DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE

Tuesday, November 8, 2005

8:00 a.m.

Holiday Inn
The Ballroooms
Two Montgomery Village Avenue
Gaithersburg, Maryland

PARTICIPANTS

Silvana Martino, D.O., Chair
Johanna M. Clifford, M.S., RN
Executive Secretary

MEMBERS:

Bruce D. Cheson, M.D.
Antonio J. Grillo-Lopez, M.D., Industry Representative
Pamela J. Haylock, RN, Consumer Representative
Maha H.A. Hussain, M.D.
Joanne E. Mortimer, M.D.
Michael C. Perry, M.D.
Maria Rodriguez, M.D.

CONSULTANTS (VOTING):

S. Gail Eckhardt, M.D.
Steven George, Ph.D.
David Kelsen, M.D.
Donna Przepiorka, M.D., Ph.D.
Musa Mayer, Patient Representative

FDA STAFF:

Edwin Rock, M.D.
Ramzi Dagher, M.D.
Robert Justice, M.D.
Richard Pazdur, M.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order and Opening Remarks

DR. MARTINO: Good morning, ladies and gentlemen. I would like to start the meeting this morning. The topic for today is essentially accelerated approval for a variety of drugs. As the first order of business, I would like the committee members to introduce themselves and where they are from. I would like to start on my left.

DR. KELSEN: David Kelsen, Sloan-Kettering, New York.

MS. MAYER: Musa Mayer. I am a patient representative. I am also from New York.

DR. GRILLO-LOPEZ: Antonio Grillo-Lopez, industry representative. I received no support from industry for my attendance at this meeting.

DR. GEORGE: Steven George, Duke University.

DR. PRZEPIORKA: Dona Przepiorka, university of Tennessee in Memphis.

DR. PERRY: Michael Perry, University of Missouri, Ellis Fischel Cancer Center.

DR. HUSSAIN: Maha Hussain, University of Michigan.

DR. ECKHARDT: Gail Eckhardt, University

of Colorado.

DR. MARTINO: Silvana Martino, the Angeles Clinic.

MS. CLIFFORD: Johanna Clifford, Food and Drug Administration.

DR. MORTIMER: Joanne Mortimer, University of California, San Diego.

DR. CHESON: Bruce Cheson, Georgetown University Hospital, Lombardi Cancer Center.

MS. HAYLOCK: Pamela Haylock, consumer representative.

DR. RODRIGUEZ: Maria Rodriguez, M.D. Anderson Cancer Center in Houston, Texas.

DR. ROCK: Edwin Rock, FDA clinical reviewer.

DR. DAGHER: Ramzi Dagher, FDA, Division of Drug Oncology Products.

DR. JUSTICE: Robert Justice, FDA, Division of Drug Oncology Products.

DR. PAZDUR: Richard Pazdur, Office director.

DR. MARTINO: Thank you. Next, the conflict of interest statements for this morning, please.

Conflict of Interest Statement

MS. CLIFFORD: The following announcement addresses the issue of conflict of interest and is made part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting, with the following exceptions.

In accordance with 18 USC Section 208(b)(3), full waivers have been granted for the following participants: Dr. Steven George for being a member of the sponsor's data safety and monitoring board on unrelated matters, for which he

receives less than $10,001 per year; Dr. Maha Hussain for ownership of stock in the sponsor, valued from $25,001 to $50,000. This de minimis financial interest falls under 5 CFR part 2640.201 which is covered by a regulatory waiver under 18 USC 208(b)(2). Dr. Bruce Cheson for being a consultant to a competitor. He receives less than $10,001 per year.

A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

We would also like to note that Dr. Antonio Grillo-Lopez is participating in this meeting as the non-voting industry representative, acting on behalf of regulated industry. Dr. Grillo-Lopez is employed by Neoplastic and Autoimmune Diseases Research.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to

exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon. Thanks.

DR. MARTINO: Next, Miss Pamela Haylock will give us a report on the pediatric subdivision to this committee, but before she does that I need to read you all a statement that relates to our relationship to that meeting:

The pediatric subcommittee of the Oncology Drug Advisory Committee met on October 20th, 2005 to present the structure and function of the Office of Oncology Drug Products in CDER; to discuss issues involved with the conduct of certain pediatric post-marketing studies for products approved for oncologic indications; review status of studies for specific off-patent drugs for pediatric oncology; and consider other off-patent oncology drugs for which pediatric studies are

needed as mandated by the Best Pharmaceuticals for Children Act.

Per the Federal Advisory Committee Act guidelines, an ODAC member in attendance of the subcommittee meeting must report back to the parent committee. Due to the short period of time between the subcommittee meeting and today's ODAC, the purpose of today's presentation is only to report the issues presented at the subcommittee meeting in October and not to discuss the issues. Advice or recommendations from the parent committee will be requested at the next ODAC meeting, scheduled for March, 2006. Proceed, please.

Report to Committee on Pediatric Oncology Subcommittee Meeting

MS. HAYLOCK: Hi. Good morning. I am Pam Haylock. I am the consumer representative and one of two members from the ODAC who went to the pediatric oncology subcommittee. Dr. Gregory Reaman is the subcommittee chair and he was unable to be here today.

Again, this just kind of goes over what

Dr. Martino just said. The subcommittees are only advisory to the parent committee and we did not directly advise the FDA. Parent committees such as this review subcommittee recommendations and then advise the FDA. At least two members of the parent committee serve on the subcommittee, and we have no charter or official roster.

These are the guidelines for the pediatric subcommittee. They are in the handout. This is a listing of the members or the people who attended that meeting or who were part of that group, including all the consultants from various places across the United States, and two patient representatives and an industry representative, as well as several FDA participants.

One of the things that we did that day was review the two basic and primary pediatric initiatives, the Pediatric Research Equity Act which was passed in December, 2003, and Best Pharmaceuticals for Children Act, in January, 2002. Both laws are intended to support and encourage drug development in the pediatric population.

The Pediatric Research Equity Act, or PREA as it is referred to, is just one of two of these laws to promote the study of drugs. One of the

goals of this law is to prevent pediatric patients from being a study of one because of the limited population. Studies in the pediatric population are required but only for the indication for which it was studied in adults.

BPCA in pediatric oncology offers a methodology to help prioritize new drugs for study; assure timely access to new treatments for children; and develop preclinical models of pediatric cancers.

Why do we need both? There is a distinction between the scope of studies requested under each one. PREA is specific to the indication in the submission and BPCA can ask for off-label indications.

We did have one open public hearing speaker, Sadhana Dhruvakumar, who is director of medical products testing for PETA.

Specifically, we spent most of the time

talking about questions from NIH to the pediatric subcommittee, including what type of prioritization process ought to occur for deciding which off-patent drugs should be studied. We talked a lot about what is the definition of a health benefit. Does it relate to the number of patients affected? Is it those areas where there is a lack of other drugs to treat that disease? And, does it relate to the severity of the disease?

Questions included also were are there other drugs that should be studied? Dr. Pazdur encouraged us to really think outside of the box, so to speak, in regards to both antineoplastics, biologics, supportive care medications and indications such as anti-emetics and pain control or analgesia.

There were three drugs that we talked about in terms of issues for post-marketing studies--one was Clolar or clofarabine--including the feasibility of the proposed populations and primary endpoints; the study designs; likelihood to permit adequate assessment of clinical benefits in

that population; and can data generated in adults be used to support efficacy in pediatric ALL patients.

The recommendations included that adult populations and primary efficacy endpoints do not permit adequate assessment of clinical benefit for pediatric patients. We suggested a focus on first relapse, known active agents in controlled settings, the ability of the regimen to induce remission and/or minimal residual disease or potential primary endpoints. It is not plausible that adult AML data supports efficacy in pediatric ALL patients based on what we currently know about the disease biologies. Another drug was Neulasta or pegfilgrastim. Will Amgen's study in patients allow sarcoma data to be extrapolated for activity and safety findings across all ages in different pediatric cancers?

Some of the issues that were discussed include the difficulty in enrolling this population of patients, especially in the younger ages in these studies; the difficulty in administering this

drug in randomized settings; and the competition from other studies where protocols demand growth factors, especially in the pediatric population.

Suggestions included allowing patients to serve as their own controls; randomizing patients for the first cycle; and considering studies in patients with rhabdo. and neuroblastoma to enhance the age range of subjects.

Other issues for this drug, palifermin or Kepivance--the suitability and feasibility of a need for dose escalation; the need for pharmacokinetic data; and the choice of patient populations, homogenous versus heterogeneous, related to their underlying disease, the source of their stem cells and cytotoxic regimens.

Again, the recommendations were that, number one, we do need data from pediatric populations. We suggested decreasing the number of doses tested in the dose escalation portion of the study, to consider evaluating other schedules and to suggest study in patients with acute leukemia, receiving allogeneic transplant would be useful and

feasible. Populations could be both autologous and allogeneic transplant recipients, and using adult pharmacokinetic data could be possible as a guidance for when and how to sample, but only as a framework for pediatric dosing.

Ongoing studies of vincristine and actinomycin-D--there were questions regarding the approach to safety and efficacy and pharmacokinetic data. Are there additional data that could be collected? Could frequency of toxicity be minimized with a dose cap? Would dose capping cause under-dosing and subsequently lack of efficacy with these drugs? And, is the application of mathematical models for dose finding appropriate?

Recommendations were clearly to agree that with vincristine it is very difficult to quantify the toxicity of this drug. One of the reasons is that there is a lack of standard assessment parameters and scoring for peripheral neuropathy and the required tests for measuring and monitoring the toxicities and efficacy of this drug.

We talked some about the off-patent BPCA process, and the question primarily had to do with could additional labeling data provide benefits for

pediatric patients related to off-patent drugs and/or therapeutic drug classes.

Discussion outcomes--there is a need for dose adjustment guidelines for many off-patent drugs, especially specifically in obese children given the epidemic of obesity among kids; administration methods to decrease toxicity, especially less frequent dosing intervals; dose optimization via systematic methods. We need tools to measure early toxicity and arbitrary age groups. There was a lot of discussion about children in the first year of life.

Suggested topics for future ODAC meetings included issues around pain control. There are actually very few clinical trials that relate to pain control in pediatric and especially neonatal populations; the symptom management issues in neonates; drug delivery systems to enhance access; long-term sequelae of all of these regimens; orphan

drug indications; end of life and palliative care studies; indications waived from requirement for conducting pediatric studies; the role of stable disease as a potential endpoint and other endpoints for pediatric cancer; preclinical predictors of clinical outcomes; and reformulations or rounding off errors on the impact of that process; and the past seven years post-PREA and BPCA to assess really whether there have been any changes in getting drugs to pediatric cancer patients earlier.

Finally, there is no routine schedule for the pediatric subcommittee, but it was suggested that the pediatric subcommittee occur sometime in the first quarter of 2006. Thank you.

DR. MARTINO: Thank you. Next, Dr. Dagher will present an update of the accelerated approval process.

Accelerated Approval Update 2005

DR. DAGHER: Good morning. In the next few minutes I would like to summarize the status of the accelerated approval program with respect to oncology drugs and oncology drug biologic products.

Before getting into the details of the program, I would like to remind everyone of the purpose of this meeting. Our goal is to review

past accelerated approvals; to discuss the current progress of Phase 4 commitments associated with specific approvals under subpart H regulations; and to solicit input for improving the accelerated approval process as a whole.

I will provide a history of the regulations governing the accelerated approval process, including a summary of a recent guidance on available therapy. I will provide a summary of the accelerated approval indications, including trial designs and endpoints utilized. I will briefly summarize indications where there is no further expectation of studies to demonstrate benefit, either due to previous demonstration of benefit and conversion to regular approval or due to restricted distribution. Finally, I will provide some concluding remarks regarding the program to date, as well as some questions for members of the committee to consider with respect

to each applicant presentation and with respect to the program as a whole.

The accelerated approval regulations were promulgated in the early 1990s with the intent of encouraging development and timely availability of drugs for serious or life-threatening diseases. These regulations allow for approval of drugs based on a surrogate endpoint reasonably likely to demonstrate clinical benefit. The regulations specify that the drug in question must demonstrate an advantage over available therapy in the disease setting being evaluated, or it must demonstrate an effect in patients for whom no available therapy exists.

Such an approval, referred to as an accelerated approval, would be subject to the requirement that the applicant verify and describe benefit, preferably in studies that would be under way at the time of approval. There is an expectation that these studies are carried out with due diligence.

In 2004, a guidance was published for the

purpose of clarifying FDA's intent in defining available therapy as related to accelerated approvals. In order to emphasize the importance of the approval process and to provide the greatest opportunity for development and approval of appropriately labeled drugs, the guidance indicates that available therapy should be interpreted as therapy that is specified in the approved labeling of regulated products, with only rare exceptions. The guidance indicates that certain established oncologic treatments are an example where such an exception could be made.

The guidance also addresses the status of drugs approved under the accelerated approval regulations with respect to the available therapy definition. That is, approval of one therapy under the accelerated approval regulations should not preclude approval under those regulations of additional therapies for the same indication.

When the accelerated approval program was discussed at this advisory committee in 2003, 19 indications for 16 different drugs had been

approved under the accelerated approval regulations. At the time, confirmation of clinical benefit had occurred for four indications. Eight indications for which clinical benefit had not been confirmed were presented.

The status now, in 2005, is as follows: Since 1995 a total of 25 drugs have been approved for 29 different indications under the accelerated approval provisions. Of these, we do not expect any further confirmation of clinical benefit for 13 indications. For 10 of these, clinical benefit has been confirmed subsequent to accelerated approval. In addition, two indications are under restricted distribution. Finally, one indication has been withdrawn due to changes in the oncology practice environment. This will be discussed later in the presentation. Of the 16 indications without confirmation of benefit, six received accelerated approval prior to 2002 and, therefore, the sponsors for these indications will be presenting an update on the status of those associated Phase 4 commitments today.

For the program as a whole, our experience has been that most approvals have been based on evaluation of surrogate endpoints in single-arm

trials of patients with refractory malignancies. However, we have experience in approximately one-third of the accelerated approvals with evaluation of less refractory patients in randomized trials.

In trials without an active comparator, objective response rate has been the most commonly evaluated endpoint, again, in patients with refractory solid tumors. In some cases complete remission rate was the basis for approval for hematologic malignancies. There is one case of medical castration used as an endpoint for a drug which will be discussed in a later slide.

As you can see, in cases where approval was based on randomized trials a variety of endpoints have been used. This illustrates one advantage for use of randomized trials, even for a strategy that includes accelerated approval, since the number of time-to-event endpoints can be

evaluated.

Now, you may notice that some of the endpoints listed, such as disease-free survival as utilized in evaluating hormonal therapies for breast cancer, or effect on ventricular function and risk of congestive heart failure as evaluated with dexrazoxane, are endpoints that FDA has used in some settings for demonstration of benefit. This illustrates another feature of the regulations which is discussed on the next slide.

Although accelerated approval is usually based on a surrogate endpoint, it can in some cases be based on a clinical benefit that is not the ultimate purpose of treatment. In these cases, the sponsor is required to study the drug further to determine the ultimate outcome. Five drug indications in this class have been approved under the accelerated approval regulations.

In the case of amifostine and dexrazoxane, uncertainty regarding a possible tumor protective effect necessitated accelerated approval, with additional studies required to demonstrate lack of

any detrimental effect on survival.

In the case of anastrozole, the letrozole indication for extended adjuvant treatment of breast cancer after tamoxifen and the imatinib indication for first-line CML, the endpoints evaluated would usually represent evidence of clinical benefit, disease-free survival for hormonal agents, and time to accelerated phase or blast crisis for imatinib. However, short follow-up at the time of data analysis necessitated subpart H approval, with further follow-up required for confirmation of benefit.

This slide and the following slide provide a list of products for which clinical benefit has been confirmed subsequent to accelerated approval. It should be noted that in most cases confirmatory trials were under way at the time of accelerated approval. In a few cases confirmatory trials were initiated shortly after approval.

There are two drugs for which no further confirmation of benefit is expected. The first, abarelix, is a GnRH antagonist, approved in 2003,

for the palliative treatment of advanced symptomatic prostate cancer. Although an endpoint of medical castration was evaluated, an endpoint utilized for regular approval of LHRH agonists intended for palliative treatment of advanced prostate cancer, the risk of anaphylactic reaction and concerns regarding loss of castration effect after 18 months necessitated approval only in a population for whom the benefit would outweigh the risks under restricted distribution provisions. The indication was limited to patients with ureteral obstruction, impending neurologic compromise and uncontrolled severe bone pain.

Gefitinib represents a different case. Here, the drug was approved under the accelerated approval regulations in 2003 for the third-line treatment of non-small cell lung cancer based on objective response rates in single-arm trials. There was no clinical benefit demonstrated in several ongoing and subsequent randomized trials of this drug in combination with chemotherapy or compared to placebo in patients with non-small cell

lung cancer. In addition, another agent became available with a demonstrated survival effect. In 2005, a limited accelerated approval program was implemented restricting further distribution to patients who were benefitting or who had benefitted from gefitinib.

At the time of issuing invitations to applicants to present at this meeting, seven drugs had accelerated approval indications prior to 2002 without subsequent confirmation of benefit. A cut-off of 2002 was chosen for issuing invitations as a period of over thee years was felt to be a reasonable interval to allow applicants to be able to provide an update on their efforts. One of these indications has been withdrawn, as discussed on the next slide.

Amifostine has received regular approval for reducing renal toxicity associated with high dose cisplatin use in patients with advanced ovarian cancer and for reducing the incidence of xerostomia in certain patients undergoing postoperative radiation for head and neck cancer.

In 1996, amifostine was approved for reducing renal toxicity associated with high dose cisplatin use in patients with advanced non-small cell lung cancer under the accelerated approval regulations.

A post-marketing study was completed in 2002. This study showed a reduction in renal toxicity but was inconclusive regarding a potential tumor protective effect. Therefore, an additional confirmatory study was required. Recently, the applicant conducted an assessment indicating that a clinical trial to confirm amifostine's clinical benefit in patients receiving high dose cisplatin for non-small cell lung cancer would not be feasible. The high dose cisplatin regimen is not often used in this setting according to the applicant. Furthermore, the applicant noted use of carboplatin in this setting as well. Based on these considerations, the applicant withdrew the non-small cell indication in October of this year.

I showed this slide earlier in my presentation. To reiterate, there are 16 indications without confirmation of benefit. Of

these, six received accelerated approval prior to 2002 since a period of over three years would be a reasonable time frame to allow applicants to provide an update on their efforts. The applicants for these 16 indications will be presenting today.

Applicants for the following approved indications will provide updates on their efforts to conduct and complete trials mandated under subpart H commitments: Liposomal doxorubicin for Kaposi's sarcoma; denileukin diftitox for cutaneous T-cell lymphoma; liposomal cytarabine for intrathecal treatment of lymphomatous meningitis; celecoxib for a number of colorectal polyps in FAP; gemtuzumab ozogomicin for the treatment of CD33 positive AML and first relapse in older patients not candidates for chemotherapy; and alemtuzumab for the treatment of B-cell chronic lymphocytic leukemia.

Before presenting questions to the committee, I would like to provide some conclusions regarding our experience as a whole. Over the past decade, 25 drugs have been approved for hematologic

malignancies and solid tumors under accelerated approval provisions. These include three indications for childhood leukemias and lymphomas which have been approved in the last three years. As discussed, there has also been progress in subsequent demonstration of clinical benefit after accelerated approval for several indications.

However, we need to continue to emphasize the integration of any accelerated approval strategy into a comprehensive drug development plan. This includes early attention to the timely design and conduct of confirmatory studies. Finally, FDA is committed to continued public discussions regarding accelerated approval and will continue to seek input on improving this process.

As you listen to and discuss individual applicant presentations, we urge you to consider the following for ongoing confirmatory studies: Has accrual been satisfactory? If not, what strategies do you suggest for improvement?

For planned trials that have not been conducted, have changing circumstances impeded the

conduct of these trials? If so, what alternative designs should we contemplate?

Regarding the accelerated approval process as a whole, we urge you to consider the following: There are several trial designs that could support accelerated approval. Although single-arm studies provide response data relatively quickly, these are interpretable for the purposes of accelerated approval only in refractory settings and will not by themselves permit assessment of the impact on time-to-event endpoints such as time to progression or survival. In contrast, randomized studies allow evaluation of additional endpoints and study of non-refractory populations. In this context, interim analysis of surrogate endpoints, such as response rate of TTP, could support accelerated approval and further follow-up of the same trial for survival, for example, could provide evidence of clinical benefit.

Please discuss the relative merits of different trial designs and patient populations for accelerated approval. Please also provide any

other suggestions for improving the accelerated approval process as a whole. Thank you.

DR. MARTINO: Thank you, Dr. Dagher. Dr. Pazdur will now address the committee.

Comments on the EMEA and FDA

Confidentiality Arrangement

DR. PAZDUR: Thank you, Dr. Martino. We asked Dr. Pignatti, from the EMEA, or the European Medicines Agency, to attend this ODAC meeting specifically to address some new initiatives at the EMEA. One initiative is the "conditional marketing authorization." That is similar to our accelerated approval program. However, there are some interesting differences, as he will discuss, compared to our accelerated approval program, including that authorization under the EMEA conditional approval process would be valid for one year and would require renewable confirmation of a successful assessment.

Prior to Dr. Pignatti's comments, I would like to address some of the recent programs that the new Office of Oncology Drug Products and the

EMEA have undertaken to increase the dialogue between the two agencies to provide a deeper understanding of the basis for scientific advice, and to provide the opportunity to optimize product development and avoid unnecessary replication.

On September 16, 2004 a confidentiality arrangement was finalized between the European Commission and the EMEA and the U.S. FDA in the context of regulatory cooperation and transparency between the U.S. government and the European Commission. Based on this arrangement, the following programs and practices, seven of them, have been implemented in the Office of Oncology Drug Products.

Number one, the FDA Office of Oncology Drug Products will routinely share special protocol assessments, or SPAs, of its three divisions with the EMEA. The EMEA, in turn, will routinely provide to the FDA letters of scientific advice sent to sponsors regarding protocols and drug development plans for oncology products.

Number two, with the advent of conditional

approval in the EU, we consider a greater dialogue on our accelerated approval commitments with the EMEA to be warranted. Therefore, the Office of Oncology Drug Products will routinely forward to the EMEA meeting minutes with sponsors that involve accelerated approval design issues and commitments. In turn, the EMEA will provide similar records to the FDA regarding discussions with sponsors on their conditional approval program. We feel that this interaction is important since many of our Phase 4 commitments have been performed either partially or fully outside of the United States, with significant accrual from EU countries. The adoption of an accelerated approval program by the EU may impact this future accrual.

Number three, the EMEA and the FDA will share current thinking on guidances providing advice on endpoints and other regulatory considerations. Each agency has already received draft copies of each other's oncology drug endpoint guidances.

Number four, monthly teleconferences

discussing pending regulatory decisions, basis for approval, clinical and non-clinical reviews have already been initiated.

Number five, the FDA and the EMEA will share and discuss any request for early stopping of clinical trials or significant changes in statistical analysis plans previously agreed with sponsors.

Number six, the FDA and the EMEA will encourage attendance of appropriate personnel at each other's key regulatory meetings, including the FDA's ODAC meetings and the EMEA scientific advice meetings.

Seven, the Office of Oncology Drug Products and the EMEA are committed to collaborate with oncology professional societies to jointly develop educational programs reflecting current regulatory thinking.

Finally, there are recognized differences between the United States and the European Union regarding aspects of drug development, drug regulation and medical practice. The programs that

I have outlined above are designed to provide transparency and an understanding of each agency's viewpoint regarding drug regulation. These programs are not intended to mandate unanimity of regulatory decisions. Thank you, and I will turn over the program then to Dr. Pignatti.

EMEA Current Thinking on Conditional Marketing Authorization

DR. PIGNATTI: Thank you for inviting me to bring here some personal views on where we are with the conditional marketing authorization. This is a program which is similar to your accelerated assessment. There is what we call the new medicines legislation, and that is outlined in an article on what are the criteria for conditional marketing authorization. That calls for additional implementing legislation, which is currently in draft format, to define exactly the scope and criteria of this provision. In turn, this is calling for additional guidance to be developed, and there is a consultation process about the guidelines as well which still has not taken place.

So, this is just to say that although discussion has been going on for years about this, and there is a fairly mature draft legislation in

place, there are still some things which might change in the near future.

So, the new medicines legislation outlines what the main approval processes are. We still have a normal approval. We have what we used to catch every other situation in the past, which is the exceptional circumstances situation. We now have this new provision which is the conditional marketing authorization.

So, I will briefly try to outline what are the differences and how this is relevant to this particular meeting. Now, for normal marketing authorization, this is easily defined. Nothing has changed. The data package must be complete. The legislation speaks in general about randomized active and placebo-controlled trials which are required, and there is a role also for follow-up studies there but it is not controversial.

In the past we had the exceptional

circumstances, which was catching all other situations. Now it becomes much better defined since conditional marketing authorization is expected to detract from that provision which was extensively used in the past.

Then, we have the conditional marketing authorization. This is really a new concept in our legislation and it is really a means to approve a drug as early as possible with confirmation of the benefit later. There is a role of specific obligations to provide the missing data which will fill the gap between the conditional marketing authorization and the normal marketing authorization. This has been written into the legislation which has been approved, so this is not going to change. And, there is the concept that conditional marketing authorization will be given for one year. At the end of each year, or earlier, the marketing authorization holders have to reapply for another renewal, and there you have an assessment of the benefit/risk, and the basis for this assessment are the specific obligations which

have been imposed on the conditional marketing authorization.

Now we move to the draft implementing regulation which might still change a little bit. We have the scope which is overlapping with what I understand is your scope of serious or life-threatening conditions, with addition of orphan drugs and emergency threats. Clearly, medical oncology conditions would fall within this draft definition. The option of improvement over existing therapy is reflected in the so-called public health interest and fulfillment of an unmet need. It is a somewhat more general concept that we have in our wording.

Then, the essence of the conditional marketing authorization is captured by the criterion of having to demonstrate presumed positive benefit/risk of the product based on scientific evidence and pending completion of further studies. It is clearly the compromise between trying to put the drug as early as possible on the market with some data missing and the draft

regulation calls for stricter criteria to be established.

Now, the draft is very clear about an effort for transparency, about the conditional nature of the authorization, and the obligation to have published time frames and clear information for patients and health professionals.

Again, the key point of the legislation is that the authorization is only valid for one year, and at the end of each year the time frame for the obligations is assessed, together with the benefit/risk, and, if at any time the product is found to be harmful or lacking therapeutic efficacy, there is the possibility to suspend, revoke or withdraw the authorization. Finally, the new thing which has been introduced now in another piece of draft legislation is the possibility to impose financial penalties in case of lack of compliance with the obligation.

Now I would like to contrast conditional marketing authorization and what we used to have as exceptional circumstances. Listed at the bottom of

the slide are all the products which have been approved under exceptional circumstances. Out of these, only one, Taxotere, reverted to normal marketing authorization.

