence, it gives you reputation. Doing a trial for industry in which you're one of 100 different sites gives you nothing. The institution may get some money for doing it, but it really gives you no academic credit. So if we are going to, again, encourage another generation of investigators and scientists, the cooperative groups are the best we have right now. It's imperfect, but I don't know of a better way of doing it.

DR. WILSON: I don't think FDA is saying that cooperative groups shouldn't be part of this, but they're not constructed to get at some of these licensing issues; so that if, in fact, there is a cooperative group trial, it shouldn't be the only one. I think that's all the FDA is saying here. And I think that we would all agree that if, in fact, the cooperative group trials were to become more like company trials, we would lose a lot of the scientific academics that we value in them.

There's probably a middle road here and hopefully a lot of the changes that Harold Varmus is going to be leading in terms of the cooperative group, will bring both the industry trial and – will bring the best of both, well monitored trials and cooperative group trials together.

Dr. Kelly?

DR. KELLY: I think involvement of cooperative groups is very, very important for the overall drug process. It's really the real world of oncology out there, because it's the private practices, it's the ones that usually don't have the best performance statuses, and it's the real world out there. But one of the things that happens in cooperative groups and when industry goes in there, there's always a backfill trial.

So cooperative groups need to be part of a prospective overall drug development plan and be part of the process, not as a retrospective, well, we didn't get this trial done, so let's try the cooperative group trial. So I think that as we go forward, we have to be part of the process from the

beginning.

DR. WILSON: And I certainly think that with some of the overhaul of the cooperative group process, if, in fact, there are fewer cooperative groups -- and with this working group, that may become more of a reality, because it does seem as though, in many cases, they go and they find a trial where the drug is being looked at and it's all being done, as well; they did this study, so maybe we can use it.

Dr. Lyman?

DR. LYMAN: I just wanted to add -- and it's similar to Dr. Kelly's comment, and that is there's probably not a situation where it's more imperative that the sponsor and perhaps the cooperative group have upfront discussions with the agency to work out these details, because I think where they've run into problems, of the many that have been identified, is when the trial has been designed, initiated, and then come back secondarily and they haven't really addressed many of the regulatory issues that would make the trial valuable for a

licensing approval.

DR. WILSON: Dr. Smith?

DR. SMITH: I would agree with Dr. Loehrer that this should be an option that companies should have, and they shouldn't be discouraged from considering that option with being aware of all the caveats that would need to go with it.

I think a couple of things. There are changes in the cooperative group program, the operational efficiency working group recommendations and implementing those. And the first year experience with that suggests that their very delayed timelines for developing protocols will be a thing of the past, and so that won't be an issue going forward.

I'd also echo Dr. Lyman's comment that part of the problem in the past has been bringing studies forward for licensing that were never meant to be licensing studies, and then trying to figure out and collect all the data that the trial wasn't designed to collect. And so prospectively work with the group and the agency working together to

identify what's needed, and I think there will be many settings in which the group will work well with the company to accomplish that.

DR. WILSON: Dr. D'Agostino?

DR. D'AGOSTINO: I didn't take this as a negative comment in the sense that they shouldn't be there. I think we want to encourage the cooperative groups, but they may not deliver on -- as we saw today with the CT scans and so forth. And if they can't do that, then this -- not fallback, but this position that the investigator has to be involved with the study I think is a way to make sure that all the Is are dotted and Ts crossed and so forth.

So I would encourage very strongly, especially if I'm in an academic setting myself, use the cooperative groups, but at the same time, be realistic in terms of you need to make sure that you're getting the study done the way it has to be done with the regulatory aspects. If they can do it, fine. If they can't do it, you need this other thing. And going back to our discussion of two

trials, it fits perfectly into our discussion.

DR. WILSON: Dr. Freedman?

DR. FREEDMAN: I think one issue that needs to be mentioned is that we still face a relatively small number of patients who participate in clinical trials across the county, and we're talking about large studies here. And I think both the NCI groups and industry should be interested in the same ultimate objective, and that is to improve care for patients. So you don't want to have a situation where you have one competing with the other.

At the same time, from what we've heard today and from other information, some of the cooperative groups function very well and it seems like, in some cases, they may have a captive audience of patients. So they have developed a process there of efficiency, and I think that it's probably a good idea for the NCI to look at their whole portfolio of studies that are being conducted across the different cooperative groups and see what's working and what's not working; what are the

barriers to doing good studies?

I think it's something that needs to be done. But, clearly, the groups can play a role and maybe, at this point, it's in selected studies, but until the processes are improved and brought up to the same standards as what industry does in terms of registration studies we're talking about, then it's going to be limited.

DR. WILSON: Ms. Mayer?

MS. MAYER: I agree with the last several speakers. And I think that in addition -- one of the comments I hear from sponsors, with some regularity, when they are disappointed at an FDA decision is that, rightly or wrongly, they've experienced inconsistent messages that have changed over time about what is required to satisfy the regulations.

I think the whole issue of having an agreed upon plan goes a long way towards dealing with that issue and specifically about the issue of cooperative groups. I think it just needs to be made very clear to the sponsors that regardless of

who conducts their studies, and that's really their decision, that these will be the requirements; there will have to be an independent review of scans, for example, or whatever the other requirements are, so that up front, everybody is on the same page. Then how they choose to go about fulfilling those commitments is up to them. And I think there is no reason to rule out the cooperative groups because of bad experiences here and there at all. In fact, they should be invited if there is a way.

DR. WILSON: Would the agency like to respond to variables or changes in requirements?

DR. PAZDUR: Well, our purpose of bringing this question is really to emphasize to the sponsor this is their requirement; this is their obligation. And if they allocate this or pass it on to another entity, whether it be a cooperative group either here in the United States or in Europe, it is still their responsibility. And, therefore, up front, they better negotiate contracts, adequate funding for these trials to be

done, adequate monitoring for these trials to be done. They cannot relegate a regulatory requirement to a third party or back to the government, basically. That's an untenable situation.

DR. WILSON: Thank you.

Dr. Loehrer?

DR. LOEHRER: I know we're beating a dead horse, but I just want to say that I would dream of the day, whether it's five years or 10 years from now, in which we do have an agreement with industry and cooperative groups how we should be doing studies.

As it stands now, we may have 20 different studies being done and we get audited either once a week, once a month, once a quarter. We have different regulatory documents. If one could, again, as Kevin mentioned, put together a cooperative agreement, if you will, between industry and with the cooperative groups, in which we have the same guidelines, the same approach, we have now created a workforce of data managers who

have been trained the same way, regulatory people trained the same way, and we can do these trials much more effectively. So that would be my hope.

DR. WILSON: Let me just summarize then, because it sounds, again, as though the group has a consensus.

I think we all agree that cooperative groups are a very useful mechanism; that if, in fact, a drug company does decide to use them, as Dr. Kelly points out, this really ought to be something they ought to work out with them and negotiate with them going forward rather than going back; that drug companies cannot give up or basically transfer their obligation; and that if there is, in fact, a cooperative group trial -- we've already talked about the fact that two randomized studies ought to be used anyway, so I think it clearly follows from that that a cooperative group trial could be one of two randomized trials. But if there is a cooperative group trial, given the competing agendas, that there absolutely should be a second randomized study.

Does that more or less summarize everyone's agreement, consensus?

[Affirmative nods.]

DR. WILSON: Okay. Great.

Any closing comments?

[No response.]

Adjournment

DR. WILSON: Okay. Well, let me thank you all for coming and have a safe trip home. Meeting adjourned.

(Whereupon, at 4:35 p.m., the meeting was adjourned.)