Clearly, the key concept between the two is that in the case of exceptional circumstances there is an expectation that the data package will never be complete. So, there is an intrinsic possibility really to have full development. There, one should not expect really that the conditions will be able to fill this gap.

It is exactly the opposite for the conditional marketing authorization. We expect not only that the studies should be feasible, but it is highly desirable that they should be completed as early as possible.

So, the key is what studies can we allow as commitments really. Here, there are relatively non-controversial studies which are already suggested in our guidelines--pharmacology studies, dose response, therapeutic use studies which can easily be accommodated there. The highest

controversy is whether any of the data that we get from the therapeutic confirmatory trials can be a part of the commitment.

So, a number of models are being discussed based on either the HIV models of short-term and long-term confirmation, or other type of soft and hard endpoints which are models borrowed from other areas. There is a renewed interest for the model which has been mentioned before by Dr. Dagher about use of interim analysis, and the concept of selective approval. But still probably the most widespread models which are being argued about is use of non-validated surrogate endpoints and some biomarkers, and then requiring confirmation in terms of clinical outcome, and typically in the context of non-randomized phase 2 studies.

I cannot predict what will come out of our guidance, but I think that it is pretty clear that from our experience these are the models which have the highest risk of rejection really. They are most likely going to be discouraged because it is, and remains, very, very difficult to come to any

meaningful conclusions on non-randomized studies. Now, there are exceptions, and we know there are exceptions well described in our ICH guidance when non-randomized studies that show dramatic effect could be considered, but on the average we must be reminded about the fact that there is a very high risk of rejection where there is a lack of randomized controlled trials.

There are a number of other exploratory techniques that most likely will be highly discouraged to be part of any conditional approval. Typically they use subgroup analysis in the context of negative studies with future confirmation.

Now, there is renewed interest in the interim analysis--I say renewed in the sense that regulators--at least in Europe we have always been rather skeptical of the interim analyses because they tend to provide much less data than one would actually want, and a number of secondary endpoints, but it does represent the only methodologically coherent approach to early approval and early rejection of the null hypothesis in the case of a

severe under-estimation of the treatment effect. So, it is something to be studied. The problem then is in choosing what is the right methodology; what is the right balance between early rejection and still being able to collect sufficient data from the same study.

There is another model, which is a model proposed by Roberts and Chabner which goes under the name of selective approval, which might gain renewed interest in the context of targeted therapies. Basically, the post-authorization studies are used to refine our understanding about who are the population most likely to benefit.

So, if I can summarize, probably the most difficult models are those which have many times been proposed in the past using some biomarkers, or single-arm studies with confirmation from randomized controlled studies. Simply, the assumptions are too strong and often we have see that they do not hold in the end. And, in the case of phase 2 studies, there is a very high risk of rejection up front and, even if there is no

rejection, there is an impossibility of performing the trials afterwards, at least in the same indication.

Probably the models which will get renewed interest are, as I said, the interim analysis and the selective approval. With all of these possibilities, our legislation allows us exploring many different models and optimizing this conditional marketing authorization. Clearly, there is a need for scientific advice early during the development being given more extensively, and we have now this possibility of parallel advice from FDA and EMEA, which is certainly a great step forward.

Looking at the current experience, if there is an expectation of a high benefit with a new drug the best bet probably is to randomize as early as possible, using a design which optimizes Phase 2 to Phase 3 design and prespecify interim analysis and early stopping for efficacy using adequate endpoints, and to reserve the use of external control and various historic control only

for situations where, unfortunately very rare, there is a dramatic effect.

In conclusion, many of the things which I said are based on draft legislation. Still, there is a very clear emphasis on conditional marketing authorization which has to be reassessed and renewed every year, and the possibility of imposing financial penalties in case of lack of compliance with the commitments. The purpose, of course, is not to restrict the use of conditional marketing authorization. On the contrary, it is to try to balance, as best as possible, the need to bring drugs early to the market for patients and medical needs and, at the same time, limiting the authorization of drugs with an unfavorable benefit/risk.

Now, what would be the ideal models? I don't know. Certainly there will be a lot of discussion and we follow with great interest the experience of the FDA with the accelerated approval.

I am going to stop here. I would just

like to acknowledge a number of people who have made significant contributions to the things which I said today. If I pick two, probably they are Bob Aronsson from EMEA and Erica Abadie from our scientific committee of human medicinal products. Thank you very much.

ODAC Discussion

DR. MARTINO: Doctor, before you leave, can you make clearer for me what countries are represented in the organization, and actually how it is set up? I don't have a clear view of that.

DR. PIGNATTI: Yes, part of the reason that you don't have a clear view is probably the fact that there have been a multitude of systems in parallel, in coexistence in Europe. Now the situation is somewhat simplified. We have 25 member states and the additional countries of the European economic area, Norway and Iceland, are all part of the system which can benefit from the centralized procedure. For all oncology drugs, as of November 20 of this year, this is the only procedure for new oncology drugs. Basically, the

organization is the body which advises the European Commission on the approval, and will be advising the European Commission on the approval across the European Union for all new anti-cancer drugs.

DR. MARTINO: So, there is no longer a need for each country to have approval of its own as of now?

DR. PIGNATTI: No, for other type of drugs where the centralized procedure is not mandatory there is still a system of national authorizations in place. But for the new anti-cancer drugs this is not the case. There is one single marketing authorization valid throughout the European Union.

DR. MARTINO: What constitutes the body that makes these decisions? Is it a group of physicians as you see here, or how do you actually structure that?

DR. PIGNATTI: I would say that as an organization we have a number of scientific committees, but there is one scientific committee which is responsible for delivering the scientific opinion, which is made up of scientists who are

independent of the actual member states but are nominated by the member states. There is representation of all the views of all the member states. It is a committee of scientists. They are responsible for the opinion on benefit/risk for all drugs which are submitted to the centralized procedure.

DR. MARTINO: And are they members that serve a certain term or are they life-long members?

DR. PIGNATTI: The committee is reappointed at regular intervals. No, it is not a life term. Actually there is one member per member state. There is the chairman and there are additional members and alternate members. So, it is a very numerous committee.

DR. MARTINO: I will take one or two more questions for this speaker. Yes, Dr. Hussain?

DR. HUSSAIN: The question I have is regarding this annual renewal, which I think is very attractive because it certainly allows you better control and gives a sense of urgency for completing commitments. Have you found that a once

a year renewal is practical?

DR. PIGNATTI: Well, we don't have any experience yet but, of course, there are some difficulties, at least in the beginning where one needs to allow for a certain time gap to evaluate. So, the current draft needs to take into account about six months of lead time and then six months into a marketing authorization is very little. So, there is that type of problem. But I think there is certainly an emphasis on the need for not longer than one year periods between assessment of the benefit/risk. The concept of reassessing the benefit/risk on a yearly basis was already there with the exceptional circumstances but it wasn't linked to marketing authorization. Here we have the marketing authorization which expires after one year so it is a somewhat stronger emphasis.

DR. MARTINO: Just a final question, I realize that your whole process sounds like it is brand-new and to-be-tried, it sounds like. Have there been actually any drugs that have gone through it at this point?

DR. PIGNATTI: So, the conditional marketing authorization is a new provision. We still need to finalize the implementing legislation

and the guidance. So, the short answer is no. In the past, the anti-cancer drugs that have been approved through the EMEA since 1995 could only benefit from the exceptional circumstances provision, which was a catch-all situation. This is now very differently defined, and probably the role of the two will now be very different.

DR. MARTINO: Thank you very much. Next, we will turn to the actual applications themselves. We are a little ahead of time but don't let any of that go to your heads. I will try and keep you on schedule as best as I can. Our first agent is Doxil by Johnson & Johnson, and Dr. Wayne Rackoff will provide that information.

Doxil--Treatment of AIDS-Related Kaposi's Sarcoma

DR. RACKOFF: Good morning. I am Wayne Rackoff, the clinical leader for the Doxil team at Johnson & Johnson pharmaceutical research and development. With me today from our company are

Dr. Alex Zukiwski, the head of oncology clinical research, and Paul Manley, the leader for oncology regulatory affairs. We are joined by Dr. Susan Krown, from Memorial Sloan-Kettering Cancer Center, an expert in the treatment of patients with AIDS-related Kaposi's sarcoma.

On June 13, 1995, prior to the approval of Doxil, agreement was reached with the FDA to conduct a blinded, randomized study of Doxil and the yet to be approved DaunoXome or liposomal daunorubicin. The study was started after the approval of DaunoXome, in April of 1996.

Study 30-38, conducted in the United States, took four years to complete because of the declining number of patients with the disease and the few sites willing to participate. During that time, highly active anti-retroviral therapy was introduced into clinical practice.

The objective of study 30-38 was to demonstrate the clinical benefit of Doxil based on patient self-assessments of signs and symptoms specific to AIDS-related Kaposi's sarcoma.

Improvement in one of five symptom categories, such as edema or pulmonary symptoms, was considered a response. While the DaunoXome-treated group was used as the reference, the study was not designed for comparison between the two groups. Patients were only eligible for enrollment on study 30-38 if they had Kaposi's sarcoma of a severity that required treatment with standard systemic chemotherapy. Tumor response, as measured according to the ACTG criteria, or AIDS Clinical Trials Group criteria, was a secondary endpoint. Patients were randomly assigned 3:1 to receive either Doxil or DaunoXome.

In our analyses there was an 80 percent response rate for the primary endpoint of clinical benefit and a 55 percent rate of objective tumor response. For both groups, 35/39 patients with tumor response also had a response in clinical benefit score. Median time to response was 30 days for the Doxil group and 27 days for the DaunoXome group.

In 2001, a sNDA was submitted to convert

the accelerated approval to regular approval on the basis of the results of study 30-38. In their review of the study, the FDA noted that the results could have been confounded by the introduction of HAART during the study period because of reports of patients with AIDS-related Kaposi's sarcoma responding to HAART alone, which began to appear as case reports in the literature in 1997.

This led to a non-approvable action letter which was received in 2002. Over the course of the next two years, we met with the FDA to consider designs for additional studies, but no agreement was reached on an appropriate design. After considering our options, late in 2003 we appealed the original decision on study 30-38. As part of that appeal process, in the summer of 2004, agreement was reached with FDA to reevaluate tumor response, as opposed to clinical benefit score, in only those patients without changes in anti-retroviral therapy that may have confounded the interpretation of the effect of Doxil.

In a reanalysis which was submitted to the

FDA in August of 2004, not confounded patients were defined as those patients who had no change in anti-retroviral therapy within 60 days before study treatment, and no change on study unless that change occurred after the first observation of a response. Our results of the reanalysis demonstrate that the confirmed tumor response rate is similar, 50 percent or 55 percent for not confounded and all patients.

The FDA reexamined the reanalysis and requested that we submit it as part of a sNDA. That sNDA was submitted in October of 2004. At about the same time this was happening, a randomized, controlled study conducted in Spain of Doxil and HAART versus HAART alone for the treatment of AIDS-related Kaposi's sarcoma was published in the Journal AIDS. At the request of the FDA, we sought to obtain additional information regarding that study and to provide it to the FDA.

In February of 2005, this year, Dr. Zukiwski and I met with several of the investigators who conducted the Spanish study.

After reviewing our report of this meeting with the FDA, the division indicated that they would like to review data from this study and we agreed to ask the investigators if they would be willing to submit to the FDA more detailed data than were originally included in the publication.

Shortly after that discussion, in March of this year, the FDA indicated that they still felt that the study 30-38 results were confounded by changes in anti-retroviral therapy and that additional data would be needed to support regular approval.

Therefore, in April of 2005, we agreed to withdraw the sNDA, to attempt to obtain data from the Spanish study and to examine again the options for conducting a new study to support conversion to regular approval. We met again in May with all of the investigators who participated in the Spanish study. At that meeting, we reached an agreement with the group that with our support they would collect additional data and then would allow us to submit those data to the FDA.

Unfortunately, shortly after that meeting we received word that three of the six hospitals at which 13 of the 28 patients were treated would not

allow access to the patient data. I will address the published results from that study in a moment.

We also examined again the possibility of conducting an additional study. We think that a number of factors mitigate against undertaking an additional randomized study of Doxil for the treatment of AIDS-related Kaposi's sarcoma. First, data from a number of recent studies provide evidence that supports the use of Doxil in patients with AIDS-related Kaposi's sarcoma in the HAART era.

Earlier I referred to the randomized, controlled study of Doxil and HAART compared to HAART alone that was conducted in Spain. This study was initiated after a single-arm study of the combination of Doxil and HAART that was conducted by the same group, in which a 78 percent objective response rate was observed. In the subsequent randomized study, which is depicted on this slide,

patients with moderate to severe AIDS-related Kaposi's sarcoma were assigned to receive treatment with either HAART alone or Doxil and HAART.

The dose and schedule of Doxil used in this study is the same as that approved in the United States. It took two years to enroll the 28 patients at six sites in Spain. The complete and partial response rate at 48 weeks, which is the primary endpoint of this study, is 76 percent for the Doxil and HAART group and 20 percent for the HAART alone group. The result of the combination group is similar to that observed in the preceding single-arm study.

In this study, 10 of 15 patients required rescue treatment with Doxil after initial treatment with HAART alone. In 9 of 10 cases, the crossover to Doxil occurred after disease progression, and in 8 of 10 cases, the patients had a CR after crossover to Doxil.

A second, recently published case control study from Germany addresses the immune status of patients treated with the combination of Doxil and

HAART compared to patients with AIDS who are treated with HAART alone. CD4 count recovery associated with HAART treatment does not appear to be impaired in KS patients who received the combination of Doxil and HAART compared to matched control patients who did not have Kaposi's sarcoma but who received HAART alone for their AIDS. The response rate of 81.5 percent among the 54 patients treated with Doxil and HAART is about the same as that observed in the two Spanish studies.

Taken together, the studies I presented support the use of Doxil for the treatment of patients with advanced AIDS-related Kaposi's sarcoma in the HAART era. The algorithm on this slide is an example of the current practice standard. As is seen in the yellow boxes that lead to the blue box, the recommendation is to use HAART and liposomal anthracycline, Doxil and DaunoXome to treat patients who progress while on HAART, or those who present with advanced or life-threatening disease.

In addition to the new data, the issue of

how to control for changes in the treatment of the underlying illness when evaluating agents to treat AIDS-related Kaposi's sarcoma remains problematic. Given the more than 20 approved agents and the promising results already observed with a number of new anti-retroviral agents represented on this slide, the standard of care for HIV-infected patients will continue to change.

Therefore, currently there is a consistent body of evidence that supports the use of Doxil in the HAART era. Not all patients require systemic chemotherapy but, in light of the available clinical study results, delay of such therapy for the sake of a randomized clinical study is not acceptable. The introduction of new agents to treat HIV still leaves any new single-arm study open to the same criticism that response may be affected by changes in anti-retroviral therapy.

We believe we showed due diligence in conducting and reporting study 30-38, the study that was agreed upon with the FDA prior to the grant of accelerated approval. Although the FDA

and we have different interpretations of the effect of HAART therapy on the ability to demonstrate the clinical benefit of Doxil, and although the number of patients is much smaller than in the early 1990s, there continues to be a group of AIDS patients whose Kaposi's sarcoma progresses to the point of needing Doxil despite the advent of HAART and who benefit from the availability of Doxil to treat their disease in the HAART era.

Doxil is a liposomal formulation of doxorubicin, an agent with known anti-tumor effect in AIDS-related Kaposi's sarcoma, and Doxil is approved now for ovarian cancer. Based on the information we have presented today, we believe the issue for discussion is what happens when a company conducts the agreed upon study, when the body of evidence shows consistently that the drug is effective for the treatment of the disease, but when changing circumstances in medical practice make it difficult to conduct and interpret clinical studies in such a way that makes conversion to regular approval problematic. We invite the

discussion of the committee on this question.

DR. MARTINO: Thank you, doctor. To some degree, we need to combine questions and discussion all in one. So, with that, I will allow both questions and just your thoughts on this issue. Dr. Perry?

ODAC Discussion

DR. PERRY: Are you ready for questions? I thought 30-38 had a dose of Doxil 20 mg/m2 every two weeks. I thought I heard you say the Spanish study used the same dose, but what I saw on the slide said 20 mg every three weeks.

DR. RACKOFF: That is correct.

DR. PERRY: That is not the same dose and schedule.

DR. RACKOFF: 30-38 was a different schedule than is on the U.S. label. The reason for that, and possibly the FDA can comment somewhat more on the study design as they were a party to it as well, but the reason for that was that the study was blinded and DaunoXome had to be given every two weeks. So, to maintain the blind Doxil had to be

given every two weeks as well. In the original NDA there were studies of Doxil given every two weeks or every three weeks. The label ended up with every three weeks because the data show good efficacy for both schedules and it is obviously more convenient for patients. Again, the reason was to maintain the blind because there were patient self-assessments in that study. That is our interpretation. I don't know if Dr. Dagher or anybody from the FDA would add anything to that.

DR. DAGHER: That is correct.

DR. MARTINO: Dr. Kelsen?

DR. KELSEN: These are rather small trials. They are actually very small trials. Could you give us a feel for how many patients in the United States and in Europe--now that we are talking about the EMEA--per year would merit treatment or you might consider treatment with these agents?

DR. RACKOFF: We don't have good data from Europe so I will have to put that aside. There is no equivalent of the SEER database in Europe but we

can put up the slide of the SEER data for the United States.

Please recognize at the beginning that although it ends in 2002, these are the most recent data published in SEER. They tend to be a couple of years behind because of their data gathering activities. What you can see is that the peak incidence of the disease occurs in the early 1990s and was about 5/100,000 population in the U.S. This is all Kaposi's sarcoma. The overwhelming majority of these patients, probably 90, 95 percent or more, are AIDS-related Kaposi's sarcoma.

Now, from that peak incidence, with the introduction of HAART in the mid-'90s, there was a rapid decline in the incidence of the disease. That occurred as the drug was being approved under accelerated approval in 1995, continued dramatically to decline during the conduct of study 30-38, and now we see probably 1000 to 1500 new cases of this disease each year. Again, a small proportion of those are not AIDS-related.

We estimate that about a third of those

patients receive Doxil each year. Of those patients, many of them--not many of them but some of them may be patients who are receiving Doxil again or who are receiving Doxil continuing over from the previous year. So, it is hard to estimate exactly how many new patients, but it is somewhere in the range of probably 150-300 new patients per year who receive the drug.

DR. MARTINO: Dr. Pazdur, I need you to explain something to me. Once a drug is approved, either with full approval or with accelerated approval, once it is available, as a practicing physician, do I know the difference? In other words, as a practicing physician, are there restrictions placed on me when the FDA says this is truly an accelerated approval?

DR. PAZDUR: If one looked at the package insert, there is wording in the package insert under the "indications" that clinical benefit has not been determined and that there are ongoing studies to look at this. But, I think this is an area that many practicing physicians would not

know.

DR. MARTINO: That actually is the issue that I am sort of getting it, that the nature of our approval process in practicality does not make a difference, once that drug is out there, to the practicing physician or actually their patient.

DR. PAZDUR: I think most practicing physicians, if you ask them what is the difference between accelerated approval and regular approval, they wouldn't have any idea of what you are even talking about.

DR. MARTINO: I actually see that as one of our major problems, however. And, it strikes me that we have a situation here where the drug is out in the public domain and, therefore, is used both as a research agent as well as a clinical agent, and it occurs to me as I listened to this presentation that there actually is a body of information, albeit somewhat limited in rigor. So, it is the rigor of that information which is an issue in my own mind rather than that there is no information on which to base the value of this

agent in this indication. I will take other questions. Dr. Kelsen?

DR. KELSEN: If I could just follow-up on my question from before, which may apply to several of the agents that we are talking about, the number of patients that are available to study a hypothesis in this disease, from what you are saying to us, is very small. If only 10 percent or 15 percent or 20 percent of patients enter a clinical trial with a given disease, it sounds like you are talking about in the range of 50-60 people per year.

DR. RACKOFF: If you captured all of them.

DR. KELSEN: If you captured all of them, or even if you captured a fraction of them. Testing the hypothesis that this does A or B for this drug and a couple of these other agents would be very difficult. I guess that is part of what we need to think about when we talk about accelerated approval for very, very small groups of patients. There is a changing medical circumstance, or the incidence of disease dropped 10-fold, if I

understand your slide correctly, in a matter of a few years. Thank you.

DR. MARTINO: Miss Mayer?

MS. MAYER: Three related questions, of patients who do have progressing Kaposi's sarcoma, what proportion are those for whom HAART does not control the progression? That is the first one. What is the length of time? I am assuming that, like other chemotherapy drugs, eventually resistance develops. What is the median length of time before that resistance develops? Also, could you address toxicity with ongoing treatment for patients?

DR. RACKOFF: So, the first question was about what happens on HAART therapy alone. That is a very difficult question to answer because there are a number of studies of this and if one looks at those studies, you find that there is a mix of patients, both advanced patients and early patients, and also a mix of patients who are said to respond on HAART therapy who also got a little chemotherapy along the way. So, it is very

difficult to assess.

What was published recently in a study by an Italian group addresses the time to response. In the early patients on HAART therapy it is three months, and for the advanced patients it can be as long as eight months on HAART alone. So, one of the advantages of using a combination, for example, is that in the 30-38 study you get early regression and clinical benefit.

As to the toxicity and length of time and actual treatment, I would like to ask Dr. Krown, who treats these patients, to comment on that.

DR. KROWN: Now, that question was about time to response and--?

DR. RACKOFF: Time to progression.

DR. KROWN: Time to progression. I am not sure that we have a really good handle on time to progression after response.

MS. MAYER: Actually, I was really asking how long patients respond to Doxil before their disease becomes resistant.

DR. KROWN: Actually, that has been very

variable. One thing I can say with certainty is that in the HAART era responses last longer, and once the patient who was on both HAART and Doxil achieved a response, they can often go off chemotherapy and have the response subsequently maintained on HAART alone and in some cases this may go on for years.

DR. RACKOFF: In study 30-38 we were not able really to assess an accurate median for survival time, duration of response and time to progression because the study was a six-cycle study and, as Dr. Krown said, the patients usually, when they respond, respond for a fairly long time and they now live for a long time, thankfully, and die from other causes. So, the data are 95 percent censored, for example, on survival and 95 percent censored for duration of response because at the end of six cycles there is very little in the way of progression or death. Does that address what you are trying to get at?

MS. MAYER: Well, I guess it tells me that you have limited data but clinical experience.

Then, my third question had to do with toxicity with ongoing treatment.

DR. KROWN: Well, in my personal experience I would say that this is probably the best tolerated drug of all the chemotherapeutic agents that are available to treat Kaposi's sarcoma. I mean, one might ask, "well, gee, you've got paclitaxel that's out there. Why not use that?" It is used in patients who progress after Doxil but with paclitaxel you have significant hair loss and risk of peripheral neuropathy, neither of which are seen frequently with Doxil. I think another quality of life issue with Doxil as compared to either DaunoXome or paclitaxel is the less frequent schedule, which is very important for patients who are trying to lead a reasonably normal life, which is possible now in patients with HIV infection.

DR. MARTINO: Dr. Eckhardt?

DR. ECKHARDT: I just had a question with regard to feasibility, you know, with something being released for accelerated approval and then

being able to conduct more rigorous trials in an indication where you have such a limited patient population. And I think you have some data suggesting that you have symptomatic improvement with these patients. So, I guess at the end of the day there are two questions that I think as a panel we have to think about in going forward, how this can impact subsequent studies, and the feasibility of those studies in diseases with such a small patient population.

I think, secondly, with regards to the specific indication, if someone were to really say exactly how long and whether or not you actually could complete a study to increase the numbers and have adequate endpoints, I think that is very important. Do you have insight into that?

DR. RACKOFF: Well, we have the Spanish study. It took two years to complete at six centers and it enrolled 28 patients. Study 30-38 enrolled 80 patients at seven centers in four years. That gives you some idea.

With regard to your question of whether a

study is possible, we feel the more important issue is whether a study would really address a new question, something about which we don't have data, and whether or not it would be acceptable for patients in light of the Spanish study, the German data and the multiple studies that we did in the original NDA comparing Doxil to ABV favorably; comparing Doxil to BV favorably--whether or not we could identify a study design that we think would be capable of addressing a clinical question in a meaningful way. Dr. Krown wants to comment.

DR. KROWN: Yes, let me just comment on this because as a clinician who has spent practically 25 years taking care of patients with KS, I think I have a sense of what kind of trials can be done right now. Maybe if you bring up that randomized study slide, I think maybe you will understand what informs the opinion of people who actually treat patients with KS.

You know, if you look at the Northfelt and Stewart trials, and admittedly all three of these randomized studies were conducted in the pre-HAART

era, you can see that there is consistent superiority of Doxil over older combination regimens, in one case doxorubicin/bleomycin/vincristine, in the other case bleomycin/vincristine, whereas, in the study that led to the approval of DaunoXome, which was a randomized trial of DaunoXome versus ABV, there was no difference between DaunoXome and ABV although there is a certain consistency of response rates when you look at ABV or BV arms.

So, I think that really informs the thinking and is actually consistent with the experience of most people in this country, and there are probably not more than two handfuls of such people who actually treat substantial numbers of patients with this disease. So, I think that the issue of, you know, does Doxil work and do patients have clinical benefit is a non-issue for those of us who do this professionally. That is why people are not willing to say, "well, gee, let's drop everything and do another Doxil trial."

DR. MARTINO: Dr. Rock?

DR. ROCK: Dr. Rackoff, I just want to respond to your point in asking what would be the point of doing another trial. What might we learn?

We agree that ODAC endorsed the notion that this agent produces clinical benefit in 1995. We also agree that FDA agreed at that time to the 30-38 trial design. Those types of trials were commonly endorsed by the FDA in the mid-1990s and are no longer endorsed in that way, in the sense of having essentially a single-arm trial with an active comparator.

Just to respond then to your point about what would an additional trial show, what concerns us is the safety question with liposomal anthracyclines because, to our own knowledge, the only randomized trial in which a liposomal anthracycline in AIDS-related Kaposi's sarcoma was compared to placebo showed that there was a mortality decrement in the patients who received liposomal anthracycline up front versus placebo up front. Although time to progression was increased with the liposomal anthracycline, survival was

shorter. That is our specific concern.

DR. RACKOFF: And to what study are you referring?

DR. ROCK: I am referring to a study of DaunoXome in patients with AIDS-related Kaposi's sarcoma. There is a letter in the Journal AIDS, in 1997, written by Dr. R.M. White, a medical officer at the FDA, who was describing a study of DaunoXome versus placebo in those patients.

DR. RACKOFF: I am not sure what concerns there are given the data that are available. Can we bring up the slide on NDA studies, please?

The body of evidence for this drug is fairly strong. This is a selection of the studies that were done for the NDA. Although the top two studies were not used as the basis of approval--and I will leave it to the FDA to comment why that was--30-10 was a randomized 258-patient study and 30-11 was a randomized 241-patient study. Those are the studies Dr. Krown just showed you of Doxil versus ABV and Doxil versus BV.

In addition, there was study 30-21 which

looked actually at cardiac biopsies of patients who received high doses of Doxil and showed less cardiac damage than was seen in dose-matched controls at the university doing that study.

Finally, on top of that, we think that the one thing we have demonstrated with this drug is tumor localization. Doxorubicin has been shown in biopsies to concentrate 2-20 times more in tumor tissue than in normal surrounding tissue.

If we can go to the next slide? I think if you add to those studies--and these are recently published studies, some of which we talked about, I don't think it is fair--it isn't fair to compare a single study of DaunoXome with a body of evidence that we have for Doxil in that way.

DR. MARTINO: Just so that we are all fair, Dr. Rock, the statement that you made about a poorer survival was, in fact, DaunoXome, not Doxil. I just want to be sure we are not confused on this issue.

DR. ROCK: That is correct.

DR. DAGHER: I just wanted to clarify

something else going back to the Spanish study, as you have all been referring to it, aside from one limitation that I think you have all acknowledged, that there are small numbers of patients available for evaluation and also some of the literature involves small numbers of patients. The other thing I just want to clarify about the Spanish study is that, aside from the difficulty with the applicant trying to get individual hospital investigators to provide much of the data, the other issue is that it wasn't clear that the responses were documented to the degree of rigor that we would normally find appropriate for review at the FDA.

I am not trying to focus on that study, but I am just trying to make the point that when we do go to this whole area of let's look at what is in the literature, we have to recognize the limitations not only of the numbers of patients that are described, but also these other issues as well.

DR. RACKOFF: Dr. Martino, can I respond

to that?

DR. MARTINO: Yes.

DR. RACKOFF: Dr. Dagher, I think that was under discussion but I don't think we ever showed that the responses were poorly documented. I think our efforts were going to be to try to demonstrate that they were well documented.

DR. DAGHER: If you listened to what I said, I only said it wasn't clear that they were documented to the degree that we would need--

DR. RACKOFF: Right.

DR. DAGHER: I was just saying it wasn't clear.

DR. RACKOFF: Right.

DR. MARTINO: Dr. George?

DR. GEORGE: We can do comments as well as questions at this point? I just have a comment about the EMEA approach which I really like with respect to the name of what they are calling the conditional authorization, which I think is much better than accelerated approval. All that is in the legislation and we can't really change that buy

it has always given the wrong impression that accelerated approval is somehow better than full approval. I have even had people actually say that to me, that they thought that was the case because, after all, if you accelerate it, it must be better. In fact, it is a conditional authorization. The EMEA is perhaps learning from the FDA's struggles in some of these areas. Also, the limitation on this authorization also helps. There is, of course, the ability to withdraw the approval by the FDA but with these accelerated approvals it hasn't happened yet.

So, we are faced with a situation, as here, where you start down the path with accelerated approval and then things change--medical practice changes and in this case even the condition gets rarer. It looks like you are going to be in a situation where it will never be possible to definitively have the information. You are faced with a real quandary, a real dilemma of having to just keep the situation as it is, that is, with this accelerated approval, or convert to

regular approval without really the same amount of evidence that you ordinarily have for regular approval, or withdraw it in the face of evidence that looks like probably something is good here. So, it is a real difficult matter.

I guess the only thing is that the original designation of giving the accelerated approval is a big step, I guess as we discussed before, but later we are going to have to face what to do with that.

DR. MARTINO: Dr. Hussain?

DR. HUSSAIN: I have a comment and a question. The comment is addressed to the company. If I interpret correctly the arrow that you showed regarding when the confirmatory trial was done and a lot of communications back and forth, it would seem to me that--considering that the trials, as they are, are not big, and the SEER data that you showed shows almost a plateau in the incidence--if you were able to get any patients into a trial in two years--four years, I apologize, there is time to do a similar trial if, in fact, the questions

that are being asked by the FDA are really key with regard to safety, and that is something that perhaps FDA can comment on.

But this is in relationship to the documents that were given to use. This is from a memorandum of October 12, 2005 to ODAC members. Point number three, if you ignore the post-approval--this is on the second page, as I understand it, a post-approval study will not necessarily be required in the exact population for which approval was granted. If you ignore this "post-approval" word--it is a time issue. Why couldn't you accept the two studies that were shown here where they have larger numbers? And, if you go by pure efficacy based on the response rate, it looked like Doxil was superior to the others. To me, this is no different than saying Iressa was good in third-line and we will accept the study plan with chemotherapy in first-line. I don't see where there is a huge difference here, other than this post-approval wording.

DR. MARTINO: Does the FDA wish to

comment?

DR. ROCK: I didn't think we were going to get into this history. Many studies were submitted to the NDA. If one reads the label--just to pick up again on what Dr. Rackoff has been saying--and one reads the clinical study information in the Doxil label, one sees that the basis of the accelerated approval in 1995 was a study in between 200 and 300 patients, of which 77 patients were retrospectively identified and based on five indicator lesions were then assessed in order to demonstrate clinical benefit in those patients. The medical charts were reviewed. So, there was difficulty, as Dr. Dagher said, at that time in documenting adequately the nature of the response. And in part, to give the sponsor credit where credit is due, as Dr. Krown has said in the literature, this is a difficult disease in which to document response.

Nonetheless, many of those studies were submitted to the NDA and what you will read in the label is simply that analysis. You have to draw

your own conclusions. As far as the cardiac benefit of this agent vis-a-vis other anthracyclines, I would refer you to the warnings in the label. With respect to the concentration of the drug in tumor tissue versus normal skin, it is a vascular lesion. Again, we would refer you simply to the label.

DR. DAGHER: I think you are asking a more focused question--

DR. HUSSAIN: I don't think my question was answered.

DR. DAGHER: Yes, that is why I am trying to address it. If your question was does the study or studies used for confirmation of benefit--does that have to be limited to studies that were conducted later, the answer is no. The earlier studies--and I would like the committee to address this, is how important is it or not to address the issue of confounding by HAART, which is the main issue--you know, the major efforts that were required by FDA.

DR. HUSSAIN: When I asked the question, I

asked it in the context of Iressa. This may not be fair. How is this different? You are introducing HAART into the picture and you have it roughly equal in both arms and it still looks like slightly better, and all of that. How is this different than saying drug X plus chemotherapy versus chemotherapy? I mean, you have a pure study, if I understood this correctly, that was randomized trials of Doxil versus combination chemotherapy. Am I correct?

DR. RACKOFF: Yes.

DR. HUSSAIN: So, two randomized trials that were presumably--I would defer to you if you think it is a clean trial, but these were looking at single agent, Doxil, versus combination chemotherapy--no complications; nothing contaminating it supposedly. This is a straightforward comparison which shows that the drug appears to be better. My question to you is why is that not clean evidence?

DR. PAZDUR: I think you used some very important words, "supposedly," "presumably"--

DR. HUSSAIN: But you can look at it.

DR. PAZDUR: And I don't know what was done in the past when the application came in. One

has to question why weren't those studies initially used ten years ago to show that clinical benefit was demonstrated. Here, again, obviously the sponsor had access to that to submit those studies. I don't know, because I wasn't here at the agency at that time, if those studies were, in fact, reviewed. We will go back and take a look at those studies. But it would be quite surprising to me that if you had two well-conducted, well-done studies, adequately controlled studies that weren't used to support this application. Again, the words that you used, "presumably," "supposedly," need to be looked at in greater detail.

If I could question one thing, I think one of the issues here that we are dealing with and I would like to focus on is lessons that we can learn from. We will have to deal with this issue with Doxil and this is a very difficult decision or situation that we are dealing with here. We have a

drug on the market for ten years, okay? Sponsors are supposed to be doing these trials with due diligence. Okay? The question here is we have one randomized trial with a relatively small number of patients. This drug also has changed sponsors. This is the third sponsor that we are dealing with. I asked Dr. Rackoff yesterday, and perhaps he could discuss this, is there any implication when drugs change sponsors, when companies are sold to different companies, where some of these commitments are put on the back burner and are not looked at in a serious fashion? I don't know. I don't work for the company, but I am very interested if that has an impact.

The other issue is, as Ramzi pointed out and as was pointed out in the European current legislation, that this be a comprehensive drug development program with, you know, early introduction of randomized trials that will attempt to answer the question here.

The other point that I wanted to bring out is as far as using literature. There is literature

and then there is literature. Okay? If we were talking about large randomized trials, several that showed a convincing survival effect, hard endpoints, that is a little bit different than small studies that were unaccustomed to getting information from certain European centers on relatively subjective endpoints. So, I think, you know, all of that needs to come into play here.

But perhaps Dr. Rackoff could answer that question because, obviously, we have a ten-year span here of the development of this drug after accelerated approval, and I wonder what the impact of mergers, acquisitions, etc. of pharmaceutical companies is in the utilization of these commitments.

DR. RACKOFF: Well, there are about five questions on the table, and I would like to take them in order, coming back to this one. If you could put back the slide with the NDA studies, I would appreciate it.

First of all, there is a long history here and some of us were not around and meeting minutes

are not always reflective of everything that was said, so when I say it was our understanding, that is one of the things that gets at the issue that Dr. Pazdur brought up of mergers and acquisitions. You may lose institutional memory. You have paper but at the FDA people turn over and at our place people turn over, and when there is a merger that is accentuated. I will come back to that question.

This package is a package that has led to regular approval, or the equivalent, of this drug in over 70 countries. So, while the ABV and BV studies were not found to be acceptable for the basis of approval in the FDA, they have been the basis for regular approval in over 70 countries outside of the U.S. So, that is the first point.

My understanding of the regulatory history--and, Paul, add anything if you want--is that those studies used predominantly an indicator lesion measurement of response and not the full ACTG criteria. If you could put that slide up, Brian, I would appreciate it.

This is one of the issues with this

disease. You combine AIDS, you combine a tumor and you combine a very complicated disease to assess. You can have hundreds of skin lesions. You can have a disease that is internal, visceral, that can't be seen on a CT scan and has to be examined with either symptoms or relief of symptoms like GI bleeding or endoscopy. As Dr. Krown will tell you, patients aren't thrilled about the latter.

Secondly, when you have hundreds of skin lesions, to get a CR and have everything go completely away rarely happens. So, that is part of the issue of why those studies weren't used. They didn't follow every one of these criteria.

But in our look at those studies, we agree with you that there is still evidence, as part of the body of evidence, that it has been very consistent and very positive over time. So, it may lack a complete picture of the tumor in every patient, but still it is not inconsistent. You mentioned Iressa. There is not a negative study in this body of evidence in this tumor for this drug.

So, I hope those answer your questions now

in terms of the regulation history. Somebody raised the ten years. Really it has been three years since we received a non-approvable letter on study 30-38. Our commitment study did not start prior to approval because there was a lot of discussion about what study to do. I am sorry Dr. Temple isn't here. He was here at the last ODAC and I think was in on those discussions. But the study that was finally agreed upon included a control which was not yet approved. So, we had to wait some months, until April of the following year when DaunoXome was available on the market. That study was then conducted with due diligence.

We approached 25 centers in the U.S. and only six would participate. To get 80 patients was four years of work. But it was done; it was completed; and it was submitted. So, I really think that ten years is not quite the whole picture. Seven years of that was taken with waiting for the comparator to be approved, conducting the study, submitting it and a one-year FDA review. So, I think the time really compresses

out to the last three years.

The next question that was on the table was with regard to the overall survival endpoint. I bring this back to the last ODAC at which endpoints that were appropriate for this disease were discussed, and the FDA at that time confirmed that the endpoints that were used in study 30-38 were appropriate endpoints in this disease, given the difficulty in following these patients long term for something like a survival where death almost always, in this day and age, depends on something else, not on Kaposi's sarcoma.

Finally, to get back to the last two questions, the use of the literature, we understand that these are not large studies but I don't think any study we would do would be much larger than that. So, I think it would be, again, far-fetched to assume that we would be doing a 500-patient study in this disease over any of our current life remaining.

Finally, the question of mergers and acquisitions I think cuts both ways. I think the

one thing that I pointed out in my talk that we are proud of is that we did convert, after the merger, the 1999 approval of the ovarian cancer to regular approval. That was based on a post-approval study. It was based on a randomized study. It was one that we had to follow up for six years to get the survival data that were mature enough to allow for approval of that study.

So, I think in terms of due diligence, we are trying to do due diligence with this particular situation, but I think it is a unique situation that is very much dependent on changes in the medical circumstances; changes in the opinion of treaters on what drugs should be used. I would add to that that this is not a drug where development is arrested. I think you know, and FDA knows, and it is public information that we are running two other registration trials, one in multiple myeloma and one in breast cancer.

So, I like to look at this more as the exception to what has happened with our development of this drug, and it is based on circumstances

which we think are unique to the AIDS-related KS situation.

DR. MARTINO: Thank you. Are you done?

DR. RACKOFF: I am, but Dr. Krown wanted to make a comment.

DR. MARTINO: I need to cut you off right now because we do need to move along. I realize several of you have questions and the questions really are the questions that you will have with all the rest of these applications. But we need to deal with this particular agent right now and I would like to focus the committee's thinking on the following:

Given everything you have heard and everything you know, do we actually think that a randomized trial in this disease that would answer issues of time to progression, survival--do we think that that can be done? Because if we don't think it can be done, all we can do today is dance but we will reach no conclusion. To me, that is the central point here, can we expect additional information in a timely manner in this disease that

will satisfy the needs?

DR. PAZDUR: We are open to any trial design here. We are not talking necessarily about a survival study. I want to make that real clear, or a time to progression study. We are open to all suggestions, whether it be a convincing study that is a single-arm study, whatever people would like to address here. But, obviously, there are issues that confound this and we realize that this is a difficult situation. We realize that to do a survival study is an impossibility. We are not even bringing that up here. So, the answer to your question is we consider that a very difficult and probably an impractical situation, but are there other avenues that we can look at here? Perhaps such as a randomized study looking at tumor measurements, for example? Are those possibilities? We are open to a wider variety of discussions here, not just a classical randomized study.

DR. MARTINO: But it would have to be of a magnitude that you would be satisfied for

traditional approval. So, already in your statement we sort of are backing down here and we are saying, well, gee whiz, if they can just show that the tumor shrinks, would that satisfy you because, again, I find that in that statement you are sort of backing down as to the degree of rigor that you would want here. I think you kind of already have the fact that this drug does do something. So, are you unconvinced that it does something? Yes, Dr. Dagher?

DR. DAGHER: I think what Dr. Pazdur was trying to point out obviously is that, as you know from other ODAC discussions and discussion of this product and others, the kind of endpoint that you consider most relevant really does depend on the disease setting. So, just because we may not use tumor shrinkage in and of itself as evidence of clinical benefit in, say, some of the solid tumors, that doesn't mean it applies across the board and we have a lot of examples.

So, I think what we are getting at is, you know, we want suggestions on really where do we go

from here. Is there some totality of evidence? Is there an additional study that could be done to really focus on the questions that have not been answered? Again, that does not necessarily have to be a huge randomized trial.

So, I guess what I am trying to get at is if we could have a sort of more focused discussion on where do we go from here really. Is it a new study? If so, what is the design of that study? If not, what is the totality of evidence that we have? Again, we have said that the problem of going with that route is that even with some of the data that is out there, it is questionable how much you can document that when it is time for FDA to review that data.

DR. MARTINO: So, then the question is, is there already enough data to satisfy the group or is there not, in which case something else should be done? That is really the question.

DR. DAGHER: Well, starting from what can be done because that is really the focus. As Dr. Pazdur said, it doesn't have to be a large

randomized trial looking at survival. We are willing to consider, for example, the Spanish study as part of the totality of evidence. In fact, Dr. Rock found the literature review put out by the company and they went out to try to get that. So, clearly, that was not a large study but we thought it might address the issues. There was a report of the responses. Also, it seemed as though there would be documentation of the HIV viral load, CD4 count and all the issues that potentially could be confounding if you don't have them documented in individual patients. But, as Dr. Rackoff pointed out, there were limitations once they tried to get at that.

So, clearly, we have already said we are willing to consider data. The issue is what kind of data. The point there is if you are willing to consider the Spanish study we would be willing to consider a new study, even if it is not large if it addressed the important questions.

DR. PERRY: Madam Chairman, this has been a very interesting dialogue between the FDA and the

sponsor, but if you want us to vote on anything you are going to have to let us ask our questions.

DR. MARTINO: Well, I don't know if there is any voting to be done here. The issue is advising them or giving them our thoughts. So, there is no voting that will be required of this group.

DR. PERRY: I can't give you my advice unless I get my question answered either. I have been very polite while the sponsor and FDA--

DR. MARTINO: You are a good man but, remember, we are here basically to provide advice so ultimately I do feel that the questions between these two groups really are critical here but, whatever conclusion we come up with, if there is no satisfaction between them it "ain't" going to happen anyway. But with that, Dr. Rodriguez is actually next.

DR. RODRIGUEZ: I just want to be sure I understand with clarity the sequence of the dialogue that originally happened here. As I understand, on slide five, six and seven, we have

the originally agreed objectives of this trial, 30-38, and specifically it is said that this trial was not designed to test the difference between Doxil and the other arm. Is that correct?

DR. RACKOFF: That is correct. The other arm was added for two reasons. One, it was felt that patients with advanced disease would not accept randomization to no treatment.

DR. RODRIGUEZ: Exactly.

DR. RACKOFF: Second, because of the patient self-assessments and some subjectivity there, it was felt that it would be better to have a blinded study. But we couldn't blind to placebo so DaunoXome was added. So, it was really added to help support the validity of the study and to get patients to enroll.

DR. RODRIGUEZ: And DaunoXome was added because at that time that seemed the likely drug to be approved as indicated for this disease. Is that correct?

DR. RACKOFF: Yes. An agreement was made--I wasn't around at the time--but presumably

with FDA's knowledge that they were going to approve DaunoXome, and they did approve DaunoXome and then after that we began the study.

DR. RODRIGUEZ: If I understand then the design of the studies, with 3:1 randomization with small numbers, you achieved. Is that correct?

DR. RACKOFF: Right. There were 60 patients randomized to the Doxil arm and 20 to the DaunoXome arm. We only ended up with 19 in the DaunoXome arm because one patient was incorrectly treated.

DR. RODRIGUEZ: So, in essence, you did complete the required study?

DR. RACKOFF: Yes.

DR. RODRIGUEZ: Or the agreed on study?

DR. RACKOFF: Yes.

DR. RODRIGUEZ: And you did this within four years?

DR. RACKOFF: Yes.

DR. RODRIGUEZ: And this was done despite a number of centers not wanting to participate, with only six centers?

DR. RACKOFF: Well, I would say we did it with six centers in the United States.

DR. RODRIGUEZ: Then, if I understand, you

submitted this information to the FDA and the FDA said this is not adequate because there is now the confounding factor of HAART responses. But, in fact, when you did design the study this was not anticipated.

DR. RACKOFF: Correct.

DR. RODRIGUEZ: Furthermore, in your randomization, one would assume that if you were randomizing this potential effect of the HAART would be equally balanced perhaps? Or, does 3:12 randomization then throw off the "evening out" effect of randomization?

DR. RACKOFF: I am reluctant to make any comparisons between the groups because that study was not designed to do so. It was really a look at the Doxil data. What it was really designed to do was to confirm clinical benefit. I think the FDA, as some people have mentioned, agreed that it is an active drug and there were tumor responses. There

was some demonstration that those tumor responses equated to clinical benefit. In fact, as you saw in the study, more patients reported a clinical benefit than there were actually tumor responses. That makes sense in this setting because to get a response is pretty complicated. To have somebody feel better, you know, happens in a different way.

DR. RODRIGUEZ: So, in fact, you did try to the best of your ability to tease out whether, indeed, there was any confounding effect from the HAART or not, and when you look at the small subset of the patients, about a third of the patients had no confounding of HAART and, yet, still you see the same benefit.

DR. RACKOFF: I want to be clear. Not all patients got HAART. So, what we did was we said no confounding by any anti-retroviral, even if they were on AZT.

DR. RODRIGUEZ: I see.

DR. RACKOFF: So, we said they had to be stable for two months before they got drug, and they had to remain stable until their first

response was recorded. Now, there had to be a confirmatory response but if their ART changed during that time we thought that was okay.

DR. RODRIGUEZ: So, if I understand the information then on slide number 11, in fact, there is no indication here, whether HAART is present or not, that it alters dramatically the overall tumor response.

DR. RACKOFF: Within the study--

DR. RODRIGUEZ: Within the study.

DR. RACKOFF: Within the study, that is our conclusion.

DR. RODRIGUEZ: Thank you.

DR. RACKOFF: And we have looked also at 128 days and 180 days. We didn't present those data to the FDA so I don't feel comfortable presenting them here, and they get to very small numbers but there was no inconsistency there.

DR. RODRIGUEZ: Thank you.

DR. MARTINO: Dr. Kelsen?

DR. KELSEN: The agency raised issues regarding concerns about toxicity as one of the

reasons for continuing to look at agents of this type. So, my first question is this, it is a really uncommon disease but the drug is approved for another indication, full approval, in a cohort of patients--I don't know how many women get it but it is a lot more than this. Is there a strategy where it is possible to demonstrate that toxicity in this population, which is different obviously--the toxicity in this population is not significantly different than toxicity in the much broader population? Would that address part of your toxicity concerns? I assume you are mostly concerned about cardiotoxicity.

DR. RACKOFF: Just to comment--I know the agency had the question, but keep in mind, please, that the ovarian cancer dose is 50 mg/m2 for four weeks and this is 20 mg/m2 every two weeks--every three weeks.

DR. KELSEN: It should be easy to do a study in women using the same dose that you used in this trial since there are many more women who are being treated than there are patients with KS. So,

I don't think it would be too hard for you to design a trial in a relatively limited cohort of women, followed very, very carefully, using that dose and schedule for acceptable endpoints for the toxicity that worries the agency. A smaller cohort of KS patients would be studied to show that there is no difference in kinetics with heart, etc., and that might address maybe one strategy for looking at accelerated approval in a very small population when the drug is available in a much larger population. Then I have a follow-up question.

DR. MARTINO: Who wants to answer that? Go, ahead, Dr. Justice.

DR. JUSTICE: The toxicity issue is an issue but I don't think it is the major issue. I think the major concern was the demonstration of clinical benefit.

DR. KELSEN: Okay. My second question is that this is a disease of declining concern in the United States and in Europe. Is there a part of the world in which this disease is still a major concern in which there are larger numbers of

patients available in whom efficacy studies could be performed ethically?

DR. RACKOFF: We actually addressed that question, and Dr. Pazdur actually said what I think should be the operating principle. He told us don't do a study overseas--I am paraphrasing here so correct me if I am wrong, but I wouldn't want you doing a study overseas that you don't think is appropriate to do in the United States.

DR. KELSEN: That is why I used the term that would be ethically appropriate to do.

DR. RACKOFF: Yes, there are patients available--

DR. KELSEN: Spain is not part of the United States yet, I don't think.

DR. RACKOFF: No, but we would have to now conduct a study where we would have to design an informed consent form that included in our thinking the data that we know about the Spanish study and still somehow have to present to patients that there is equipoise. We don't think that is acceptable in the United States and, therefore,

based on Dr. Pazdur's principle, we don't think it is acceptable to export that question when it is not appropriate to conduct in the United States. And, the reason it is not appropriate is because we don't think it is appropriate to delay therapy in those patients with advanced or life-threatening Kaposi's sarcoma.

DR. KELSEN: But you don't think that there is any trial that can be done anywhere in the world then, even a single-arm study, to address this issue. I thought I just heard at least a hint from the agency that they weren't requiring a randomized study; they were requiring new prospective data that was more precisely performed and was more valid to put to rest any concerns about efficacy, since in the era that the drug was originally approved the endpoints were quite soft. So, you don't conceive of any possible trial anywhere in the world or the United States that could even address that issue? I certainly agree with you that if it is not ethical in the United States, it is not ethical anywhere in the world. I

think we all agree with that.

DR. RACKOFF: I am going to ask Dr. Krown to address that from the standpoint of somebody who does such investigations.

DR. KROWN: Maybe you could put up that summary slide? You know, I think that people don't really appreciate what a heterogeneous group of patients we are talking about, and how difficult it would be to get the kind of pure answer that you would like. I have gone over patients that I have treated over the past several years who have AIDS-associated KS whom I decided to treat with Doxil, and I tried to formulate what kinds of clinical scenarios they fell into. And, clearly, I am only using this in patients with advanced KS but they fall into several groups. There is a group that has not had prior HAART. There aren't that many of those patients around. There is a group that is HAART intolerant or who failed on HAART, and there are many of those patients around but they have different reasons for failure. Then, there are actually some patients with progressive

KS who have had both a virologic and immunologic response to HAART but their KS progresses nonetheless. Then, there is a fourth smaller category of patients who undergo rapid KS progression when they start HAART, which is part of a so-called immune reconstitution inflammatory syndrome.

So, this is an extremely heterogeneous group of patients and I think it is going to be very, very difficult to get a substantial number of patients that are comparable patients and where the issues about, you know, are they on HAART, are they not on HAART, etc., are going to be impossible to control.

I mean, I can go through several cases here that illustrate these but I don't think we want to take up the time, but maybe if you go to the fourth slide, maybe this will bring home to people some of the types of patients that we get to treat.

I think if you see a picture like this, you don't need a clinical trial to understand what

a drug like this can do for somebody's quality of life. I mean, this is a foot on the left--we call this "the foot"--before Doxil in a patient who actually had at the time control of his viral load but was intermittently compliant with treatment. This is a patient who was treated with Doxil and within one or two doses he had major symptomatic relief and that is the foot several months later, after treatment with Doxil.

The next slide just shows a different view of before and then after in the same patient. So, you can see the kind of clinical benefit. I don't think that you need a case report form or tumor measurements to understand what this meant to this particular patient.

DR. RACKOFF: To follow-up and to come back to your question, so what we face in a randomized study would be asking that patient to delay treatment and we don't think that is appropriate. What we would face in a single-arm study is the ongoing issue of changes in anti-retroviral therapy. We have not, I don't

think--I know we have not come to any agreement on how to address either of those issues. We have not been able to do that.

DR. MARTINO: Dr. Przepiorka, please?

DR. PRZEPIORKA: What is your sense of the response of KS to HAART alone, other than the Spanish study, in your own practice?

DR. KROWN: That is more than one question because I have reviewed the world's literature of what is published on the response of KS to HAART. If you actually read the fine print, what you find is that almost invariably people who were treated with HAART alone for KS have a relatively small tumor burden or are not symptomatic and have no immediate need for chemotherapy, so they are not the people that I would consider candidates for Doxil. Whereas, almost all, with very few exceptions--almost all of the patients with advanced KS in the clinical trials that have been reported in the literature got concomitant chemotherapy with HAART. If you just read the abstracts of these articles, a lot of the abstracts

neglect to tell you that the high response rate they saw with HAART was chemo-aided.

So, I don't really have a sense because I would never take a patient like that and say, "well, gee, let's see how HAART does." I would do that in a patient who had, you know, a few lesions scattered and was not either physically or emotionally suffering from their disease. So, I think that that is not a question that is relevant to the target population for Doxil.

DR. PRZEPIORKA: I have two comments and then a question for the agency. My first comment is that I am fairly convinced by slide 11 that there is no difference in response in patients who were on HAART and patients who were not on HAART, and the trial was blinded. If the trial had not been blinded, I would sway but the trial was blinded. I think that is fairly good evidence that there is something going on here and it is not mediated by HAART.

My second comment is that I think there are enough patients to do a Phase 1 study, but I

don't think we are going to be able to answer any question when it comes down to the definition of rigor.

So, I would go back to the agency, having dealt with all sorts of studies looking at cutaneous diseases, and ask what is their definition of a well-documented response in cutaneous disease considering how cutaneous disease resolves? It doesn't go away like a tumor shrinks. There are degrees of inflammation that are consistent with activity and degrees of scarring that are inconsistent but irreversible. So, before we decide to suggest a study, my question is going to be is it actually going to be possible to ever say to the agency this is the data that you wanted and have the agency accept it?

DR. MARTINO: Before the agency answers I will let the group know that you have about three minutes to end this entire topic. So, whatever answer comes here in one or two more questions that will be it.

DR. DAGHER: Just briefly one thing on

slide 11, the slide indicates that there were 11/22 patients on Doxil who were not confounded. Our review disagreed with that. I think we had a slightly lower number that we felt was not confounded. So, that is just one comment.

In terms of the documentation, we would be very willing to discuss with any sponsor the kind of documentation that you would need. I think the kind of documentation that you showed with the digitalized photographs, etc., I am not sure that that was available back when the original NDA was submitted, for example, and I don't know if that was part of the problem.

DR. MARTINO: Dr. Perry?

DR. PERRY: I would like to see the slide again that shows the duration of response, if I could, please.

DR. RACKOFF: Duration of response?

DR. PERRY: Duration of response. That was on a previous slide, if I remember, something like 113, 115-something days. Oh, time to treatment change.

DR. RACKOFF: On the ABV, BV slides probably. On the randomized studies?

DR. PERRY: Yes. My point is going to be

that--

DR. RACKOFF: Is this what you wanted, Dr. Perry?

DR. PERRY: Yes. So, the time to treatment failure in all of these is relatively short. If we were treating melanoma we would say these were pretty good. But I want to make the point that this is not a home-run drug. We are not curing people with this drug. We are clearly rendering symptomatic, very troubled people with less symptoms but we are not curing people with this drug, and we need to do something beyond this particular drug.

I think that this drug does have a place. I would be happy if it just continued in this sort of suspended animation until a better circumstance could be derived because it seems to me that the nature of the disease has changed over the last ten years and, therefore, designing a study that would

have been acceptable ten years ago is going to be very difficult now, and I don't see any great reason to change. I think we are all, hopefully, waiting for a better Doxil rather than trying to improve upon what we have now.

DR. RACKOFF: Dr. Perry, one point to make there is that that was in the pre-HAART era and what happens now-- and Dr. Krown can comment on this if you want but I know we are short on time--is that patients will go on HAART and Doxil. Their disease will get better to the point where they can be taken off the Doxil, and they do get long-term remissions, if you will, and continue to be maintained on HAART, maybe getting Doxil intermittently. Those were in the pre-HAART era where, without control of their AIDS, they sometimes died of AIDS KS. So, we have to balance those two things.

DR. MARTINO: Dr. Eckhardt, last question?

DR. ECKHARDT: I just have a comment. I think one comment is that I don't think we can necessarily have this continuing in a fugue state

forever. I think what I would like to see is that we at some point don't have to go through hammering again a set of criteria that would, you know, specifically address when you run in a situation where the supportive care baseline is changing; where you have a narrowing disease indication; you have difficulties with response assessment. I do think that we could derive a set of criteria that could be followed in assessing these types of applications.

I think, secondly, you have to balance what is unknown versus or against what actually is known. What is the body of the data, and what is the feasibility of actually satisfying that element of the unknown? I think that you can't really look purely at what is unknown and propose a randomized study without really factoring in the other two components.

DR. MARTINO: That is the end of this portion of the program. I hope you have gotten something out of this, folks, but I will leave that to your own good judgment. A ten-minute break and

I want us ready to go at 10:30, please.

[Brief recess]

DR. MARTINO: Ladies and gentlemen, if you would take your seats, please, I would like to get started in a few moments. The next application up for discussion is from Ligand Pharmaceuticals. It is the agent Ontak. Prior to the company's presentation Miss Clifford will read the conflict of interest statement that pertains to this application.

Conflict of Interest Statement

MS. CLIFFORD: The following announcement addresses the issue of conflict of interest and is made part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting, with the following exceptions.

In accordance with 18 USC Section 208(b)(3), a full waiver has been granted to Dr. Steven George for being a member of a competitor's

data safety and monitoring board on unrelated matters, for which he receives less than $10,001 per year.

A copy of the waiver statement may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

In addition, Maria Rodriguez has been recused from participating in this portion of the meeting. We would also like to note that Dr. Antonio Grillo-Lopez is participating in this meeting as the non-voting industry representative, acting on behalf of regulated industry. Dr. Grillo-Lopez is employed by Neoplastic and Autoimmune Diseases Research.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to

exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

DR. MARTINO: Thank you. Dr. Negro-Vilar will now present for the pharmaceutical company.

Ontak (denileukin diftitox)

Post-Approval Commitments

DR. NEGRO-VILAR: Thank you, Dr. Martino. I am glad to present to you today the information we have on Ontak, denileukin diftitox, and our post-approval commitments.

We are joined today by Dr. Jim L'Italien, who is our vice president of regulatory affairs; Dr. Zofia Dziewanowska, who is the vice president of clinical research; Dr. Elyane Lombardy, our executive medical director of clinical research and she joined our company recently and is now in charge of the Ontak project; and Dr. Eric Groves,

who is our vice president for project management, also involved in the Ontak project. We also have an expert advisor and clinical investigator, Dr. Francine Foss. She is a professor of medicine and oncology at Yale University and she has been involved with the study of this drug from the very beginning and has continued to be involved throughout today.

The objectives of our presentation today are to review with you very briefly the structure, the mechanism of action and the clinical characteristics of denileukin diftitox or Ontak, and for the sake of simplicity, I am going to now call it Ontak because I have problems pronouncing the other two words together; also, to review the clinical basis for accelerated approval and key development milestones; and also to describe to you the outstanding clinical commitment for final approval; to show the progress that we have made on both protocols, the main one study L4389-11 which was formerly, prior to 1999, described as 93-04-11, and then study L4389-14, a companion study which

also was prior to 1999 described as 93-04-14. Finally, we were requested also to describe to you briefly the difficulties we encountered in conducting these trials.

Ontak is a fusion protein. It combines two parts of molecules. One is an IL-2 molecule and, as such, it targets the binding domain of the IL-2 receptor. Then, the catalytic and cytotoxic unit of the diphtheria toxin also has an internalization component. The protein then targets IL-2 receptor containing cells primarily and then, once the molecule is internalized, as I will show you on the next slide, it exerts its action to induce apoptosis and cell death.

The target for this treatment is cells that contain the IL-2 receptor, particularly leukemic and lymphoma cells of T- and B-cell origin, including cutaneous T-cell lymphoma. Many of these have been described to constitutively express one or more subunits of the IL-2 receptor.

Just briefly describing the receptor itself, it contains three subunits, alpha, beta and

gamma which are also commonly described, in the case of alpha as CD25; in the case of beta as CD122; and in the case of gamma as CD132. The gamma is common to several other interleukin receptors. The alpha is specific, as well as the beta, for this receptor. When you have beta/gamma you have what we call an intermediate affinity receptor which is quite sensitive to the drug. When you have all three subunits, alpha, beta and gamma, you have a high affinity receptor which potentially is even more sensitive to the drug.

Once the drug gets into circulation, it binds to the binding domain of the receptor, is internalized and then in an acidic environment there is cleavage of the protein. The cytotoxic portion of the toxin is released and that inhibits protein synthesis and induces apoptosis or cell death. The clinical characteristics of Ontak are that it is indicated for the treatment of patients with persistent or recurrent CD25-positive cutaneous T-cell lymphoma. The drug has an acceptable safety profile and one of the

characteristics is that it induces minimal myelosuppression.

To update you on the process of accelerated approval, we received approval in February, 1999 on an accelerated basis with data in CTCL patients from two clinical studies. The first one was a Phase 1/2 study, 92-04-01, which showed a response rate in a subset of patients that had CTCL of 37 percent. The second study was a pivotal Phase 3 randomized, double-blind, two-arm study looking at two doses of Ontak, 9 mcg/kg versus 18 mcg/ kg. That was formerly known, as I told you, as 93-04-10. That showed an overall response rate of 30 percent.

As part of the commitments after the accelerated approval, the main commitment was to complete a three-arm blinded, placebo-controlled study comparing the two doses of Ontak, 9 mcg/kg and 18 mcg/kg, in CTCL patients together with a placebo arm. That is what I will describe from now on as 4389-11 or simply study 11 with a final target, as I will show you later, of 195 patients.

In addition, we have a companion study which required the completion of an open-label study using the higher dose of Ontak, 18 mcg/kg

also in CTCL patients and the target for this study, study 14, was 86 patients. As I described, it was a companion study to 11 and includes essentially patients from three distinct subgroups, the CD25-negative patients, with a target of 29 patients; then placebo crossover patients from study 11, and I will describe the details in a minute; and then re-treatment of patients who had been treated in three prior trials, prior to 1999. After 1999, that particular group was not formally included.

The study design has patient selection and randomization schema. Across the sites that I am going to describe to you in a minute, we looked at patients with CTCL that are stage Ia to III, that have had three or less prior therapies and those that were CD25-positive got randomized in study 11 into the three groups that I described before, the two doses of Ontak 9 mcg/kg and 18 mcg/kg and the

placebo group.

Those that were CD25-negative can be randomized in study 14, the companion study, but also there are two other groups. For the placebo patients that were in study 11, at the end of eight cycles of treatment or if they progressed while treatment, the physician and the patient had the potential to break the blind for that particular patient and then randomize the patient into study 14 and offer them the possibility of treatment. Finally, prior to 1999, there were patients entered here that were retreated after being previously treated in other studies.

For the study 11 design I have already described the three groups. The treatments are given as five daily doses every 21 days. Tumor burden is assessed at baseline and day 1 of each course or after course 1 for 1-8 courses. Of course, the primary endpoint is the response rate.

When the accelerated approval had been obtained, the study originally was assigned to randomize a total of 120 patients on 1:1:1 basis,

40 patients per group. In discussions we had at the time with the FDA, anticipating that there would be some problems with accruing patients to a placebo trial once the drug was out on the market, the randomization schedule was changed to a final randomization of 1:2:2 to maintain the number of placebo patients the same but increase the chance of patients to get into an active arm whether it was 9 mcg or 18 mcg. That resulted in a total number of 195 patients. The number of 40 or 39 patients was derived from a statistical perspective, assuming that placebo patients may have up to 10 percent response rate and, in that case, we wanted to have enough power in the study to distinguish a difference between the placebo group and the active arm groups.

Briefly, in terms of the challenges we have encountered in conducting this study, of course, the first one is the small population size. As you know, SEER database suggests or indicates that the annual incidence of this disease is about 4 per million or about 2.2 percent of the lymphoma

patients. And, there are about 11,000 new U.S. cases per year. I think more or less the same incidence appears to be true in other regions of the world. That is important because, as I will show you, we have moved to do studies internationally as well. Another issue is that there are few clinical research centers in each country that see a significant number of patients that are appropriate for this study and have the characteristics that are required by the trial.

The impact of the placebo arm in a symptomatic patient population is very important, particularly once you have not only this drug but drugs on the market that can be used for the treatment of these patients, as well as the impact of a number of prior therapies on eligibility. These are all factors that have contributed to make the accrual for this trial challenging.

Since 1999, we initiated a large effort to open additional sites to conduct this. I have to remind you that we had 20 sites conducting this trial prior to approval. Most of the sites closed

during the review process and we were able to reopen three of them later on. Since 1999, we have evaluated and started the process of activation of 90 sites worldwide. Of those, 38 were actually opened and started accruing patients. Currently we have 25 active sites. The difference between these two reflects the fact that periodically we lose some sites and we have to continue to replace them to maintain about that number of sites, which is what we think is the minimum requirement to have a reasonable accrual rate.

Patient enrollment for CTCL studies prior to approval--I mentioned the two studies, one that was Phase 1/2 that included 35 patients, and then the pivotal Phase 3 trial that included 71 patients. To put into perspective what we have done so far, study 11 has so far accrued 137 patients. The companion study, 14, has accrued 90 patients. So, between the two we have 227 patients, which is several times larger than the population we had treated or studied prior to approval.

To put it into further perspective, the prospective clinical trial conducted for CTCL was an NCI study by Kaye and others that was published

a few years ago. That study was at the time the largest one conducted, with 103 patients in CTCL. That study took eight and a half years to accrue.

The other difference with ours it included patients--there was no placebo arm. There were two active arms, and included patients across a spectrum of CTCL regardless of the CD25 or seronegative, and also included patients in all stages of the disease.

I wanted to summarize for you, when we re-initiated activities after the accelerated approval we opened sites in the U.S. and then we went outside the U.S. because we realized that it was going to be very difficult to maintain active sites in the U.S. So, we went to Canada and opened two sites there; in U.K. we opened two sites; in Germany and Australia. We also tried to open sites in France and we actually had six sites and went through the process of review and local review

approval but then the ministry of health in the country did not approve a trial that included a placebo arm for oncology patients. So, that one, unfortunately, we lost. We ended the year then with 12 active sites. We enrolled nine patients that year and that increased the number of patients to 82. We had 73 at the time we re-initiated the trial.

Then to go fast forward to 2003, by then, as you can see here, we had a number of additional sites that we opened in Canada. We had one site remaining in the U.S. We had additional sites in the U.K. and the Netherlands. In Austria we opened two sites that year; Germany. In Poland we opened five sites. We had five sites open and opened one more, in Russia five and one in Australia. At that time we started collecting screening information as well so we screened 48 patients, of which 16 entered into study 11 and that increased the total number of patients in the trial to 114.

In 2004 we continued with the distribution of patients with little variation around the world.

However, we had a major setback. We had identified 16 sites in Brazil and Argentina that went through the process. We had an investigator meeting in Brazil in November of 2004. Fourteen of the 16 sites received IRB approval but then, again, both the ministries of health of Argentina and Brazil rejected the trial because of the placebo arm, even though we provided assurances (a), that we had a companion trial to which the patients could rotate and (b), that we would provide drug to patients throughout the life of the patient if that was needed to increase their interest. So, we ended the year with 23 sites. That year we screened 70 patients, 14 of which enrolled in this trial and increased the number to 128.

Finally, to give you an update of where we are today through the end of October, again, the distribution has remained relatively the same, except that we don't have any sites in the U.S. any longer. We have in Canada. We have one site in Switzerland. It took about two and a half years to get that site open. We finally did that. We added

two more sites in Australia. Now we again have a total of 25 sites. Thirty-one patients have been screened so far this year and nine have been enrolled, leaving the total now around 137.

Just to give you an idea, since 2003, in the last almost three years, we screened 150 patients; 39 of those entered study 11; 31 entered study 14. About 25 percent of the patients that we screened entered the trial. Remember, they had to meet first CD25-positive or negative in one case; second, then the number of prior therapies, etc. Just to put it in perspective, in our pivotal trial we entered 26 percent of the patients that we screened in Phase 3. So, I think the efforts are consistent and I think we are making some progress.

In terms of study 14, essentially the enrollment goals of the study have been met. We had a target of 86 patients. We have enrolled already 90 patients. We have a target for CD25-negative patients of 29. Currently we have 32. In addition, we have another 58 patients that are CD25-positive. So, that provides two distinct

subgroups contributing important additional information. The first is the patients that have been in placebo treatment in study 11 and they either responded in eight cycles or progressed and moved into study and those are 31. By the way, 31 is now getting much closer to the 39 target that we have. We don't know that all the patients will enroll into the study but at least we know that 31 have. Then, re-treatment after relapse of those patients that were treed until 1999, we have 27 patients.

In summary, I think with our intensive efforts in study 11 we have total accrual to date of 137 patients. That gives you an average enrollment of about 12 patients per year, or about half a patient per site per year.

In study 14 we met the enrollment goal of 86 targeted and 90 enrolled, and the study continue to accrue. It will remain open because it offers the patients in study 11, the placebo patients, the therapeutic option of receiving Ontak after progression.

In terms of finalizing our next steps, we would like to open a dialogue with the FDA in the future to discuss strategies to satisfy the

requirements of our post-approval commitments, including the possibility of achieving earlier study closure following an evaluation of total patient accrual from both the 4380-11 study and the 4389-14 study. Thank you very much.

ODAC Discussion

DR. MARTINO: Thank you, doctor. So, am I correct in estimating that if you continue at the present rate it is going to take you at least another four or five years to reach that magic number for trial 11?

DR. NEGRO-VILAR: That is correct. We think that the number of 12 patients per year is pretty solid. With our best efforts, it has been pretty consistent. On the other hand, as I showed you, I think we are pretty close, or we may be close to getting the number of placebo patients we need. Again, I remind you that the reason for expanding the number of patients was to make sure

that we had at least that number to provide the potential to have up to 10 percent response in the placebo group. By the way, I have to remind you that there is no data on placebo responses in this patient population that is reliable or that has even been documented. That is an important observation as well that will give us a chance to maybe do an evaluation, plus additional information that we are going to collect from study 14 which I think will be complementary as well.

DR. MARTINO: Thank you. At this point I want to remind the committee what our goal is right now. There are two questions that apply to this application which is for ongoing trials, has accrual been satisfactory? If not, what strategies can you suggest to the company for planned trials, if you think there are such? Have changing circumstance impeded conduct of trials? If so, are there alternative trials to suggest?

So, again, I will remind you that there is no voting on whether these are good or bad drugs. That is not the issue today. The issue has to do

with the design of the trials. Can the required number be met? If not, what advice can we give both to the company and to the FDA on these issues? So, please, keep in mind what our real objective is here. With that, I will open this either to questions or discussion. Yes, ma'am?

MS. MAYER: I have a question based on the challenges encountered slide; I believe it is slide number 12. The last item there has to do with the impact of number of prior therapies on eligibility. I am wondering if you have looked at expanding the eligibility criteria as a way of expanding recruitment for the trial.

DR. NEGRO-VILAR: Very well. Let me first show a slide that we have that I think will help you understand this. This will be number one in the backup or number 28.

If you look at all the stages of the disease, we have in the early stages of the disease the prevalent topical therapies that apply here, and they are listed there including another drug that we have which is both topical and oral for the

treatment of this disease. From there, you move to oral and parenteral therapies which are usually applied in a crescendo, first on an oral basis, and then you move to Ontak or combination chemotherapy, etc.

The trial does not include patients in stage IV. So, those are ineligible for this study. So, we are left with Ia to III, which is still a reasonable population. However, we also have patients that receive topical therapies which are typical particularly in the early stages and if they receive more than three then, of course, they are not qualified for this. At the same time, we have the combined issue of different number of therapies.

You know, I think in retrospect one could look at this and say, with hindsight, many years ago we probably could have allowed a larger number of therapies to be received, or make a differentiation between topical versus oral, etc. However, at the stage we are in right now, where we are close to the end, I think it would be a little

complicated to start changing the criteria because that would create a different pattern of statistical evaluation analyses that we might have to do. So, I hope that answers your question.

DR. MARTINO: Dr. Eckhardt?

DR. ECKHARDT: I guess looking at these questions, you know, it looks like the accrual has been satisfactory and certainly the strategies. It seems to me that the patient screen fail rate has been fairly consistent, and you know the reasons for that.

But I have a question and maybe, Steve, you can address this. That is, what you brought up with regards to looking early at the data in this randomized study. I didn't actually see what your statistics are, but the question is whether or not if you were then to pool both of the two different doses versus placebo group you would have any statistical confidence for the endpoints.

DR. NEGRO-VILAR: Well, that is always a possibility. Again, this is one of the things we want to come back and discuss with the agency in

terms of a statistical plan and how we are going to evaluate this. We already have a statistical plan in place but I think we need to recognize that quite some time has gone by and we may need to tighten a few things in the plan as well. That may include also looking separately at the two doses. Remember, there are two components. One is the efficacy and the other one is the safety, to look at both things. Again, for all I know, we may have enough patients in each of the groups to have enough power to calculate those differences. But if not, I think a potential approach is to combine the two doses and certainly have a better comparator with the placebo arm.

I want to remind you again that in the case of the placebo we have those patients that have been demonstrated not to receive any favorable outcome of the treatment or, in many cases, they may have progressed while on placebo. Then we have the other side of the coin, which is to treat them in this case with a high dose. So, that gives another comparator. I think it is very valuable to

say, okay, this patient did not do well on placebo, and then we put them on treatment, and what happens? I think that is an important component as well.

DR. MARTINO: Dr. George?

DR. GEORGE: I had a question related to this. Is there a monitoring plan for this study? Is there a monitoring committee?

DR. NEGRO-VILAR: The protocol calls for a data evaluation committee to do the analysis of all the responses.

DR. GEORGE: Is there a formal plan, statistical plan for monitoring?

DR. NEGRO-VILAR: There is a statistical plan. Essentially, it basically says that for efficacy evaluation the patients have had to have completed the prescribed number of cycles of treatment, and at least two-thirds of the patients will have had to have up to six months of evaluation.

DR. GEORGE: Just to be clear, there is a plan to do some kind of analysis of those.

DR. NEGRO-VILAR: What we would like, as I said earlier, is to come back with a proposed plan to the FDA and discuss the statistical plan and

analyses in detail, get agreement on that and then move on.

DR. GEORGE: Again to be clear, no one has done this analysis yet?

DR. NEGRO-VILAR: No.

DR. GEORGE: So, you are talking about potential design changes in the absence of knowledge.

DR. NEGRO-VILAR: In the case of protocol 11, it is a blinded study so, obviously yes, you can do that. Study 14 is an open-label study so that is why we know how many patients we have and, of course, at any point in time we can look at what kind of responses or activity we have there. But that is not the case for study 11.

DR. MARTINO: Dr. Perry?

DR. PERRY: Did I observe correctly that there are no U.S. sites participating at the current time?

DR. NEGRO-VILAR: At the current time, that is correct. I think the last one was open through 2003.

DR. PERRY: And the reason for that?

DR. NEGRO-VILAR: The reason for that--I will give you my answer and then I will let Dr.

Foss, who I think had the last open site in this trial, answer. I think it is the availability of the drug and the difficulty in putting patients on a placebo-controlled trial. Dr. Foss may want to elaborate on that because it is not just the placebo, but there are some components of how that is evaluated.

DR. FOSS: Right, I actually was the last site in the U.S. to finally close down after a couple of years of not being able to convince patients to go on this trial. We had this trial open when the registration study was open. At that time we could put a number of patients on because, again, the goal was to try to address a group of patients who had had fewer prior therapies, who weren't as refractory. Once the drug became

available, it became the practice in the CTCL treating community to use this drug, even use it earlier on for patients who had more advanced disease. So, it became very difficult to convince a patient to go on this trial.

Also, you have to remember that all of these patients are symptomatic. That is why they have a couple of topical therapies or other treatments before they even get to the oncologist's office. So, it is very difficult to have a patient sitting in front of you who is symptomatic and, by and large, most of these people are functional and they work, etc., and tell them that you are potentially going to offer them a therapy that is ineffective that they have to be randomized to. So, that has been a very, very difficult hurdle to overcome. I think that is really the reason why we were unable to put patients on this after approval.

DR. PERRY: Thank you.

DR. MARTINO: That actually brings up the issue with all of these events, which is the very fact that a drug has been approved then becomes a

critical problem in being able to complete and get any other information. So, you know, we can all keep dancing around the problems of individual drugs and companies but there are some basic themes that we all sort of know about. As much as I love sitting here and going through these individual drugs--and I do love it obviously--you know, it strikes me that unless we deal with the underlying issues at some point nothing is going to change. Yes?

DR. KEEGAN: I just want to take a minute and sort of put in perspective the reason why we have a placebo control on here. The issue is both to get a better handle on the response rate in a disease where response is sometimes a little bit confounded by some of the waxing and waning of the cutaneous manifestations, but also to get a better sense of the clinical symptomatic benefits in a placebo-controlled trial where we could really [not at microphone; inaudible]...of the active drug. The third reason is because of the toxicity associated with the drug. We sort of went through

that kind of quickly, but the drug does affect all T-cells, both normal and malignant, that bear the IL-2 intermediate and high affinity receptor. So, it carries the potential for infectious complications and that is very difficult to tease out in this population. It is associated with infusional toxicities which have been fatal, and with capillary leak syndrome associated with the toxin portion.

So, for all of those reasons, we felt it was very important to have a placebo arm to put the drug in context and to deal with one of the aspects of the accelerated approval, which is, is the short-term benefit balanced by the long-term outcomes? And, we didn't really feel there was a better way to do that. So, we asked that the study be conducted in a population where it would not be totally unreasonable to delay therapy in the placebo arm with the idea that they would all be offered active drug upon progression.

DR. MARTINO: Well, I don't think any of us would argue with you on the value of placebo.

That is, you know, well founded scientifically and we all appreciate that. The issue is that we create our own problems and unless we figure out how to get around the fact that we create the problem--and I think that has to do with the actual design of what we accept as accelerated approval level of information--nothing is going to change. Dr. Pazdur?

DR. PAZDUR: I feel your pain!

[Laughter]

The issue here is--and I think we addressed this in our previous meetings, and I think one has to reflect that these are early examples of accelerated approval. Okay? We are talking about a learning process here. We did in our last meeting also address some issues that I think are important that we reiterate here.

Number one, we made a big emphasis that we look at these accelerated approvals as part of a comprehensive drug development plan; that the sponsor should--we would look favorably, we want them to have ongoing trials prior to the

accelerated approval of a drug. We understand fully that once a drug is approved here, in the United States, it is going to be very, very difficult to do that trial in the exact same indication. So, I emphasized in our last meeting to please have these trials ongoing. Fortunately, many companies have heard us and they have initiated ongoing trials before they bring they applications to the agency.

The other alternative that we have is to examine the drug in an earlier stage of disease. That is frequently done with many of the accelerated approvals. The initial approval for CPT-11 irinotecan was in a 5FU refractory population, and subsequent studies have shown benefit in earlier stage of diseases.

So, there are ways around it but I think you have hit on a key issue here. This requires some forward thinking. You could have the trial ongoing with significant accrual, with plans to then supplement that accrual in geographic areas where the drug is not available. That was done

recently with the Velcade study. Or, you could look at it in an earlier stage of disease. But these are practical issues that sponsors have to be aware of.

Here, again, one of the reasons why we are holding this entire ODAC session is to bring out these examples and give real-world examples. Silvana, we are stuck with past problems that we have had and past agreements that we have had and past decisions, and it is very difficult sometimes to revisit those. But, in revisiting those, the whole issue here is to learn and to emphasize these issues.

DR. MARTINO: Go ahead.

DR. KEEGAN: You know, I do think that the one additional point is that we did go into an earlier stage of disease and we did have the trial accruing so I think the only thing that wasn't done is that actually sites were not on line prior to approval. Am I right? Yes. The entire study was being conducted in the U.S. So, I guess really the only other lesson that applies that the company did

not take was to have actual U.S. sites open prior to approval because as soon as it was approved all the U.S. sites dropped out.

DR. MARTINO: Dr. Kelsen?

DR. KELSEN: I think actually this last discussion was addressing what I was going to say, but just to reinforce it, on the previous application one of the questions I asked was regarding non-U.S. sites and just to clarify this, because the sponsor made a comment that I was struck by and I think the policy--I guess the right word is policy--is that the agency and sponsor would be encouraged to perform ethical trials, trials that would be performed in the United States, both in the United States and outside the United States particularly to address this issue of drug availability in very rare diseases. This disease has about the same incidence as the application we heard just a couple of seconds ago, but sponsor chose to pursue extra U.S. sites, and is vigorously pursuing that as I look at it, and is able to address the issue. So, you encourage

sponsor to think about extra U.S. sites where data that is reliable can be obtained to more expeditiously answer these questions.

DR. PAZDUR: Yes, and in situations that have been successful there are two problems. It is not just the initiation of the trial; it is adequate accrual to that trial prior to any regulatory decision. I am not talking about just getting it past an IRB, I am talking about actual enrollment on a confirmatory trial and then plans being made. Since this is a comprehensive drug development plan, we have asked the sponsor when we approve this drug what is the plan for maintaining enrollment on trials, and I think that needs to be explicitly brought forth to the sponsor, or those questions need to be raised because this is obviously a serious obligation. They can't have the accrual plummet at the time of approval and then be stuck in this very nebulous area about where they are going to go with the trial.

DR. KELSEN: Could you give us a feel for recent accelerated approvals? Do you have a feel

for how often the development plan considers the dropping enrollment within the United States and begins to look to either a partner in EMEA or a partner in some other part of the world, just rough numbers?

DR. PAZDUR: I don't have a number at hand, but this is a discussion that we have with all sponsors at the time of approval, especially for ongoing trials where we do consider that there would be dramatic curtailment or drop in accrual, what effect would the approval have on accrual in the United States. Here, again, that was one of my concerns, and I mentioned it in my opening comments. As the EU goes to a conditional approval system, we have been counting usually on the accrual to be caught up by some of the European sites and to expand enrollment in European sites. That may or may not be a possibility, depending on what new regulatory mechanisms are available in those countries.

DR. MARTINO: Mrs. Mayer?

MS. MAYER: Dr. Pazdur just made one of my

points. I guess my concern is that there is sort of a window of time, it seems to me, where overseas sites may be a little slower to approve these drugs where companies might be able to test them in randomized trials in that population, and I wonder if that will always be the case. That is just one question.

But it strikes me that Ontak is an example of a drug that is a targeted therapy for a patient population selected by a biomarker, and I think we have seen some recent examples of drugs developed that work in a rather small part of the population for which biomarkers have not been developed and, as a breast cancer advocate, I am a great fan, since we have drugs that work as targeted therapies with Herceptin and the hormonal treatments, of drug development going in this direction.

But it strikes me, looking at this example, that as the defined groups get smaller and smaller who are available for trial enrollment this is likely to become an increasingly large problem. I think as we look at drugs for accelerated

approval we really need to anticipate this issue in realistically predicting whether or not trials can be carried through to completion.

DR. MARTINO: Dr. Eckhardt?

DR. ECKHARDT: Actually, I have a question. If you were to go back and ask, based upon the accrual that seems to have been pretty consistent from year to year, knowing going forward that this was clearly almost a ten-year process of essentially satisfying this requirement--and I think that is something that we are going to have to think about. I mean, is that really reasonable when you have a population that you know steadily accrues at so many patients per year whether or not it is really reasonable to think of a ten-year period for essentially satisfying those requirements.

My concern is that over time paradigms shift with regard to therapy and many other issues with regards to regulatory issues and ability to continue to accrue those patients. So, it almost seems like you need an earlier assessment of

exactly what is the timeline and whether or not that is reasonable.

DR. MARTINO: Yes, doctor?

DR. PRZEPIORKA: The question I have is regarding the comment regarding redesigning a statistical analysis plan. It is very clear from trying to get sites on board that the problem may not be at the level of the patient immediately as opposed to the minister of health and the issue with the placebo. Would the agency accept a statistical analysis plan, since my understanding is that this trial was designed with a relatively large number of placebo patients specifically to exclude spontaneous regression at 10 percent, to pool placebo arms from several studies that are going to be given to the agency so that you can minimize the number of patients treated with placebo and so that you don't have to worry about unethical studies being accrued to?

DR. KEEGAN: We would certainly be interested in discussing what the proposal is. I will say, and I don't know if it was as a

consequence, but certainly about the time we last visited this issue we, in fact, had just undergone a reassessment of the trial design and changed the allocation to the different treatment arms, which was a somewhat tricky issue to do. We can certainly revisit it, but it will not be a particularly easy thing to do, and it will require some time for evaluation of that proposal.

DR. PRZEPIORKA: But my question perhaps is not so much specific to this trial as opposed to any other trial that may be coming up. If one is forced to use a placebo arm, are there ways that you can minimize the number of patients on placebo if the N is there just to make sure that it is not greater than 10 percent spontaneous remission?

DR. KEEGAN: I would say that really wasn't the only reason. That is why I mentioned three. Toxicity is also an issue. The kind of data collected across studies may vary. So, you know, the patients enrolled may vary. Making comparisons, therefore, is a little bit difficult. But, you know, I suppose we could always reconsider

the ways to use data from various sources.

DR. MARTINO: I need to understand this a little bit more and I think the question is going to Dr. Pazdur. Once you have given accelerated approval, the company then is able to brand their drug for that particular indication and it then becomes public property. Physicians can use it as they deem appropriate. Once you give something full approval the same thing has happened. So, from a company's perspective, what do you view as the advantage to actually having full approval? Does it actually make a real difference to them? What can they do that they cannot do otherwise?

DR. PAZDUR: Well, that you are going to have to ask the companies what their opinion is.

DR. MARTINO: Actually, I would like yours first.

DR. PAZDUR: And I will give it to you. Obviously, there are advertising restrictions that they don't have to clear. They are not required obviously to do a confirmatory trial. We have several types of post-marketing commitments. The

most stringent, as far as adhering to and having some regulatory power to take a drug off the market would be with accelerated approval. Okay? But for the vast majority of patients that are using it and prescribing physicians, I don't think that there is a major distinction between those. Do you have something you want to add?

DR. DAGHER: Just a minor point maybe, but with the guidance that I described on the updated thinking of what we consider available therapy, another obvious advantage is that to pursue a regular approval strategy you no longer are having this uncertainty about if you come for filing and there are other drugs that have become available, that that is going to influence the agency's ability or interpretation of what is available therapy. In the United States we don't have necessarily a specific comparator standard as long as the trial, let's say a randomized trial, has an appropriate comparator. So, that is the other kind of additional thing at this point. I would be interested in what the sponsors say about that.

DR. PAZDUR: But the point here is that an accelerated approval is an approval.

DR. MARTINO: That is the point I am sort

of getting at here. Now I would like the company's answer to that question. What is different for you if you have full approval versus accelerated approval? And, I also want you to consider my question from the point of view of dollars and cents because I think that is the bottom line.

DR. NEGRO-VILAR: Well, there are two components to that question. I will try to address one and then I will ask my colleague to talk about that. I think that you obviously want to move as quickly as possible to have full approval. I mean, this is like renting with a lease that is going to expire in a period of time or owning the property. Also, the way the studies usually are designed, we agree that they are going to provide additional useful information. You want to have the ability to make those claims. You want to be able to say, hey, we looked at this; we looked at that. At the end of the day, if we have CD25-negative

activity--and I think there is a possibility where we see that--we would like to be able to make that claim. If we have differences between the safety of the dose that gives you the best responses not different than one that gives you less response, we want to be able to make those claims too. So, the quicker you get there, the better off you are because now you can move into the more appropriate way to talk about these.

Cost-wise, I have to tell you that on a per patient basis these are the most expensive trials that we ever run because we have to keep sites open; we have to keep monitoring groups and CROs, etc. Whether it is for half a patient every year or for 100 patients a year, you still have to have those open. You want to get that done and move on from there.

So, I think the compelling reason is to move there. I agree that these are approvals and we perceive them that way, but if we can get to the full approval status I think that is what we would all like to do.

DR. MARTINO: I guess what I am struggling with in my mind is, is there a serious price tag to a company when you only have accelerated approval

status? Is that really a disadvantage to you?

DR. L'ITALIEN: I would like to comment. My name is Jim L'Italien. I head the regulatory affairs group at Ligand. Really the data I think is important to us from two perspectives. One is that it does actually facilitate our ability to market in the U.S. because we have a much different process that we go through in terms of preparing any marketing materials. In the accelerated approval situation, it requires prior approval for all marketing aids by the agency. So, we have to go to back and get the prior approval. That can be juxtaposed to for a full approval product where a company is able to seek that advice if they wish it, but more routinely the company prepares marketing materials which are then able to be submitted to the agency simultaneous with their use. It really does facilitate the preparation of the marketing materials. So, that is one.

Another aspect of this particular case of Ontak is that these additional trials that we are conducting are also going to form the basis for us to seek approval in other major geographies, such as Europe. In that case, if we consider that the U.S. market and the European market are possibly

the same size, it actually represents a doubling of our market potential. So, we have had that in mind and that has also been one of the key motivators for us to try to accrue and complete these trials.

DR. MARTINO: Thank you. I need to discuss this further at some other point. At any rate, I will drop it for right now. We need to go on at this point. Thank you, all.

The next presentation is the drug Mylotarg and we need a few moments to set up the audiovisual. While we are doing that, Miss Clifford will read the conflict of interest statement that relates to this agent, please.

Conflict of Interest Statement

MS. CLIFFORD: The following announcement addresses the issue of conflict of interest and is

made part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting, with the following exceptions: Drs. Michael Perry and Donna Przepiorka have been recused from participating in this portion of the meeting. We would also like to note that Dr. Antonio Grillo-Lopez is participating in this meeting as the non-voting industry representative, acting on behalf of regulated industry. Dr. Grillo-Lopez is employed by Neoplastic and Autoimmune Diseases Research.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with

any firm whose products they may wish to comment upon.

DR. MARTINO: Dr. Allen with present for Wyeth Pharmaceuticals.

Mylotarg (gemtuzumab ozogomicin)

DR. ALLEN: Good morning. My name is Lee Allen and I am vice president for medical research for oncology at Wyeth Pharmaceuticals, and I have responsibility for Wyeth's oncology development portfolio. I am joined today by two medical colleagues from Wyeth, Dr. Mark Shapiro from our clinical research and development group and Dr. Jay Feingold, from our medical affairs group. In addition, we have two of our collaborators from the Southwest Oncology Group, Dr. Fred Appelbaum and Dr. Steven Petersdorf, who are also attending this meeting.

We appreciate this opportunity to update you on the status of our post-approval commitment

for Mylotarg, and I will be discussing some of the challenges of the study and the interventions that have been taken to address them. We also welcome your feedback and guidance today on this ongoing trial.

I would like to say at the outset that Wyeth is fully committed to completing our obligation in a timely manner. As we prepared for today's presentation, we felt it would provide the most clarity to specifically address our progress on Mylotarg's post-approval commitment by reviewing our commitment-related activities in two main categories, the first being the period of time from Mylotarg's approval to the time the post-approval commitment study was initiated; and the second, the period since that time was initiated to the present time.

Using this as a framework for our discussion, I will start off with a brief review of Mylotarg's indication and then review our subpart H clinical commitment. Next I will talk about the preparatory activities that were required before

the post-approval commitment study could be initiated, including the prerequisite pilot combination studies and protocol development review and approval.

Then we will move to a discussion of the ongoing S0106 study, starting with a brief review of the study design, and then I will give you the current status of that program. We will next review the study challenges that were identified in our recent study progress assessment and talk about our accrual action plan to ensure that this study gets completed in a timely manner. Then we will discuss the opportunities we have to fulfill our post-approval commitment and finally I will wrap up with some conclusions about the study and then open it up for discussion and your feedback and recommendations.

Mylotarg received orphan drug status in November of 1999. Based on a robust complete response rate in Phase 2 studies, it then received accelerated approval in May of 2005. Mylotarg is indicated as a single agent for the treatment of

acute myeloid leukemia in first relapse in patients whose tumors are CD33-positive and who are 60 years of age or older and are not candidates for other cytotoxic chemotherapy.

The focus of our post-approval commitment, and the reason we are here today, is to address what is stated in our label and provide an update on our controlled clinical trial with Mylotarg that is designed to demonstrate clinical benefit.

The subpart H Phase 4 commitment for Mylotarg targets a combination study in first-line therapy for newly diagnosed patients with AML. This study also has the potential to broaden the population which could derive clinical benefit from this agent. It described a randomized, controlled study of Mylotarg with daunorubicin and cytarabine versus daunorubicin and cytarabine alone as induction therapy for patients with de novo AML.

As a prerequisite for this study, it was necessary for us to perform pilot combination studies to define the appropriate dose and patient populations for the randomized study, and to ensure

that the toxicities observed with the combination were both tolerable and acceptable.

This chart summarizes the key tasks since the approval of Mylotarg in May of 2000 and the last ODAC review in March of 2003. This included the implementation and completion of the necessary pilot combination studies and the development of the S0106 protocol in collaboration with the Southwest Oncology Group and the FDA. Planning for the combination studies was started in advance of the accelerated approval and the studies were initiated three months after Mylotarg's approval. These studies were completed shortly after the ODAC in 2003. This is showing you the span of those pilot studies.

These pilot studies in de novo AML patients demonstrated a robust complete response rate for Mylotarg in combination of 43 percent in older patients and 77 percent in younger patients. It is important to note that this 206 study, shown here, served as the basis for the design of the post-approval commitment study. The safety profile

in these combination studies was similar to Mylotarg as a single agent.

In parallel with conducting these pilot combination studies, discussions were ongoing regarding the post-approval commitment study with both the FDA and SWOG, and a protocol was submitted to the FDA for special protocol assessment in December of 2002. A few weeks before the last ODAC review in 2003, we received feedback from the FDA on our special protocol assessment. In June, we had a meeting with the FDA and SWOG to further discuss their feedback on this protocol.

Once we had agreement on the study design with the FDA and SWOG, the protocol was then submitted for the required review and approval by NCI/CTEP as part of their administrative process for cooperative group protocols. Following incorporation of the feedback for CTEP, the final protocol was submitted to the FDA in November of 2003. This triggered completion of contract negotiations with SWOG and the protocol first became available to study sites in May of 2004, at

which time IRB reviews and approvals were initiated. The first subject was enrolled in the study in August of 2004.

So, this completes the first part of our review of the necessary preparatory activities that were completed from the time of the approval of Mylotarg to the time of the initiation of the post-approval commitment study. Now we will switch our focus of attention to the S0106 study. I will briefly review the design of this protocol and summarize progress since the first patient was enrolled in August of 2004.

Study S0106 is a study of Mylotarg in combination with standard cytotoxic chemotherapy. It is designed to address two clinically important questions. The first question specifically addresses our subpart H post-approval commitment and compares the use of Mylotarg in combination with standard induction therapy to standard induction therapy alone.

Because of strong investigator interest and important unmet medical need, this study was

also designed to answer a second important question in post-consolidation, the potential role that Mylotarg would have in patients in post-consolidation therapy. To answer this second question required that the study be expanded in size from approximately 400 patients to nearly 700 patients which, in turn, increased the duration of the study.

This slide shows the schema for this protocol. Patients were randomized to one of the two treatment arms, either standard induction therapy alone or standard induction therapy with Mylotarg. Patients achieving a complete response then received three cycles of high dose Ara-C in consolidation, and patients remaining in remission were randomized a second time to post-consolidation therapy with Mylotarg or no therapy at all.

It is important to note that, as agreed with the FDA, the durable complete response rate from the first part of the study, from the induction phase of this study, could potentially support registration and fulfillment of our

post-approval commitment. This is something that I will come back to later in this presentation. The disease-free survival endpoint from the post-consolidation phase could support an additional registration for Mylotarg as maintenance therapy.

Our target enrollment for both components of the study was 684 patients. The projected accrual rate is an average of 160 patients per year which was based on SWOG's prior experience in enrollment in similar studies. This would require approximately four and a half to five years to complete enrollment in this study. In addition, patient follow-up was for three years.

In the planning of the study, planning was made for several interim analyses to evaluate both safety and efficacy during the course of the study. Two interim analyses were planned during the induction phase and three during the post-consolidation phase.

In terms of the current status of this study, as of the end of October, we have 234

centers with IRB approval. Now, 14 months after enrollment of the first patient, we have 57 patients enrolled in this protocol. What is important to highlight is that 32 of these patients were enrolled in the last six months. Wyeth and SWOG have had an ongoing dialogue regarding this study, and with the majority of the study sites now open and this relatively slow rate of enrollment we carefully reevaluated the study and assessed the need for additional interventions.

This assessment focused on two main questions: are there any challenges with the drug itself, or any challenges with the study design? Feedback from discussions with key SWOG investigators and thought leaders supported that Mylotarg was considered a valuable drug in the treatment of AML, and also that it had a safety profile consistent with other chemotherapeutic agents. So, there did not seem to be any major challenges here to study accrual and completion.

As far as study design itself, the feedback we received here was that this study was

still considered to answer clinically important and relevant questions, and that Mylotarg could potentially address an important unmet medical need if successful in this study.

The study's inclusion and exclusion criteria were considered to be appropriate and not unduly restrictive or impacting enrollment. There were three main enrollment challenges that were identified. The first is the issue of enrolling a relatively large study in an orphan disease, something we have heard about earlier today as well; that study sites were slower in getting their IRB approvals and were taking longer to identify and enroll patients on the study; then, lastly, that many of the historically high enrolling study sites had only recently been able to join the study as they completed prior study commitments.

Based on this analysis, our accrual action plan to address these issues, in collaboration with SWOG, is to continue to drive high enrolling study sites to complete their IRB approvals over the next few months, and we have a commitment from the

majority of those centers to do so.

In addition, discussions with NCI Canada are now reaching completion and sites are expected to be initiated in December and January with the target of adding approximately 50 patients per year to this study. Between the current SWOG enrollment of six to eight patients per month and the addition of the Canadian sites we will be nearing the rate of enrollment we need to complete this study.

Wyeth will also be providing additional study site support for data management to SWOG to facilitate the study and ensure data quality. We will be working together with SWOG to increase investigator awareness and participation through two mechanisms. One, a quarterly SWOG newsletter that will highlight all ongoing leukemia studies, including this protocol; and, the second, through the publication of the Mylotarg pilot combination studies. We will continue to actively monitor enrollment with SWOG and rapidly address emerging issues, and we plan to do another formal study at re-assessment in the second quarter of 2006 to

assess the impact of these current interventions on study enrollment. At that point, we will again make any necessary additional interventions.

In addition to these specific actions, we have also been discussing other options with SWOG, including the addition of other countries and cooperative groups. While there are several challenges to doing this, we have such discussions ongoing. We will consider the need for additional interventions if the expected impact of the current interventions is not realized.

With the majority of the study sites now on board and the actions being implemented, we expect that there will be a marked increase in the rate of enrollment into this study, and we have not identified any insurmountable challenges to study completion.

We recognize the importance of completing our post-approval commitment as rapidly as possible, and have looked for opportunities to do so before the final data from the completion of this S0106 study become available. Based on our

agreement with the FDA in June of 2003, the durable complete response rate endpoint from the induction phase of this study could fulfill our commitment, and this would be achieved by a positive outcome for Mylotarg at either of the currently planned interim study analyses for the induction phase, targeted for the first quarter of '07 or the third quarter of '08.

In addition, we have initiated discussions with SWOG and the FDA on a proposal to amend the current statistical analysis plan for this study, to add another analysis of durable complete response rate on all the patients from the induction phase. This proposal could potentially accelerate the delivery of our post-approval commitment by at least two years.

In conclusion, through accelerated approval we have been able to provide patients with a valuable treatment option for AML. The prerequisite pilot combination studies with Mylotarg and chemotherapeutic agents have been completed. The ongoing S0106 study is showing

increase in its enrollment rate, and will provide answers to meaningful clinical questions and has the potential to expand this clinical benefit to a broader patient population with unmet medical need.

Wyeth and SWOG are actively partnering in monitoring the progress of this study and implementing additional interventions to enhance study accrual, and Wyeth will continue to respond to study challenges.

As I said at the beginning of this presentation, Wyeth is committed to meeting its post-approval commitment in a timely manner and is diligently pursuing opportunities to fulfill it. With that, I will stop at this point. Thank you for your attention, and we welcome your feedback and guidance to make this study successful. Thank you.

ODAC Discussion

DR. MARTINO: Thank you, Dr. Allen. Can I ask a question of the representatives of SWOG? Your thoughts as to whether bringing on the NCI of Canada will, in fact, bring you up to where you

need to be, or are you going to have to go beyond that?

DR. APPELBAUM: We are optimistic that it should bring us to where we need to be, but we will continue to explore other opportunities at the same time.

There was a considerable delay between our last up-front AML study and the activation of this one. It was over two years. There is no point in pointing fingers at anyone but it was just hard to get a study together that had to have approval of SWOG, of CTEP, of the FDA and of Wyeth and to do all the contractual arrangements that were required. It was quite a chore, but it was accomplished.

But the result of having over two years without an up-front AML study was two-fold. Some of the centers decided, well, we could in the interim start other studies, industry-sponsored studies. The other thing was that they got out of the habit of entering patients onto AML studies, or had their data managers place them elsewhere. So,

we were quite concerned when we activated the study and saw that the accrual was low.

So, Steve Petersdorf and I have called every one of the SWOG sites, and of the 20 top accruers, 18 of them are absolutely committed to doing the study, with two exceptions: Tulane, which has been difficult to talk to recently for obvious reasons, and City of Hope, which is going to be moving to their own independent study where they will be transplanting everyone. But, otherwise, every one of the SWOG sites was enthusiastic about participating, but many of the high accruers hadn't even put it through IRB until late in the year. So, now we should see all of them coming through. In fact, over the last two months we have been accruing at about two patients per week, which would be 100 patients per year which is sort of what we expected. With that and the addition of NCI Canada we should be up to about 150 patients a year.

Unfortunately, because of the first year's slow accrual, we probably won't be able to make up

for that unless we were to go beyond that. So, we are continuing to look at other possibilities. We have ongoing discussions with Sweden right now. Recent changes in the FDA policy may allow us to do that without having to have assurances with each separate hospital in Sweden. So, that may make that more doable. We are also pursuing other possibilities.

DR. MARTINO: Questions or comments from the committee at this point? Yes, Dr. Cheson?

DR. CHESON: This study actually does not suffer from one of the major problems that we see today. In fact, this is a very good question, it is a question that will remain a good question for sometime to come, like a number of the other trials which the companies have been suggested to do.

I think one of the biggest pushes you may get is the publication of those data. Now, your primary endpoint being durable complete remission, reading the briefing packet suggested that you were including not only CRs but this Wyeth endpoint of CRp, which is not included in the international

response criteria for AML published in 2003. So, when you say durable CR in this study, which are you referring to?

DR. APPELBAUM: Really we are looking at CRs, not CRp. We readily accept the fact that CRp, which may or may not have importance particularly where relapse patients may have quite a different implication when it is used in first remission patients where, conceivably, it could interfere with the ability to give subsequent chemotherapy. So, we are looking at CRs.

DR. ALLEN: Again, if you remember the data from the 206 study, the 77 percent was a CR rate, not a CR combination rate.

DR. APPELBAUM: Also, while the 206 study was very important, there is also the other publication, by Kell in Blood, where they had an 84 percent true CR rate when they added Mylotarg to 10 and 3. Their schedule was slightly different than in the 206 study but, again, adding impetus to the reason to do the randomized study.

DR. MARTINO: Dr. Kelsen?

DR. KELSEN: In all three of the applications this morning the issue of global sites being part of the trials have come out as sort of a

theme. So, I have a question and I guess it is for the agency but maybe for the sponsor. It doesn't apply to this particularly because there are so many U.S. sites. Do you have a policy, or have you thought about how you deal with a perception that could arise in other parts of the world if there is a study under way like the previous application with no U.S. sites--we can't do it here, or we don't want to do it here, or it might be perceived as we don't think it is good for Americans but it is going to be exported abroad so that foreign people will participate in a trial? I notice that several countries rejected participating in a study if there was a placebo arm. Do you have any thoughts about how one would deal with that perception? You would only allow an ethical study, obviously, but it could be mis-perceived.

DR. PAZDUR: I think that is a difficult question, you know, because it has to do with other

people's perceptions and how one would address those. Here, again, as I stated before and as was reiterated by one of the other companies, we would have to have confidence that, you know, this would be ethical to be done here before we would say that the study could be done. Dealing with how other people perceive that is a difficult issue for anyone to deal with because a perception is out of one's control.

However, we do look at the data, and the data should represent, you know, the practice here in the United States and those results and can be extrapolated to U.S. practices of medicine, etc. so they are not just out there without any context. So, the answer to your question is almost unanswerable, Dave.

DR. KELSEN: I think you actually have given me a hint of it though. My guess or my understanding then would be that sponsor X says, look, we can't do the study in the States; it is just not going to be done here; the drug is approved here--this actually only applies to

accelerated approval because only in accelerated approval are they committed to a post-approval study, as opposed to we would like to do a post-approval study--we are going to do it abroad. The FDA vets the design of that study; has meetings with the sponsor and says that even though all accrual is abroad, we have reviewed the protocol--I assume you review the consent form too but I am not so sure about that--and this study is a study that would be done in the United States if it wasn't for this circumstance that you just logistically can't do it. That is correct, you vet the trial?

DR. PAZDUR: Oh, yes. We basically don't approve trials; we allow them to proceed in a sense. So, we are in active discussion with the sponsor in looking at the design, the comparator arm, the statistical plan, the eligibility criteria, etc.

DR. KELSEN: That kind of statement would help to address any incorrect perceptions abroad.

DR. MARTINO: Dr. George?

DR. GEORGE: I have a question about this

study and then a comment about the latest discussion. In the interim analyses you planned for this study, at the time of doing the analyses in the induction phase will there be any information that will be released or discussed with the FDA concerning the other analyses? That is, you do an analysis, say, of complete response, the duration of complete response, but there are also the post-remission questions that you will have information on but I assume you are not planning to release that information or discuss that at that time. In other words, you will be evaluating the complete responses and the duration of those from the induction phase in the absence of information from that. I just want to be clear, is that what you are planning to do? I ask this question for a specific reason because I know of at least one case in which the FDA asked for information about the other part of the trial even though it wasn't time for it.

DR. ALLEN: Again, the interim analysis obviously will focus on the induction data and, as

you say, the other data would be available. In terms of communication, that is an area that we have active discussion with SWOG about in terms of what could be released to the agency at the interim analyses, particularly the additional analyses that we are planning to add.

DR. GEORGE: I would just point out that it can be a problem if the FDA requires information on further kinds of things that you weren't prepared to do. You can run into difficulties in interpretation later.

The other thing I wanted to talk about isn't really about Mylotarg per se but the issue that has come up before--a couple of things. One is that in serious and life-threatening diseases placebo-controlled trials are always difficult. It is not an implication because of accelerated approval or something; I think it is difficult in general. We don't have time to discuss all those issues. I know they have been discussed a lot in the past.

The other thing has to do with the

statement that a trial that is unethical in one country shouldn't be done in another country. I think there are subtleties there that need to be discussed, again maybe not here. But the idea of the ethics of a study may be tied up with the practicalities of a study less than the real ethics of it. That is, it is entirely possible that in different cultural, social settings, medical settings, some country or group of countries may be a lot more skeptical about the results or may be reluctant to believe things and, therefore, it would be entirely appropriate to do trials in that country because of equipoise, whereas, in another setting the prevailing medical notion may be that things have already been established enough that we are not worried about it so we can't do a trial because we already think we know the answer. To me, that is not saying that if it is unethical here we can't to it anywhere else. That is sort of the wrong kind of statement. Of course, that is true on the face of it; you can't do an unethical trial anywhere. But I think there are issues that need

to be discussed before you just say because it can't be done in the U.S. it is difficult to do elsewhere or wouldn't be ethical to do somewhere else.

DR. MARTINO: Dr. Hussain?

DR. HUSSAIN: I just have a comment in the spirit of how does accelerated approval process get approved. I have to commend you on a very well-thought out process. I do think--even though this is self-serving as I am a SWOG-ee--that engaging the cooperative groups early on in the intellectual process of getting the protocol and moving it through, as much as it is painful to get through CTEP and FDA and all of that, and I had recent experience with that, the point of it is that I think it results in a better well-thought out protocol at the end of which, if something unforeseeable happened, you had done everything you can. And, I would like to suggest to sponsors in the audience that this would be a model to follow. It was well thought out. It is a large number; a lot of people put intellectual work into it and it

is a model that we should perhaps consider pursuing more often by engaging the cooperative groups.

DR. MARTINO: Dr. Cheson?

DR. CHESON: Yes, perhaps I am a little confused or more confused than usual, but in the conversation we just had between Dr. George and the sponsor concerning the release of information it would be my understanding that it would be the SWOG DSMB that is monitoring this trial, not the company. So, I would be really surprised if there were any information released prior to the conclusion of the study. Am I right, Fred?

DR. APPELBAUM: I think you are exactly right.

DR. CHESON: That is how it should be, right?

DR. APPELBAUM: Yes, Bruce. What will happen is that the issue that we talked about with the SWOG biostatisticians, it would be totally up to the DSMB, the ability to perhaps release CR data after the last patient had been randomized and received all their post-randomization Mylotarg to

maintenance, but not likely till then. But once that would happen, to look for disease-free survival you would still need two more years of follow-up after the end of maintenance, or at least a year follow-up after a year of maintenance. So, this could allow us to look at CR rates in advance of that without having to wait until the final analysis. It would have to be after the last patient, randomized to maintenance, received their last dose of maintenance. It would be my suspicion that that is what the DSMB would say, but it would be up to the DSMB to make that decision, and it is SWOG's DSMB, not Wyeth's.

DR. ALLEN: Again, that is option three with the two years earlier delivery. Again, I think there would be an issue or something for DSMB to consider if, again, the activity in the induction phase was robust and perhaps, again, continuing that enrollment into the induction arm into the two arms if the data was strong may have to be modified. In that case, I think we would have another discussion about what could be

released.

DR. MARTINO: Mrs. Mayer?

MS. MAYER: I was impressed during the presentation about the careful and well-documented timeline for the various stages of the post-approval study design. Yet, I am still left with the fact that in the most optimistic of cases it is still going to be seven to eight years following accelerated approval. At the least optimistic, it would be 12 years and that is 2012.

It seems to me that there is something wrong with a model that permits a drug to be marketed without clear evidence of clinical benefit for up to 12 years which, I don't need to say, probably is the majority of its patent life. So, somehow I would like the committee and certainly the agency to address that issue, that even under the best of circumstances where there is due diligence it can still take that long.

DR. MARTINO: Dr. Pazdur, you may answer.

DR. PAZDUR: Due diligence is vague. Okay? And, I think it is deliberately vague and we

have had scientific evidence on this for various indications such as pediatric indications that may take a long time. But there are some issues that I think, again, since this is a learning curve are peculiar about some applications. That is, when a drug comes along, is it going to be used alone or is it going to be used in combination? Well, it is quite apparent from this drug in the treatment of acute leukemia that Mylotarg was going to have to be used in an up-front setting in a combination.

So, the question is should those combinations be initiated very early on since that is where kind of the trail of this drug is going on. So, here again to reiterate a common theme, it is a development plan that we are emphasizing here, although this drug alone provides benefit to a select group of patients, the true benefit of this drug is going to be in drug combinations. So, how do you move that up front and how do you actually promote earlier drug combinations.

We had an example in our last go-around of temozolomide where the drug was going to be used in

combination and we found out the combination could not be delivered because of excessive toxicity. So, here again, you know, you may have road blocks on any pathway also that need to be at least anticipated. But here, again, the issue with combinations, and this is a good example and is true of most drugs that are going to be implemented in most of the diseases that we deal with--they are going to be in combination and how to earlier implement those combinations are other discussions that I think need to be had.

DR. MARTINO: Dr. George?

DR. GEORGE: Miss Mayer brought up the point that I was really going to bring up so I will mention just one thing, that at the time of accelerated approval these kinds of issues probably should be more explicitly addressed. For example, in this case we are generally very impressed with this approach. Even though it is going to take a long time, the ones that bother us might have actually taken a slightly shorter time but we can't quite figure out how they are going to get there in

the length of time. So, in some ways it is less the time issue than it is a clear understanding of that up front that we probably could have known it back when this was approved that, well, this is going to be used in combination; it is going to take a long time to do, no matter how you do it; and those are the facts. Whether that influences our decision at the time of granting accelerated approval is another issue but we could have known it clearly and could have faced up to it.

DR. MARTINO: Dr. Mortimer?

DR. MORTIMER: What I was going to say was mostly addressed, but the biggest problem that we have here is that these are sort of boutique drugs for a very small population, and I wonder if there is a possible way to establish a mechanism for registry so that you don't lose these patients to clinical trials that will ultimately meet the endpoint that both the consumer and obviously industry would like to have.

DR. MARTINO: Dr. Eckhardt, Dr. Grillo-Lopez, and that will be the end of this

morning's presentations.

DR. ECKHARDT: I just want to make the comment that this is an interesting situation because actually what I think is a very valuable second endpoint of the post-consolidation maintenance therapy as has been added on, with good scientific rationale, which is to essentially increase the numbers that are required, you know, to really reach even the first endpoint of CR. So, I think this is something that needs to be considered because it is a value added approach. It will add to the development timeline but, you know, how do you integrate this with the idea of getting the full approval. So, I like what has happened to get the most out of the numbers of patients, but in the process it has lengthened then the time to full approval.

DR. MARTINO: Dr. Grillo-Lopez?

DR. GRILLO-LOPEZ: In my view, an important question is what does the FDA regulate and, therefore, what does the FDA need to confirm when there is an approval? Again, in my view, I

believe that the FDA regulates the approval of new single-agent anti-cancer therapies, and not combination therapies and certainly not the optimal use with any combination because there might be many combinations with that drug.

So, I think the operative word is "simple." Keep it simple. If the FDA has granted an accelerated approval to a product, the question that needs to be asked is what is the simplest study that will generate the minimum amount of data that will satisfy the FDA that, yes, this study does confirm the clinical benefit. In fact, the regulations do allow for accelerated approvals without the need of confirmatory trials. This might be an exception but within the wording of the regulations it is a possibility and should be considered. If that is not the case, and a confirmatory trials--and I don't think there have been any exceptions up till now--are required, then first give consideration to the possibility of a single-arm trial because a single-arm trial, historically controlled or with a patient as his

own control, is going to be conducted twice as fast as even the simplest randomized trial. It will require fewer patients and can be done faster and earlier.

If it is a randomized trial that needs to be conducted, then certainly try to do a two-arm trial rather than a three-arm trial or a trial with two randomizations which are going to take two, three or four times longer to conduct and get to the results. I think it is an inordinate amount of time for the FDA to have to wait for ten or 12 years for a result. And, I am not referring to this particular study. I think this is a very worthwhile study and at the end may even change the way that we think about the standard therapy in this disease. But, again, I think in the discussions between the FDA and the sponsor, with the participation of the cooperative groups or investigators, these things have to be taken into consideration. Just keep it simple.

I would also like to comment on studies outside of the U.S. It is interesting to consider

the historical perspective for this in that 30, 35 years ago we were doing studies outside of the U.S. because we could get started earlier because requirements in many countries outside the U.S. were less than the requirements in the U.S. in terms of initiating a trial of an anti-cancer drug. Then 20 years or so ago that changed and we started doing studies abroad because it was cheaper because you could do it for a lower per patient grant than in the U.S. Then more recently it has again changed and we are doing studies abroad because we cannot do them in the U.S. because we cannot get a sufficient number of patients enrolled on studies.

We have to look at the causes of that and address that. Why is that in the U.S. five percent or fewer of the available patient population actually enters protocol studies, and address that. It is not drug availability, something that is approved and is available. Yes, that is a factor but there are multiple other factors out there that we need to address because we should take care of this internal U.S. problem that we have with

clinical trials and patients going on protocol studies.

DR. MARTINO: Thank you. With that, I think what I am hearing around the table is that we have no arguments with the design of the randomized trial. The issues are purely those of compliance and I think the company has given their thoughts as to how they plan dealing with that. So, I don't know that we need to do anything with that, and with that, I will bring this morning's proceedings to a close. The committee will resume its proceedings at 1:00 p.m.

[Whereupon, at 12:07 p.m., the proceedings were recessed for lunch, to be reconvened at 1:00 p.m.]

A F T E R N O O N P R O C E E D I N G S

DR. MARTINO: Ladies and gentlemen, I would like to start this afternoon's meeting. There will be three applications discussed this afternoon and then at the very end we have some time to discuss just some general principles and issues related to the accelerated approval process.

The next application is the agent Depocyt, by SkyPharma. As Dr. Gordon Schooley starts to prepare himself for the presentation, Miss Clifford will read the conflict of interest statements that are specific to this presentation.

Conflict of Interest Statement

MS. CLIFFORD: The following announcement addresses the issue of conflict of interest and is made part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of

interest at this meeting.

We would also like to note that Dr. Antonio Grillo-Lopez is participating in this meeting as the non-voting industry representative, acting on behalf of regulated industry. Dr. Grillo-Lopez is employed by Neoplastic and Autoimmune Diseases Research.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

DR. MARTINO: Thank you. Dr. Schooley, you may proceed.

Depocyt: Enrollment Completed

DR. SCHOOLEY: Thank you. Good afternoon.

Listening to the presentations this morning, there is a fairly common thread in that trying to conduct post-marketing studies in small populations is difficult and we are faced with difficult decisions on how to speed up enrollment without compromising the results of the study and, clearly, that is a theme that runs through this presentation.

Depocyt is a sustained-release formulation of cytarabine, an image of the DepoForm particle that contains approximately 10,000 little chambers that have cytarabine in aqueous form inside of them, released over a period of time. These are about 20 micron particles made up of phosopholipids and cholesterol.

After an intrathecal injection the particles spread throughout the neuraxis and slowly release Ara-C over approximately two to three weeks. The indication that Depocyt was approved for was in the treatment of lymphomatous meningitis and accelerated approval occurred on April 1 of 1999.

Just a brief graph here to show the

concentration as a result of a ventricular injection and ventricular sampling comparing 50 mg of Depocyt versus 30 mg of free cytarabine, and the half-life of approximately 3.4 hours versus 141 hours is an example of the ability of DepoForm particle to release cytarabine over an extended period of time.

The basis of approval for Depocyt was upon cytological response rate in a lymphomatous meningitis population, a small one indeed, 33 patients, 17 of which received Depocyt. The number of responders, 7/17 or 41 percent compared to 6 percent in cytarabine, the comparator arm, which was statistically significant.

The Phase 4 commitment was to conduct a randomized trial to determine patient benefit as the result of a clinical endpoint and the safety of Depocyt for the treatment of lymphomatous meningitis. Also, it was the desire to have additional pharmacokinetic information and a goal of initiating a trial within six months.

The objective of the trial was to confirm

clinical benefits of Depocyt versus the standard therapy in adult patients with lymphomatous or solid tumor neoplastic meningitis. Obviously, the objective and the commitment differ a bit because of the solid tumor patients that were enrolled in this trial, and I will talk about that in a bit.

The design was prospective, open-label, randomized and controlled. The primary endpoint was progression-free survival. There was a neurological evaluation prior to treatment and the start of each treatment cycle. Investigator's decision that progression had occurred was documented with specific signs and symptoms on case report forms. We had secondary endpoints of course, survival and then cytological response rate and chemistries and improvements in neurological symptoms, individual ones, and quality of life and safety.

Key eligibility criteria was a biopsy-proven lymphoma or malignant solid tumor; also neoplastic meningitis diagnosed on the basis of positive CSF cytology which was the requirement

in the Phase 3 program, and added to this study was characteristic signs and symptoms plus MRI or CT scan indicating the presence of meningeal tumor. That was added into this study compared to the prior study, and I will get to that in a moment as well.

Here is a schematic of the study design. Patients were randomized to either intrathecal Depocyt 50 mg or intrathecal 50 mg of cytarabine or, if they were solid tumor patients, 10 mg of methotrexate. Induction of six cycles every two weeks. For Depocyt they would receive an injection every two weeks for 12 weeks, whereas the comparator arm would receive two injections per week for 12 weeks. On the maintenance cycle, an injection once every four weeks for 16 weeks for Depocyt and twice a week for 16 weeks for the comparator arm. There were no patients that went on beyond the maintenance cycle so I won't discuss the follow-up visits.

There was stratification in the randomization procedure for patients who had either

lymphoma or solid tumor and whether those patients came from U.S. or Europe. All patients received dexomethosone as indicated.

The objective of the PK study was to evaluate CSF PK of free and total Ara-C following intraventricular administration of Depocyt. We had two sites in Europe and 12 subjects were treated and they provided PK samples.

Current status of our Phase 4 commitment, we initiated the trial in September of '99 and completed enrollment about a year ago. There was a follow-on of about six months follow-up for each one of those patients. The pharmacokinetic study was initiated in September of '04 and se completed enrollment this last April, and we expect to submit final study reports this December.

In terms of the timeline, as I mentioned, we began in September of '99. Soon thereafter we had a product recall and so we had no product for 17 months. So, it wasn't until March of '01 that product was available again and, going through another IRB process and so on, it took about

another three to four months to bring study sites on-line so, in July of '01, we actually began enrollment and we completed enrollment, as I mentioned, in November of last year. The four and a half years was approximately the time that we had estimated it would take to conduct the trial. It is obviously 17 months delayed because of the product being unavailable.

In terms of patient accrual, the total number of study sites we had was 45 and 25 of those sites actually recruited patients. In North American we had 26, 12 of which recruited patients and in Europe we had 19, 13 of which recruited patients. We recruited 100 solid tumor patients and you can see the split between North American and Europe, and 24 lymphoma patients. Our accrual rates for the study were approximately three patients per month considering all of the study sites and for North America it was about one and a half patients per month. In our Phase 3 trial, which was North America only, we had approximately three patients per month. So, we had about half of

the enrollment rate in the same geographical area when we tried to conduct this follow-on trial. The average enrollment was approximately one patient per site per year, and the average enrollment of one lymphomatous meningitis patient per site per four years. So, it is easy to see the difficulty of trying to conduct such a trial.

This is a schematic of the Depocyt trials that have been conducted to date. Those that are in grey are single-arm trials. The ones in color are comparative trials. We have studied about 296 patients that have been administered Depocyt either in lymphomatous meningitis or solid tumor.

Some of the challenges that we face--it was anticipated that enrollment of 75 lymphomatous meningitis patients within five years was not possible. There was--I guess urging would be a good word to try to conduct this trial within five years. In fact, we only enrolled 24 of those patients in four years. So, what we did was discuss with the FDA the possibility of including solid tumor patients into the trial. It was agreed

that that was probably the best way to get enrollment completed.

Looking in hindsight, that probably wasn't the best decision for trying to assess the efficacy of the drug in the lymphomatous meningitis population. Obviously, the population is different than for which the NDA was approved. It increased the variability due to multiple populations in the study and, of course, there is still a small subgroup of lymphomatous meningitis patients to assess in the study.

Here is just one example of some of the problems that occurred over the course of the trial. This is a design factor because of the availability of high resolution imaging equipment and it was being used for diagnosis of neoplastic meningitis to a much greater extent when we conducted this trial compared to 1992, when we started the Phase 3 trial. So, the investigators were fairly demanding in terms of having inclusion criteria using the MRI/CT scan instead of positive cytology which was the only characteristic that we

had for inclusion in the Phase 3 trial. As a consequence, less than 50 percent of the patients have cytology available for assessment. So, if we were to do a comparison to the prior trial in which cytology was used as an endpoint, the surrogate endpoint, we compromise that ability a bit.

The endpoint of progression-free survival, which is the primary endpoint for this study, was half of what it was compared to the Phase 3 study. So, did the reliance upon CNS imaging or other factors have an impact upon the type or severity of lymphomatous meningitis patients enrolled? I think the obvious answer is yes, but trying to define which ones and the extent of that relationship is a difficult thing in such a small trial. As a final consequence, the ability to detect meaningful progression-free survival between the groups when there is not much survival left is a very daunting task, indeed.

Challenges to study completion, well, there is obviously a few number of lymphomatous meningitis cases and only a small fraction are

available for trial participation. As we have heard previously, the same things have occurred here. With Depocyt being commercially available, there was little interest in participating in the trial. There is actually fear of randomization to the cytarabine group, where four intrathecal injections per cycle versus one for Depocyt was certainly a consideration on the patient's part, especially when quality of life issues for the remaining months of survival they do have is of concern. And, there was competition for patients for other trials that are ongoing.

I mentioned this earlier, but North American recruitment rate was too slow to meet the Phase 4 commitment in a timely manner. I think when we met in 2003 we were only a third of the way through our enrollment after several years, and prior to the meeting we have had discussions about including European study sites, with the FDA, and we agreed that we would move in that direction. There are standards of care and patient management differences between North America and Europe. It

does contribute to the variability of the results and obviously increasing the number of sites from 26 to 45 increases the variability as well.

One of the consequences of the results of this trial appears to be that European sites have complicated the data interpretation. There are differing results on some parameters that you wouldn't expect and you wouldn't believe that regional differences are the real meaning--there is something hidden below that parameter that we are still investigating.

So, turning to answer some of the questions, has the post-marketing study commitment been fulfilled? Well, we are working towards that. The draft report was sent to the FDA although analysis is continuing. We are trying to ferret out more precise results to get away from the confounding that seems to have occurred because of the two populations and due to the regions. Our next step is to meet with the FDA to try to work towards a plan that seems acceptable on how to present the data.

Does the study provide useful information? In terms of safety, yes, I think it does support what we had found as a result of the NDA that was

submitted. We don't see anything new or unusual. In terms of efficacy, as I mentioned, that is to be determined as the confounding factors in a small sample of lymphomatous meningitis treated patients is problematic and subject to some additional analyses.

Is it feasible to conduct a confirmatory trial of a clinical endpoint in lymphomatous meningitis? Well, to conduct a study in that population within a reasonable time frame--let's say five years--some compromises must be and were, indeed, made in this trial and have confounded the interpretation of data, and I would expect that to be the case in most trials because of enrollment rate. To enroll a sufficient number of patients, based on most clinical endpoints in a controlled study in this population, may take 10-15 years. So, there are obviously some things that can be done. We are obviously interested in continuing to

study Depocyt. Our licensees are interested in doing additional studies. We have talked with the European EORTC on possibly conducting a trial in this patient population because we are as interested as anyone in trying to find out additional efficacy in this population. Thank you.

ODAC Discussion

DR. MARTINO: Thank you. I need to understand a few things. Am I understanding then that the study has completed accrual and will be forthcoming to the FDA? Is that correct?

DR. SCHOOLEY: That is correct. We have a draft report to the FDA and they are in the process of reviewing that. Then, at some point in the near future, we plan to meet with them to discuss issues about how the data should be best presented and interpreted.

DR. MARTINO: The study design, was it to basically show superiority of the agent or was it to be equivalent to the "standard?"

DR. SCHOOLEY: This study was designed as a superiority trial not a non-inferiority trial.

We already knew that there would be a sufficient problem with sample size calculations with a superiority trial and it is much worse, of course, with non-inferiority. So, we designed the trial so that we could see an improvement over cytarabine alone.

DR. MARTINO: And was it the intent that both patient populations would be viewed separately and not in any way be brought together so that lymphomatous patients would be viewed as one entity and the non-lymphomatous patients as a discrete second?

DR. SCHOOLEY: Initially the design was to include the solid tumor patients with the lymphomatous meningitis patients and use that as a basis for making a decision. I think though in our review of the data--I think to do that you have to assume that those two populations respond similarly and what we found is that that may not be the case. So, then you are left with possibly looking at the subgroup of lymphomatous meningitis patients.

DR. MARTINO: Dr. Cheson?

DR. CHESON: Thank you. I have a question and then a comment. The question is how many patients in the U.S. have received Depocyt in the

last, say, 12 months?

DR. SCHOOLEY: The last 12 months? Oh, I am taking a guess and I am just going on the number of lots manufactured, probably 300, 300 or 400 maybe.

DR. CHESON: In the whole country 300 or 400? I am really troubled by this. I was kind of quiet in the morning but I am really troubled by this. The drug was approved, if my memory serves we well, on the basis of a randomized trial with about 21 patients in it.

DR. SCHOOLEY: Yes.

DR. CHESON: Okay, small numbers to begin with. Now we are faced with a study, particularly in lymphoma, which is confounded by all kinds of stuff--throw in some solid tumors. Now we are looking around to see how we can extract data from this or that. Europeans do things differently than we do. It has taken a really long time to do it.

It just seems like there are all these confounding variables and it was approved on the basis of really minimal data to begin with. I am really troubled that we really, at the end of the analysis of these data, are not going to know anymore than we did on the basis of the original 21 patients.

As our Chairperson just asked, first you put in the solids and then you take them out. I think it is going to be almost uninterpretable and I am not sure how useful these data are going to be. It is unfortunate that you allowed yourselves to change the parameters in the study in so many ways rather than finding other alternatives to improving the accrual. I am really, really concerned about this.

DR. MARTINO: Questions, comments, ladies and gentlemen? Yes, doctor?

DR. PRZEPIORKA: Earlier we heard about some alternative strategies to provide supporting data for the accelerated approval. It was clear from your first study that there weren't a lot of patients in the subgroup and once the drug was

approved, since everyone thought it was effective, obviously nobody wanted to be on a trial. I am just wondering if this is not one of those situations we are moving to where another indication for your Phase 4 study might have actually helped since there is a relatively large number of patients out there with ALL who all get intrathecal therapy and hate getting stuck in the back twice a week, which I think could have been an alternative way to show efficacy and probably would have had enough patients to show equivalence, rather than to try to do this in a much smaller population.

DR. SCHOOLEY: It is an excellent point. That is, in fact, the population that we are pursuing. We are starting a trial in Europe with our licensee in that population.

DR. MARTINO: Dr. Mortimer?

DR. MORTIMER: I guess our mission is to figure out different ways to address these studies. Obviously, in this setting where MR has now really supplanted doing an LP in these patients, this

really is an opportunity to figure out a different way to assess response to this agent.

So, if you use MR, which I think most of us tend to do right now, get MRs and make a diagnosis of lymphomatous meningeal involvement on the basis of an MR--then how would you propose assessing response by MR, or do you have an idea that these patients are managed not with intrathecal therapy but with whole brain irradiation? So, my question is do you assess response by MR, and has MR changed how we approach the treatment of these patients?

DR. SCHOOLEY: I don't know that I can answer if MR has changed the way we treat the patients, but clearly it has changed the way that patients are diagnosed, which has changed dramatically from the time that we conducted the Phase 3 trial to this post-approval trial.

DR. MORTIMER: Are patients more likely to get whole brain irradiation because of what we see on MR, or are patients still getting intrathecal therapy? If they get intrathecal therapy, then how

do you assess response by serial MR?

DR. SCHOOLEY: Well, we had no difference in the proportion of patients receiving radiation in the Phase 3 or the post-approval study.

DR. MORTIMER: No, I understand that. But with the practice patterns in the community right now, are people more likely to get whole brain irradiation because of the MR?

DR. SCHOOLEY: I don't know the answer to that.

DR. MARTINO: For me, the problem really from a clinical perspective comes down to being unclear of what the evolution of the disease is if your diagnosis is not a fluid diagnosis of cells but is purely an x-ray diagnosis. I am not sure that those patients are really the same. I mean, I know the progression once you see their cytology positiivity. Those patients don't do well. They are usually quite symptomatic, which is why you actually did that spinal tap in the first place. But MRI of the brain is often done for a multitude of other things--you know, headaches, etc. So,

bringing those two groups together, unless they somehow are stratified or, you know, in some way balanced, I am not sure that they are actually equal patients.

DR. MARTINO: Dr. Grillo-Lopez?

DR. GRILLO-LOPEZ: I would like to know if there is a plan B. It sounds like both the sponsor and the FDA would assume, no, this study isn't interpretable and doesn't fulfill the confirmatory requirements. If it is not interpretable, then what happens and what is plan B?

DR. MARTINO: Is your question to the sponsor?

DR. SCHOOLEY: As I mentioned earlier, we are continuing to prepare study designs for patients with ALL and other groups to study Depocyt in those populations. Whether or not we can conduct another study in lymphomatous meningitis, it is doubtful given the problems we have observed and the enrollment rate. I mean, if we were to embark on another trial, as I mentioned, it is going to take 10-15 years unless we can find a more

sensitive endpoint than what we have designed that is oriented towards the clinical assessment.

DR. GRILLO-LOPEZ: Since approval, if you discount--what?--two years, 17 months or so--

DR. SCHOOLEY: Yes.

DR. GRILLO-LOPEZ: --that the drug was not available, there have been several years that it has been available. Are there any publications either from Europe or from the U.S. where investigators have done protocol studies? If so, what are the results?

DR. SCHOOLEY: No.

DR. MARTINO: Dr. Cheson?

DR. CHESON: There is another population of patients that might be considered, and those are the virus patients who are at risk for developing lymphomatous meningitis. You can define a number of criteria for patients with up to, say, 20, 25 percent or higher risk of developing it and do a randomized study to try and prevent it. We do, in fact, prophylactic CNS intrathecal therapy on a number of patients based on data from Europe and

NCI and elsewhere showing a higher risk in certain patients based on the size of the tumor. So another possibility is to do a prophylaxis study.

Getting back to the issue of MRI, yes, MRI is pretty good at detecting pretty advanced CNS disease. I am not sure that there are any data out there, at least in lymphoma, showing that it can be used to measure response in a reasonable time frame. I don't know that it gets better that quickly, I don't know if anyone has looked at it. So, that is an issue. In fact, there are some places which are even more sensitive in not only looking for cells with spinal fluid but flow cytometry. So, there are a lot of ways to do this but I would think that, rather than try to find these rare patients, it might be to your advantage to do a prophylactic study in high risk patients.

DR. SCHOOLEY: We agree with that as well. We are also looking at a prophylaxis study to be conducted--well, it is being designed in Europe as our licensee in Europe has a high interest in performing that trial. Our interest is, of course,

to have that trial run both in Europe and the U.S.

DR. MARTINO: Dr. Kelsen?

DR. KELSEN: I was looking at the list that was put in our packet of drugs that have been approved for accelerated approval since 1995. It has about 20, 25 drugs on the list. Some of them are for diseases that are very common and some of them are for rare diseases. I think what we are hearing today is about the rare diseases. This is in line with Dr. Pazdur's question about going forward and not looking back. You had a slide that implied that even at the time there was approval you thought it was really unlikely you would have 75 or more patients with lymphomatous meningitis and you ended up with 26.

I am not sure whether you knew then that it would be really, really hard to get 75 patients or whether that became clear later on, and I wonder when accelerated approval is done in some of these diseases, like this disease, you sort of can begin a policy of we will never, never, never answer this question in this disease entity and when you

prepare your post-marketing studies to not even try and begin to focus on diseases where you may be able to answer it.

DR. SCHOOLEY: I think you are spot on. When we looked at the hurdle of trying to get a number of patients enrolled in this trial we were anxious about that. We tried to do what we could up front, but we were still under-estimating the difficulty of enrollment. That is why we made some changes during the course of the trial, which now have been probably detrimental to the result. If we were at the start of this I would, indeed, look at other populations rather than the lymphomatous meningitis population as follow-on studies to demonstrate efficacy.

DR. KELSEN: Is there a mechanism in place as you sort of monitor these trials--this is for FDA, in which you would have like a red flag dropping that this is simply not going to work and we shouldn't continue to beat this sort of dead horse and we ought to move on to a totally different revamping of it? Is that ever done?

DR. PAZDUR: We do review these on an annual basis, and I think this is one of the reasons why we are bringing this here to refine the

program and maybe, as a recommendation, have more stringent internal analysis of where our sponsors are going with these.

I have a question also. Obviously, the company that you have is a relatively small company. Was any attempt made to engage the NCI in the conduct of post-approval studies here? Because here, again, you might get a larger catchment area of patients and resources to do a trial in a more expeditious fashion. You know, we generally think of the NCI doing, you know, large Phase 3 trials but this would not be unheard of, for the NCI to conduct such a trial. Were any negotiations conducted with the NCI, and would you like to discuss those?

DR. SCHOOLEY: There was no discussion with the NCI.

DR. DAGHER: I just wanted to clarify one more thing, Dr. Kelsen. I think you are also

alluding to this issue of, you know, what are the populations that you can use for the confirmatory study. We have always had the position that the population that you use in the studies for confirmation of benefit do not have to be identical to the population that was used for accelerated approval. We gave ten examples of those that were actually converted to regular approval subsequently because of trials that were ongoing or that were initiated shortly after the accelerated approval. There are examples there of situations where it was either the identical population; others where it was a very closely related population; and others where there was sort of a related population but nowhere near identical population.

DR. KELSEN: I saw that. There is clearly precedent for that. What struck me today was somebody used the term boutique drugs, drugs with a very small number of patients. I suspect that in the future you will be able to identify them more sort of up front and say, look, you know, four years and 26 patients; let's not even go down that

road.

DR. MARTINO: If I can think back to the presentation from our European colleague this morning, they dealt with this issue in a different way, didn't they? They have actually chosen another category, which is those unusual disease states and taken them out of the accelerated approval process so that, in fact, one can think about them in their own way because they are different and somewhat special.

DR. PAZDUR: The situation there was that the exceptional approval process was the conditional approval process in a sense. Okay? Because they did not have conditional approval, that exceptional approval process was used to approve many of the drugs that we have done under accelerated approval. As Dr. Pignatti pointed out, I think they are going to be reevaluating where they use that process.

Now, for rare diseases we have looked at what is substantial evidence to warrant approval and, obviously that may be based a on different

risk and benefit decision. Perhaps, again, when we have applications such as this maybe we need to have further discussions. A lot of times when people are voting for accelerated approval they don't realize the comments that you have brought forward, that this truly is an approval of a drug. It carries with it all of the ramifications of that approval.

So, you know, questions that I think people need to answer is do they have adequate information for an approval? Will they ever have that? Could we, for example, because this is a relatively unusual population, take a look at a different risk/benefit relationship here? Obviously, the American public, as far as numbers of patients that are affected with this disease, are much less than, for example, a large disease such as breast cancer, etc. So, we handle that type of rare disease in the context of a risk/benefit relationship to the American public.

DR. MARTINO: But maybe even the requirements to giving accelerated approval should

be somewhat different is the point I am making. Because when you have so few patients, the very fact that a drug is out there means that, you know, you will probably have zero patients with whom to do anything further, no matter what you do or how you scour them. So, I am suggesting that maybe a basis for giving approval to a rare entity is that perhaps a lot of the work be done before the approval is given so that then perhaps you can avoid all of this subsequent sort of running around that one has to try to do. Dr. Cheson?

DR. CHESON: I would like to ask you a question about the protocol since I don't have it here. A patient presents with, let's say, severe headache and a spinal tap is done showing cells that appear to be lymphoma cells. How does this patient get on the study? Because if we suspect that the patient has lymphomatous meningitis, leukemic meningitis or whatever, we use that first stick for the first treatment and we don't say, okay, it is positive, let's go back and stick him again and treat him. Did your study take this into

account in any way? We would never put a patient on a study if we had to wait for randomization and a second stick.

DR. SCHOOLEY: The randomization occurred after confirmation.

DR. CHESON: That is another serious problem. There has to be a way to get around that, and there are ways we can talk about outside of this situation. But that would make it impossible for some of us to do it because I teach my people, you know, it is one stick that you don't want to waste unless you think it is an infectious etiology, but if you think it is malignant you use that stick for treatment and that would make the patient ineligible right there.

DR. MARTINO: Dr. Rodriguez?

DR. RODRIGUEZ: We have been talking about the type of data that would be required in very small patient populations, and we just heard that perhaps as many as 300 patients with lymphomatous meningitis or with some form of meningitis have received this drug and, yet, we don't have any

track record of them. I wonder if perhaps in diseases that are very rare a different data source might be considered or a different strategy for data collection be considered along the lines of a registry, along the lines of a tumor registry which can be coordinated with the drug companies because, after all, they are the ones that do provide the drug. I am just throwing that out there. So perhaps in very limited number of patients where a randomized trial does not work the strategy will not work for data acquisition, prospective cohort data might be the best we can do. I am just throwing out the thought for discussion.

DR. SCHOOLEY: Just a point of clarification, are you referring to, let's say, a registry or are you talking about, let's say, an information card on every patient that is sent in?

DR. RODRIGUEZ: It could be along the lines of a tumor registry where you would have information about the patient's diagnosis and pertinent disease information and monitoring of outcome of that patient.

DR. MARTINO: Dr. Cheson?

DR. CHESON: There is tangential precedent for that concept in the old standard access

protocols. We conducted quite a number of those when I was still with the government. Admittedly, those were in that window between we have all the data, the drug looks good and the FDA hasn't approved it yet. But it is possible. What would happen is a physician would call and say I want drug X? We would ship that physician a protocol on how to use it and collect rudimentary data on toxicity and response. It is possible that that sort of mechanism could be used even post-approval if you had agreement, you know, from the physician to do it, send that protocol and just have some follow-up and you could probably get those data.

DR. MARTINO: But inherent in these concepts is the assumption that that data would meet some rigor that the FDA would find acceptable. You know, I think these are issues that the FDA will have to consider.

Are there any other burning comments? If

not, we need to move on. With that, I thank you, doctor. The next part of the program is the open public hearing and I believe we have two speakers that have asked to address the committee. There is a microphone we will ask you to come to, which is at the end of the table.

But before you do that or as you prepare to do that, I need to read a statement to you. Apparently one of you has slides and you are welcome to use the podium.

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 open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the

topic of this meeting.

For example, the financial information may include a company's or a group's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationship. If you choose not to address this issue of financial relationship at the beginning of your statement, it will not preclude you from speaking. Miss Clifford, if you will announce the presenters, please?

MS. CLIFFORD: Mr. Frank Burroughs.

Open Public Hearing

MR. BURROUGHS: I will give you a little break from slides. I am Frank Burroughs, president of the Abigail Alliance for Better Access to Developmental Drugs. A lot of you know who we are and what we have been doing. Before Steve Walker, our Abigail Alliance chief advisor, gives his presentation, I just have a few words I would like to say to people who don't know us, and a little

update for people who do know us.

The Abigail Alliance, unlike any other group, represents patients who are fighting for their lives and cannot get into clinical trials and have exhausted approved therapies. I have discovered recently that no other advocacy group is working like this but the Abigail Alliance. The Abigail Alliance is working hard on getting expanded access programs for promising new therapies and we, of course, work with the pharmaceutical companies.

By the way, we do not have any financial ties with the pharmaceutical industry unless a couple of them that came to our gala last Saturday counts. But since it is open to the public, I think that is okay. I paid for my trip here but the Abigail Alliance paid for the paper.

Our logo is over on the table there, next to the wall. I didn't have time to do a slide of it. Anyway, I want to note that there are many hard working advocates. I have met many of them, cancer advocates and advocates for other

life-saving illnesses [sic], and I think most people in that group of advocates believe in fairness.

However, there are some advocacy groups which don't seem to understand fully that the Abigail Alliance represents a particular group of people, and that is people who have run out of approved FDA options in their battle to live. They can't get into a clinical trial and we are trying to give them access not to just any drug--one writer recently kept using the word "experimental," "experimental," "experimental." Anybody in the FDA and the advocacy community knows that is not an appropriate word--developmental and, as the FDA says, investigational drugs. We are talking about investigational drugs. We are not talking about experimental drugs, which can imply something made in someone's garage. As I once said to a "New York Times" reporter, we are not talking about drugs made in somebody's garage.

I want to update further on something, you know, sometimes incorrect information gets out

about the Abigail Alliance. I am sure that happens with everybody, every organization which is represented in this room today, including the FDA. But recently one advocate made some very, very unkind and irresponsible remarks about the Abigail Alliance. It was in some obscure publication but, still, it shouldn't have been done the way it was.

This advocate knows, and we absolutely know, that she is not an advocate for the people whom we represent. I don't understand why this person decided to get so mean and so very unkind. Why would an advocate make a slam that not only included me, the Abigail Alliance and the patients we fight for, but my daughter--my daughter who died of cancer in 2001. That is her, over there. The Abigail Alliance is not a memorial to Abigail. It is not a vendetta. Abigail is a face to put on our efforts, the efforts for tens of thousands of people.

That smiley face, as this writer wrote, was taken on a trip to Europe in 1999 with me. She and I went to England, and that was just a few

months before she was diagnosed with cancer. But there are always people who have to throw mud. There are people who say, Rosa Parks, you can't sit in the front of the bus. The Abigail Alliance would like to sit on the bus, not necessarily the front; we would like to be able to move around.

But we are not represented the way we should be and we are not represented today at this table. I am not angry. I am just pointing out how hard we have worked for tens of thousands of people and we don't have a representative at this table. I know there is a patient representative but what I am talking about is a patient representative who has run out of FDA approved options and cannot get into a clinical trial. We want representation.

What is interesting is that the person who had the audacity--I can handle insults to the Abigail Alliance or myself, but to drag my dead daughter into it, that person is sitting at your table today. What is wrong with this system? We want representation. The last time I checked, this is a democracy and I think you all ought to find

out where that article is. I am not even going to do the person the respect of saying her name or his name. You will find out.

The last time I checked, our founding fathers and mothers worked very hard and creatively to protect the individual rights of everyone. Well, that includes patients that we represent. Have a few not read John Stuart Mill's words regarding tyranny in a democracy? Do a few not understand that all of us need to look beyond our own self-interest? This is a democracy. Thomas Jefferson put it well: enlighten the people and tyranny and oppressions of body and mind will vanish like spirits at the dawn of day.

And in closing let me use some words of Abigail from her 1998 high school valedictorian speech, please listen to these words: Success is temporary. When all is said and done, all you have left is your character. This is a democracy. Thank you very much.

DR. MARTINO: Thank you. Our next speaker, please?

MS. CLIFFORD: Mr. Steve Walker.

MR. WALKER: My name is Stephen Walker. I am the chief advisor to Abigail Alliance for Better

Access to Developmental Drugs. I am a volunteer. I receive no compensation of any kind for my efforts as a patient advocate or for my work on behalf of the Abigail Alliance. I paid my own expenses today. I have no financial relationships with drug companies or any other entity involved in drug development and approval, including NCI and FDA.

A few people here earlier today felt my anger and frustration. I wish you could have been in ORGALA. I was the one calming people down. I think the subject today is a timely one. We spoke in March 2003 on this subject and pleaded for the FDA not to launch what we now call decelerated approval. We were ignored. We have a petition on the desk of the FDA that has been there for 29 months, asking for a conditional approval program that now Europe has. We have yet to receive a single work in response to that petition.

I will get on with my presentation--no, one more thought, the anger I expressed to a few people here before lunch was based on my observations during this morning's discussion that the drug sponsors were making arguments about the ethics of putting patients into some of these

trials. The FDA was taking the position that these trials will be conducted, including--and I don't mean to get personal here--but perhaps posing financial disincentives for not finishing them. I will talk more about this as I go through my talk and it is probably going to run over a little bit but I think you need to hear it because nobody else in this room is talking about the perspectives, the views and the rights of the people who are being put into the trials that you are talking about today, and I think you need to hear it.

I suspect many of you were here a year ago or two and a half years ago when the first meeting on this was conducted. Frank and I were here as well and we spoke at the meeting, asking the FDA not to proceed with the policies they rolled out on

that day. In my opinion, the FDA wasn't really looking for ODAC's advice on its plans at that time but, rather, used the meeting as a platform to roll out what can only be described now as a decelerated approval initiative.

The FDA also should have known, and in fact it is hard to believe that they did not know that this decelerated approval initiative would be devastating for terminally ill cancer patients whose only hope was gaining access to medical progress while still alive.

I would now like to walk through some revealing points in the start and evolution of FDA's decelerated approval initiative. I am going to read you some of the statements made by FDA in ODAC meetings to launch the decelerated approval initiative, and then talk about a couple of examples that illustrate the effect those policies have had on the effectiveness and ethics of our clinical trials in translation system. I might add that those policies have had devastating effects on people that we have tried to help and are no longer

with us.

I am going to have to pick on Dr. Pazdur here because he was speaking for the FDA at that meeting. Dr. Pazdur stated that accelerated approvals have been grated with a trial design using single-arm trials in refractory populations, as stated previously. These trials obviously allow more rapid trial completion and, hence, expedite drugs to patients with life-threatening diseases. Now, this statement seemed to demonstrate that the FDA understood the purpose of accelerated approval. It is an accelerated approval process. It is a delivery mechanism.

But then, the next statement gave us pause: An alternative trial design uses a randomized trial allowing accelerated approval on the basis of an interim analysis of surrogate endpoints, for example, response rate or time to progression. Anyone who has been the FDA's policies over the last two and a half years realizes this was not an idle comment. This is I think what sponsors are hearing at their end of

Phase 2 meetings. The accelerated approval door is not open for single-arm trials.

Next, Dr. Pazdur stated randomized trials also may optimize the evaluation of novel cytostatic agents by allowing an assessment of slowing or retarding or preventing tumor progression. This may simply not be possible with single-arm trials--more of the message, no single-arm trials for accelerated approval.

Obviously, randomized trials are more expensive than single-arm trials and take more time. Clearly, the FDA knew this would slow down the delivery of breakthrough cancer drugs and drive up the cost of translation.

Next, and this is one of my favorites, survival analysis can be complicated and confounded by crossover and subsequent therapy. That means patients in some trials ended up being put into placebo controls with no crossover and they were allowed to die without ever having an opportunity to try a drug that had been proven substantially safe and effective in an earlier Phase 2 trial.

There are multiple examples of this and those trials are still going on.

Then Dr. Pazdur made it clear how this was going to work in the context of Phase 4 trials. Mandatory confirmatory trials to confirm clinical benefits are equally important as the initial trials demonstrating an effect on a surrogate endpoint leading to that drug's approval. FDA was making it clear that post-approval trials that Congress said may be required which, by the way, anyone who has ever been involved in drafting legislation knows the choice between "may" and "shall" is a very careful, pointed and on purpose choice. But FDA was making it clear that there would be a Phase 4 trial every single time.

Then we heard how this would fit into the FDA's new policy paradigm. Hence, confirmatory trials must be an inherent and integral part of a comprehensive drug development plan and drug development strategy. Although not obvious at the time, it also meant that FDA would start delaying accelerated approval until unethical, unnecessary

double-blind, randomized, placebo-controlled and in some cases no crossover Phase 3 trials could be started, enrolled and run to an interim analysis point. In some cases that has delayed the approval of good drugs that we know are going to be approved by more than two years. All you have to do is go to the American Cancer Society web page to find out how many lives those decisions shortened.

This constituted a major policy shift in the standard for accelerated approval. Accelerated approval was moved very close to the standard for regular approval and very close, in fact, to the time and effort it requires to achieve regular approval.

So, what do we get from all of this? From the patient's perspective, we got a punitive enforcement program for Phase 4 clinical trials, punitive for sponsors; punitive and potentially lethal, in fact definitely lethal for a lot of cancer patients. And, we got the potential for withdrawal of safe and effective cancer drugs based on any failure to complete the Phase 4 trials or to

unequivocally achieve regular approval endpoints. We have already seen an example of that.

Accelerated approval would be available only for sponsors whose development program had already achieved substantial compliance with endpoints intended for regular approval. Accelerated approvals would be denied or delayed to ensure--and this is very important because this is the perspective of patients--that a large desperate pool of patients, facing death from their disease, would be coerced, under duress of that death from their disease to enroll in marginally and even clearly unethical clinical trials, thus, resolving the Phase 4 trial enrollment problem. Phase 4 trials became Phase 3 trials. We are talking about delaying approvals to coerce enrollment in unethical trials.

The accelerated approval initiative is in direct conflict with the intent of Congress. The idea to speed up delivery of medical progress to patients who need it to live--trust me, we are talking to people on the Hill, they thought that is

what it was about. The initiative was conceived and implemented unilaterally by FDA staff over the protest of some stakeholders, including us. The policies happened in plain view of agency leadership who can't now legitimately claim they did not understand the implications because we told them repeatedly. Most tragically, many thousands of patients died prematurely, waiting for drugs and product progress that should have been quickly delivered to the clinics.

A compelling example that the effect of the decelerated approval initiative has had on medical progress and patients is what happened with Bayer's BAY349006, now known as sorafenib. We had two patients we were trying to get this drug for. They are both gone now. They never got it. Coming out of Phase 2 in 2003, sorafenib certainly appeared to be the kind of drug that Congress intended would be eligible for accelerated approval. There was an overall 70 percent response rate in stable disease and tumor regression. Of course, we can only speculate why because we are

never invited into the discussions between the FDA and sponsors. But we suspect that they were told at the end of their Phase 2 trial that the gate was closed for single-arm trials--and that, in fact, was not a single-arm trial; it was a placebo-controlled trial with a notch so there was a control.

I think they were told that accelerated approval was essentially off the table based on a single-arm trial. Maybe it wasn't put in precisely those terms but certainly that was the signal they and many, many other companies have gotten. In fact, Dr. Pazdur said earlier today that a lot of companies have gotten the message on this and it is his message.

They entered into an SPA. We know Bayer negotiated a special protocol assessment because they were very careful to announce it in their press release when the trial was stopped by the data safety monitoring board because patients on placebo, predictably, were not doing well. The SPA negotiations which, by the way, is a binding

agreement between the sponsor and the FDA, produced an astoundingly unethical randomized, double-blind, placebo only controlled, no crossover trial for a drug that had an over 70 percent response rate coming out of Phase 2. The result, of course, was that the patients on placebo were dying prematurely inside the trial and many thousand of patients were dying prematurely outside the trial because they couldn't get the drug by any means. I am not saying that these patients would have been cured by this drug but many of them, as we now know, would have seen longer lives, better lives, more time with their families, more time with their children and that is all they wanted.

Early this year, after an interim review showed that sorafenib was far better than a placebo, a result that should have been confidently expected, Bayer came under intense pressure to allow a crossover. I believe internally they wanted to do it anyway and they did. But they had to negotiate that because they had an SPA. Then they eventually started an expanded access program

but, again, under an SPA you have to ensure that the FDA is going to still approve your drug based on the data you produce.

So, that took a lot of time. I was on conference calls and it was clear Bayer was frustrated. While this is an essentially egregious example, it is far from isolated but I don't have time to talk about the 10 or 15 trials that we know about. Sorafenib, as you all know, remains unapproved.

I will fast forward to just a few weeks ago to the ODAC meeting for Revlimid, held on September 14. More than two and a half years after the introduction of the decelerated approval initiative, the devastating effects of the initiative were on full display. Revlimid was before the committee with compelling data from two Phase 2 single-arm trials. Celgene was asking for regular approval in the treatment of a targeted patient population with myelodysplastic syndrome, or MDS, which everyone in this room knows is an almost universally fatal disease.

Dr. Richard Pazdur explains FDA's advice to Celgene from before the time they started the single-arm trial. On several occasions, as will be

mentioned by the FDA reviewer, we have recommended to the sponsor before they began the study that we look at randomized studies of this drug in MDS to have a better understanding of the disease in relationship either to other therapies or the natural history of the disease.

Despite the fact that the data from an earlier Phase 2 trial was extremely compelling and from the second Phase 2 trial even more compelling that there is a targeted population that can derive tremendous benefit from this drug, FDA appears disappointed that a randomized trial was not conducted. It makes you wonder why we are doing this.

Fortunately, Celgene kept its own counsel and proceeded with a single-arm, highly ethical trial in a targeted population based on the earlier Phase 2 data, and the Phase 2 trial proved undeniable efficacy in that targeted population.

I think ODAC did a pretty good job in September. You approved three drugs, or recommended approval for three drugs that should have been approved. I was hoping for more today.

FDA, even after hearing the compelling results from the Revlimid trials, still seems

unsatisfied with the Phase 2 single-arm trials and Dr. Pazdur reminds the ODAC I want to bring people back to the kind of regulations--and there is a mantra--adequate and well-controlled trials, adequate and well-controlled trials, adequate and well-controlled trials. I am mentioning that three times because I think that is at the heart of the question here.

I have a question. Whose mantra is this? Why does it have to be repeated three times? It seems that the FDA is saying that safe and effective drugs should not be approved because the conditions of the mantra have not been met. There has been no randomized trial. I am a scientist. I work in the environmental field. It is multi-disciplinary. I practice in many areas. I

have an advanced degree. My wife was a biologist, a marine scientist and geologist. She is dead. We understood that science is a broad field. There are no mantras in science.

Later in the meeting on Revlimid a question came from ODAC and it was an extremely important question. One of the members asked--I think it was Dr. Hussain, and why you chose not to do a Phase 3 trial when you were asked to do that? And he was referring to the randomized placebo-controlled trial that is now I think being run in Europe.

DR. HUSSAIN: She.

MR. WALKER: I am sorry?

DR. HUSSAIN: She, not he.

MR. WALKER: She, okay. I am sorry. Thank you for the question, by the way. We are going to go to Phase 3, was Celgene's response. We are going to be doing a placebo-controlled trial. I have to say that in discussing that trial with the investigators, there is actually reluctance to put patients on placebo for very long based on the

benefit that has been seen here. He went on to say, and I believe his name was Dr. Zeldis, the patients who received placebo received that for four months. If they are not responding, and we think that essentially none of them are likely to respond from what we know--which is what you should always expect with a placebo since, by definition, it cannot provide any therapeutic benefit--then they will have the opportunity to go on Revlimid and continue as long as it seems to be benefiting them.

Again, we weren't in the meeting, but I can imagine the exchange, a negotiation of a wide-open out to survival significance, placebo-controlled trial for a drug that was already proven beyond any doubt that it is safe and effective and will provide clinical benefit to the patients. That is the FDA's position. Celgene is arguing we don't want to do that. This is where they land and what they are being told is you want your drug approved? Do the trial. Again, I am speculating but I think I am pretty accurate there.

On October 3, 2005, only a few days before the FDA's deadline for a decision on Revlimid, FDA decided to extend its review time for a decision on

Revlimid, citing new information submitted for the risk management plan, the same risk management plan that was provided to ODAC and judged by ODAC to be adequate.

This exchange turned the relationship and missions of the FDA and the sponsors upside down, and I have seen more of that this morning. The sponsor was looking out for the patients they were going to put in their trial and the FDA was attempting to force conduct of an unethical placebo-controlled trial for a drug that had already been clearly shown to be compelling effective in a refractory terminal patient population.

Just who is protecting who here? Isn't it the FDA's job to do that? I sure haven't been hearing it today and we sure didn't hear it on September 14. We have a problem. We need to deactivate decelerated approval. We need to banish

inflexible mantras from the FDA's lexicon. We need ODAC to stop supporting inflexible mantras and instructing FDA when they start heading down that road. We need to remember who this is all for. It is for the patients. It is not about p values. It is not about endpoints. It is not about regulations. It is not about policies. It is not about your careers. It is about the patients out there, the patients we represent and work for every day. The patients we have personally lost, waiting for this process to run its laborious, tortoise-like course; the patients who you are talking about today who will be going into these trials that you are talking about, these placebo-controlled trials. Delaying approval so you can coerce patients into an unethical Phase 3 trial is beyond the pale. It is the kind of stuff that has been written about in books as being crimes of medical investigation. We are not going to do that, and if you insist on doing it we are going to find a way to stop it.

The Abigail Alliance works for patients

and for no one else, and you need a lot more input from the people we work for because they are the people you are talking about when you have these meetings. Thank you. Any questions.

DR. MARTINO: Thank you but there actually are no questions that can go to this meeting, nor do I want any rebuttal. We appreciate your comments. They are food for thought for each and every one of us and we thank you.

At this point, I will give you about a five-minute break for everyone to take a stretch and to readjust the audiovisual materials.

[Brief recess]

DR. MARTINO: Please take your seats, ladies and gentlemen. I need to begin the meeting again. The next agent that we will be discussing is Celebrex, from Pfizer. Dr. Eagle, before you start we need to have the conflict of interest statement which will be read by Miss Clifford.

Conflict of Interest Statement

MS. CLIFFORD: The following announcement addresses the issue of conflict of interest and is

made part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting, with the following exceptions.

In accordance with 18 USC Section 208(b)(3), a full waiver has been granted to Dr. Steven George for being a member of the sponsor's data safety and monitoring board on unrelated matters, for which he receives less than $10,001 per year.

A copy of the waiver statement may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

We would also like to note again that Dr. Antonio Grillo-Lopez is participating in this meeting as the non-voting industry representative,

acting on behalf of regulated industry. Dr. Grillo-Lopez is employed by Neoplastic and Autoimmune Diseases Research.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon. Thanks.

DR. MARTINO: Dr. Eagle, you may proceed.

Celecoxib (Celebrex) Therapy for Familial Adenomatous Polyposis (FAP), Subpart H

Phase 4 Commitments

DR. EAGLE: So, I would like to take this opportunity to thank the committee for time to present and update them on the commitments for celecoxib in familiar adenomatous polyposis.

By way of introduction, my name is Craig Eagle. I am head of the worldwide medical oncology group at Pfizer. Also today, I would like to

introduce Dr. Patrick Lynch who is a clinical expert in FAP and is able to provide answers to any questions the committee may have. He is from M.D. Anderson.

So, what I would like to do before I start my presentation is really talk about that this has been a challenging area from several fronts. The first thing is that FAP is a very rare disease. Secondly, it is in a pediatric population that we are looking it. Thirdly, there is a need to globally standardize treatment in an area that traditionally has been isolated to very specialized registries within the world. Finally, it is in a chemoprevention setting rather than advanced cancer. Lastly, the issue around cardiovascular disease from non-steroidal anti-inflammatory drugs that came up in the last 12 months also needs to be considered during this program.

I would also like to comment that we have

been working very closely in collaboration with the National Cancer Institute and also with investigators, including Dr. Lynch, to try and move this program forward in the most appropriate manner and solve some of the challenges that I just mentioned.

So, what I would like to cover today is that I would like to remind the committee a little bit about familial adenomatous polyposis and, given that it is a mouthful, I am going to call if FAP from now on, and basically remind them also about the basis for the celecoxib approval in the pivotal study in this condition, and then review the actual commitments that were made at that time.

So, just again to remind the committee that FAP is a rare inherited disease. It has an annual incidence of one to two cases per one million people in the population, with a prevalence of around three to four per 100,000.

The natural history untreated for FAP, it is a condition that affects adolescents. It results in hundreds to thousands of polyps in the

colon which ultimately leads to increased risk of colorectal cancer in particular. If untreated, there is 100 percent risk of colorectal cancer, with a median life expectancy of 42 years.

Currently, management for FAP involves lifetime endoscopic surveillance with initial colon resection in late adolescence to early adult life. Often there are repeated surgeries, particularly on the other remaining segments of the gastrointestinal tract where there is also increased risk of cancer and malignancy. Surgical prophylaxis has certainly reduced the risk of mortality from this condition, but at the cost of substantial morbidity and even, to a lesser extent, mortality from the surgery. There is also a immense interest in developing other therapies that are adjunct to surgery, in particular of a pharmacotherapy nature.

So, this led to the pivotal study that ultimately led to the initial approval of celecoxib in this condition. This is a double-bind, placebo-controlled study of celecoxib in FAP. It

was performed at two centers at doses of celecoxib of 100 mg BID and 400 mg BID, with the primary endpoint of looking at the change in adenomas in the colorectal area. The duration of they was six months.

Again, just to remind you of the results of the pivotal study, 81 patients were enrolled in the study. The duration of therapy was six months. You notice in the blue bar on the left side of the screen that 400 mg BID resulted in a 28 percent reduction in polyp numbers after six months of therapy, and this was statistically significant.

It is also interesting to note that the lower dose, the 100 mg BID, also reduced polyps but this did not reach statistical significance, suggesting again a dose trend relationship.

Also, in a subset analysis the study was not designed to do, there is a reduction in duodenal polyps and, as I mentioned, FAP can also result in increased malignancy in other parts of the gastrointestinal system.

So, this led to the FAP indication listed

there. This was approved in December, 1999, and it is important to note the comment that it wasn't known whether there was a clinical benefit from a reduction in the number of colorectal polyps. It was also not known whether celecoxib effects will continue after discontinuation of therapy. Similarly, the benefit beyond six months was also not known at the time of approval.

So, this led to two Phase 4 commitments. The first one was a Phase 3 placebo-controlled, randomized study looking at genotype positive patients who were yet to express the phenotypic disease. The second commitment was to develop a registry-based observational study assessing clinical outcome in the FAP population receiving celecoxib and compare this to historical controls.

So, what I would like to do now is go through both those studies to update the committee. Firstly moving to the Phase 3 genotype/phenotype negative study, before I move on, I would just like to highlight the format of my slides, consistent from this point forward. On the left side there

are arrows that show the year and the month in which the events occurred. Then, on the right-hand side of the slide obviously are the events.

As I have already mentioned, focusing on the Phase 3 study, the FDA approved the indication in December, 1999 and, in collaboration with the NCI/Pharmacia at the time, put out a proposal to develop the Phase 3 study. In July of 2000 the contract was awarded to the institutions listed there, with M.D. Anderson being the lead institution.

So, through 2000 there were issues raised about the unique nature of this population. It is a young population. It is a pediatric population. So, then there were questions raised and issues raised about exploring the dosing and tolerability of celecoxib in this younger population and a draft Phase 1 protocol was developed and, in review with the FDA, it was agreed that a Phase 1 protocol was appropriate, moving into a Phase 3 program after completion.

The Phase 3 protocol then had a series of

negotiations through 2001, looking at the issues around placebo control in a Phase 1 study and the protocol was finally approved by the NCI early in 2002.

The protocol then went through the IRB approval through 2002 and ultimately the first patient was enrolled in late 2002. Because it was a pediatric population, there was consideration of using something other than capsules for this group of patients and there was immense interest in dispersible oral medication. So, attempts were made to develop a dispersible oral medication during 2002 but, unfortunately, due to technical reasons, this could not be developed so ultimately the study had to back to capsules, and it was started at the end of 2002. The expected completion time, because of the study design, was the third to fourth quarter of 2004, so just last year.

Again, just to remind the committee, this is the design of the Phase 1 study. It is basically a study that is looking at patients 10-14

years of age. It involves dose escalation with each cohort given 4 mg, 8 mg and 16 mg for three months. Each cohort was only initiated after review of the previous cohort's safety by the data safety monitoring board. Each cohort had four patients plus two patients on placebo. So, the total sample size was 18 patients and the duration of therapy was three months. Remember, this study was due to complete towards the end of 2004.

While the study was being conducted and continuing during 2003, Pfizer assumed responsibility for the Phase 4 commitments from Pharmacia and continued to develop the Phase 3 protocol design, waiting for evaluation of the dose from Phase 1. We found that there were limitations when we looked into the information about the type of patient population we were going to enroll--again, rare disease; subset of population being phenotypically negative. So, again there was review on how to expand that population to try and move this trial forward. Also, there were discussions in early 2004 about a clinically

meaningful endpoint other than polyp reduction and that discussion revolved around multiple investigator meetings including M.D. Anderson and NCI.

During 2004, in June, the last patient was enrolled in the last cohort of the Phase 1 study. That last cohort completed in December of 2004, as expected. The DSMB reviewed the last cohort at 16 mg/kg per day and found the dose was safe and recommended that to be the appropriate dose for the Phase 3 study. This was on December 16.

Here are the results of the tolerability and the adverse events of the Phase 1 study. I would like to draw the committee's attention to the fact that all the AEs, the adverse events, were grade 1 and 2. Also, I would like the committee to note that there is no difference between the placebo group and the different doses of celecoxib. If you break those adverse events out, again, there were no cardiovascular events. Most of them were gastrointestinal events. Again, if you break them out as I show here, there is no difference between

placebo and the different doses of celecoxib.

Interestingly, the study also showed reduction in polyps from baseline. Even though the study wasn't designed to measure these, it did show a dose-response relationship, with the maximum dose producing the maximum reduction in polyp numbers.

Unfortunately, on December 17, the day after the DSMB met, there was the announcement of the cardiovascular safety issues with celecoxib. So, for the next three to four months we reviewed the cardiovascular safety data, along with health agencies around the world and along with the investigators of this particular trial, to discuss the implications for this study. The conclusion by the investigators was that the study should proceed, even given the new safety data from non-steroidal anti-inflammatory drugs, and through 2005 we proceeded to have a special protocol assessment with the FDA for the Phase 3 study, and we are hoping to enroll the first patient in January of next year.

Just to update the committee on the design

of the Phase 3 study, it is placebo-controlled versus celecoxib 16 mg/kg a day, 1:1 randomization, aiming to recruit 200 patients and the treatment duration is five years to assess long-term efficacy and long-term safety. The primary endpoint is time to treatment failure, which is defined as time from randomization to the earliest occurrence of patients developing 20 polyps or more or developing colorectal malignancy.

What I would like to do now is shift and talk about the FAP registry study, the second part of our Phase 4 commitments. The registry study is an observational registry-based study. Patients who received celecoxib were compared to historical or concurrent controls from the same registries. Participating sites are around the world, and I have listed them there, Canada, U.S., Denmark, Germany and Australia, with the main aim of this observational study to describe the patterns of use of celecoxib in this disease; also to review the long-term benefits, given the limitations of an observational study; and also to evaluate and

record the long-term safety of celecoxib in this particular patient population.

I am pleased to let the committee know that the study was initiated in the third quarter of 2004. Again, we expect the study to complete towards the fourth quarter of 2010 because of the long-term follow-up.

Again just to remind the committee of the sequence of events and the close collaboration we have had with the NCI and M.D. Anderson investigators to try and move this challenging study forward, again, in December, '99 the drug was approved. Initial discussions centered around an alternative to an observational study--randomized controls. However, the FDA still concurred that they would prefer an observational type study in this setting. So, in collaboration with M.D. Anderson and investigators, in 2001 a proposal was put forward. By early 2003 the registry protocol was sent to the members of the clinical group and they felt, given the amount of work in entry of the data and the size of the patient population of

registries, this particular protocol would not be practical to implement.

So, then an alternative was proposed where on a web-based design patients would enter their own data to try to simplify the procedure. In early 2003, this proposal was put forward to the M.D. Anderson IRB as the initial lead investigator. The IRB was not comfortable and rejected the proposal as a web-based registry so again the protocol had to be revised.

In 2003, the protocol was revised and ultimately led, towards the end of 2003, for a new protocol to be reviewed by investigators, this time limiting the type of data that had to be entered in trying to automate it through computer technology. So, in 2004 there were kick-off meetings with CROs, with Cleveland Clinic IRB approval and, as I have already mentioned, towards the middle of 2004 the first patient was enrolled.

Since 2004 and the initiation of the study, we have now initiated several sites through December, 2004 but, again, there were issues around

the cardiovascular safety which occurred in December, 2004. So, this study was then put on hold while that safety data was again reviewed with the investigators and the suspension was felt to be temporary also while it was reviewed by the health authorities.

In the middle of 2005, approximately five months ago, the study was reactivated at Cleveland Clinic and is subsequently undergoing reactivation at various sites that I mentioned before. I have just listed here, to give the committee an example of the sites, there are five sites involved, involving USA, Canada, Denmark, Germany and Australia. You can see that these sites have been initiated or re-initiated at the times that I have listed there.

This is the current enrollment as of June of this year. You can see that eight celecoxib patients are enrolled and currently we are looking for matched controls and there is one matched control.

I would also like to comment that as of

October 27, approximately ten days ago, the enrollment of celecoxib patients has increased to 33 patients and we now have in our system 52 possible matched controls to draw them from. So, this study is moving forward.

So, I would like to summarize by reminding the committee that FAP is a rare, life-threatening genetic disease with few therapeutic options. Pfizer, in collaboration with M.D. Anderson investigators and the NCI remains fully committed to compliance with subpart H requirements and there has been significant activity since the last time this was presented to the committee, in March of 2003. Despite the challenges that are encountered with a rare population, with the pediatric population we have been able to get the Phase 3 confirmatory trial ready to enroll patients in January, and we are currently enrolling patients in the FAP registry. Thank you for your attention.

ODAC Discussion

DR. MARTINO: Thank you. At this point we will take questions from the committee. Let me

start, please. I am concerned with long-term follow-up. It seems to me like therapy is supposed to be a five-year experience.

DR. EAGLE: Yes, that is correct.

DR. MARTINO: You are going to treat for five years.

DR. EAGLE: Yes, that is correct.

DR. MARTINO: Within the protocol as it is presently written, what happens at that point? How long will patients be followed subsequently?

DR. EAGLE: At this point in time, the protocol follows all patients for five years; the last patient is followed for five years before we will stop the protocol. For the follow-up after that, the patients certainly could be enrolled into other studies or a registry study but there is no planned protocol assessment after that point.

DR. MARTINO: The issue I am getting at in my mind is again cardiac toxicity. I mean, there is very little known in children and it strikes me that if you are dealing with a very young population you may see no cardiac toxicity during

the time of therapy. You are much more likely to see it as they age. So, that really is the issue I was getting at, is there an inherent follow-up within the protocol, and I am hearing that there actually is not.

DR. EAGLE: No.

DR. MARTINO: Do you see the point I am getting at?

DR. EAGLE: I understand where you are coming from. Certainly, during the study we have increased and augmented the cardiovascular assessment and we probably feel that this study, in terms of long-term follow-up, is something that isn't probably the best population or study design to look at that. It is only 200 patients. Granted, it is pediatrics but it is probably not the sort of study that we feel long-term follow-up would be providing the best answers.

DR. MARTINO: Well, then how are you going to get that long-term answer? It is going to be left to the rest of us who, you know, will deal with these people later in time when they are in

their 40s and then have a cardiac disease at age 40. I do understand what you are getting at, but it just leaves me concerned because my expectation is that you are not going to see the cardiac toxicity when they are in their teens. The issue is long-term consequence and I am not hearing any mechanism by which to address that.

DR. EAGLE: And I think that raises a whole new series of issues and questions about that sort of program. Your point is well taken.

DR. MARTINO: Who wants to start? Yes, doctor?

DR. PRZEPIORKA: In the original pivotal trial, in the placebo group what would be the expected time to development of cancer?

DR. EAGLE: Well, again, it depends on where the cancer is. If they will have colon surgery they wouldn't, in fact, get colon cancer.

DR. PRZEPIORKA: The entire GI tract, top to bottom?

DR. EAGLE: Probably the best person to answer that is actually Dr. Patrick Lynch. I might

ask him to address that question because he will have a better understanding.

DR. LYNCH: So, you question, if I understood it right, was the time to development of cancer in the original study if these patients were untreated.

DR. PRZEPIORKA: Untreated, exactly.

DR. LYNCH: Well, it is important to emphasize because our pediatric study actually includes endoscopic polypectomy. When you do endoscopic polypectomy, which is what I do very day, the idea is to prevent cancer by polypectomy. So, in patients who were in the pivotal trial or who continued being followed after that, the rate of cancer has actually been extraordinarily low. We actually have had a couple of cases of duodenal cancer in patients who already had advanced stage duodenal involvement. But because of the role of endoscopic polypectomy, as well as the fact that many of the patients did continue on treatment after exiting the trial, we have not had any examples of colon cancer or rectal cancer.

DR. PRZEPIORKA: And are patients in that trial still being followed?

DR. LYNCH: They are still being followed

but not as part of the original protocol.

DR. MARTINO: Dr. George?

DR. GEORGE: I would like to support the concept of these registry-based studies as important in sort of adjuncts to the more traditional trials, with the caveat though that these studies should not simply be registry-based studies in the usual concept of what a registry is but that it be more like a clinical trial, with the treatments being carefully defined, the results all being carefully analyzed in a protocol, and particular eligibility criteria. And, the definition of those treatments are very important, not just people who may or may not have gotten some therapy but they should be specified. So, the only difference between that and a real, say, randomized clinical trial would be the assignment of the treatment, which is a very important difference. The mechanism of the assignment of treatment is a

very important difference. But, on the other hand, it is a good way to get information when you can't do those kinds of studies. So, I just support that concept in general. I don't know the details of this particular registry-based study.

DR. MARTINO: Do want to maybe add a little bit more information, doctor, in terms of what information is being gathered from that trial?

DR. EAGLE: Basically to that point, it is an observational study. The aim of the study is to look at all FAP-related events and also safety, and to try and provide some control arm based on historical controls. The challenge, of course, when you base on historical trials is that you need to have databases that provide enough information on a rare disease backward in time. So, that does tend to limit the amount of registries you can enroll in this type of design. Again, it is protocol driven. It is being collected as per protocol with the appropriate inclusion and exclusion criteria.

DR. GEORGE: But the point I really wanted

to make is that to do this really well may be almost as difficult as a clinical trial. It might take a lot of resources to really do it right. I think you could make mistakes if you go with the historical type of data. What I was really talking about is a prospective part of the registry and careful definition of what the treatments really are that you are comparing. That is where the tricky part comes in. If you are not doing a trial where you have carefully defined the treatments, then you are going to be in trouble deciding who is in what group, and so forth.

DR. MARTINO: Educate me a bit. Why have you chosen such a young group to look at? Why have we not chosen people in their 20s or 30s or actually as they approaching the point where malignancy is more likely to be coming in the near future? Why have we chosen this very young age as where to start? I mean, I do appreciate the point that this is a prevention trial but I do ask the question in view of that.

DR. EAGLE: So, there are probably two

things I would comment about that. The first one is that the pivotal trial was done in patients that already had prophylactic surgery and so that is where the observational study is really going to try to pick up data there. So, the pediatric population makes it a slightly different population where celecoxib is maybe already being used.

The other important facet is that this disease results in surgery and significant morbidity and mortality associated with that surgery in the younger population. So, if we are ultimately trying to show benefit, and sometimes these benefits are best shown at the time to delay or prevent surgery in a way to show that there are other ways to manage the patient. So, the aim would be to keep patients in that endoscopic, non-invasive management part of the disease rather than moving to the more aggressive and invasive surgical techniques.

Also, the issue around cancer is that that might take, you know, 20, 30 years to develop and so, again, the focus would have to be on an

endpoint that helps us interpret the impact of this drug on this disease sooner rather than going for that cancer endpoint.

DR. MARTINO: Dr. Hussain?

DR. HUSSAIN: I may have missed it but in the randomized Phase 3 trial, what would be allowed for the placebo patients? Standard of care or what?

DR. EAGLE: The standard of care is what they are allowed. There are obviously exclusions with regards to use of other drugs, non-steroidal drugs for example--

DR. HUSSAIN: Surgeries would be allowed?

DR. EAGLE: If they are appropriately indicated, yes.

DR. HUSSAIN: And what is the endpoint?

DR. EAGLE: The endpoint is time to treatment failure which is basically defined as the development of 20 polyps or more within the colon--

DR. HUSSAIN: [Not at microphone; inaudible].

DR. EAGLES: Well, these patients enrolled

with an intact colon.

DR. HUSSAIN: I understand. On placebo how would you reach that endpoint to be able to assess [not at microphone; inaudible].

DR. EAGLE: I understand. So, the enrollment criteria is that the age of the patients has to be in the range between 10 and 17, and they must have a colon that either has no polyps at entry or has under 20 polyps that can be removed at entry, with the idea being that surgery isn't indicated until the polyps are out of control. So, effectively, the aim of this is to see how long it takes for these patients to have their polyps get out of control. That is the endpoint. We would expect most of these patients over the five years of the study to not get to that uncontrolled need for surgery prophylaxis. So, we are trying to do it before surgery becomes another fact that we have to consider.

DR. MARTINO: I need to get back to the cardiac issue again. How is that concern described in the patient consent form, which I am trusting

will be read both by the pat as well as the parent?

DR. EAGLE: I am not able to recall the exact wording in the consent form but, again, the consent form, in collaboration with NCI, is being carefully worded, both the assent and the consent form are being worded in that area and that is something that I just can't recall at this point time, the exact wording for that but it will be in the assent and consent form.

DR. MARTINO: Are there other issues?

DR. HUSSAIN: I guess my concern is this, how do you control the treatment in the placebo? You know, you can't legislate this and say you can't do this and you can't do that, and my concern I guess about the study design--and this is perhaps a situation where maybe a large Phase 2 trial that is well controlled and well specified might have been adequate and I guess we are not here to discuss that. But my concern is that you are going to have so many things that could be happening in the placebo arm that the end result may be that you will end up anyway having data from your

therapeutic arm but not the placebo arm.

DR. EAGLE: So, maybe I will make an initial comment and then again I will ask Dr. Lynch to comment. My initial comment is that for the patients in the age range that enrolled in this study, shall we say, the standard of care at that time was regular endoscopic surveillance with occasional polypectomy, depending on the size of a particular polyp or a polyp that looks particularly large. That is the standard of care. So, that will be sort of the standard of care in placebo; it is the standard of care globally as we have talked to multiple investigators. So, the surgery issue doesn't really come into it apart from endoscopic polypectomy. It doesn't come into this age population. I don't know if, Dr. Lynch, you want to add anything.

DR. HUSSAIN: That answers my question.

DR. MARTINO: Are there other comments, questions? Yes, doctor?

DR. PRZEPIORKA: Just reading through your chronology from your pivotal study up to your Phase

3 trial, it seems like there are multiple things that held up the timeline. Am I reading this correctly?

DR. EAGLE: I think the main thing here is that there are multiple issues in an area where we haven't been before. We haven't been in the pediatric population and we haven't been in chemoprevention. So, with the timeline getting out to Phase 3, one of the biggest important facts was the Phase 1 study and development of the protocol, and having long enough exposure to record that data.

DR. PRZEPIORKA: The timeline that you have gave as 12/99 being the time that the FDA agreed with the study concept, meaning a Phase 3 study in pediatric patients.

DR. EAGLE: In phenotypically negative patients that are genotypically positive which, by the nature of the disease, tends to be in the pediatric population.

DR. PRZEPIORKA: So, in December of '99 the FDA agreed with proceeding with a randomized

trial in patients for whom you had no safety data and you weren't sure what the appropriate dose was.

DR. EAGLE: Yes.

DR. PRZEPIORKA: Thank you.

DR. MARTINO: Mrs. Mayer?

MS. MAYER: I suspect the answer will be no but I just wondered if there was anything existing in the way of another indication with Celebrex for adolescent patients that might look at heart toxicity, or might have been designed to capture any data that could be informative for this indication.

DR. EAGLE: So, that is always a challenging area, how much indications and patient populations compare. We do have other trials ongoing in the pediatric population because this drug is also used in arthritis and pain. Those trials tend to be non-placebo comparative studies. They are very small numbers and very short duration, and they are ongoing. We don't have any data at the moment on that, but there is that opportunity as well.

DR. MARTINO: Can I ask a question about how you are going to monitor drug intake in these patients? I am assuming that they are typical

teenagers who sort of do what they want. How is that issue dealt with both in the placebo and the treatment arm?

DR. EAGLE: Yes, I can sympathize with the teenager comment about compliance. Again, the compliance will be associated with pill counts, returning the pills and boxes, as well as a diary in some cases. And, in a subset we are also looking at pharmacokinetic data but that is in a subset of the population. That is a very valid point.

DR. MARTINO: Are there any other questions or comments? Does the FDA have anything they would like to add to this particular application? Are you guys happy?

[No response]

Thank you, doctor.

DR. EAGLE: Thank you.

DR. MARTINO: The next application is

going to be actually our last one, from Genzyme Corporation and Campath. As you folks change seats, I will need our secretary to read the conflict of interest statement that pertains to that specific application.

Conflict of Interest Statement

MS. CLIFFORD: The following announcement addresses the issue of conflict of interest and is made part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting, with the following exceptions.

In accordance with 18 USC Section 208(b)(3), full waivers have been granted for the following participants: Dr. Steven George for being a member of a competitor's drug safety and monitoring board on unrelated matters, for which he

receives less than $10,001 per year; Dr. Maha Hussain for ownership of stock in a competitor, valued from $25,001 to $50,000. This de minimis financial interest falls under 5 CFR part 2640.201 which is covered by a regulatory waiver under 18 USC 208(b)(2).

A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

We would also like to note that Dr. Antonio Grillo-Lopez is participating in this meeting as the non-voting industry representative, acting on behalf of regulated industry. Dr. Grillo-Lopez is employed by Neoplastic and Autoimmune Diseases Research.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with

any firm whose products they may wish to comment upon.

DR. MARTINO: Thank you. Dr. Cynthia Sirard will present for Genzyme Corporation

Campath (alemtuzumab):

Status of Phase 4 Post-marketing Commitments

DR. SIRARD: First off, I would like to take this opportunity to thank the committee for allowing Genzyme to come in today to talk about our Phase 4 post-marketing commitments. By way of introduction, my name is Cynthia Sirard. I am a medical director and oversee the Campath oncology.

Listed on this slide are Genzyme participants that are with me today that I may call upon to help answer some questions as they arise later in the presentation.

By way of agenda, today we are going to discuss four main points. First off, we are going to have an overview of the treatment options for

CLL. We are going to look back in our registrational data for Campath supporting our approval. We are going to move forward and look at our Phase 3 study, referred to as CAM307, which was really our study that was to resolve the remaining of our post-approval commitments. Lastly, the FDA has asked that all sponsors come in today to discuss challenges that occurred during conduct of these post-approval commitments and ways sponsors actually overcame some of those challenges.

By way of review, chronic lymphocytic leukemia is the most common form of adult leukemia in the United States. It has an incidence of approximately 9700 patients per year in the United States. The overall prevalence is approximately 60,000 patients. It is thought to be a progressive and often fatal disease. However, this only accounts for only approximately 4600 deaths per year. No current therapy is thought to be curative, nor has demonstrated prolonged survival.

Chronic lymphocytic leukemia often has a variable clinical course. The most aggressive

forms of this disease are thought to cause demise in two to three years, whereas there are some indolent courses of upwards of 20 years and, in fact, patients do not die of this disorder but die of other co-morbid conditions.

Chronic lymphocytic leukemia requires multiple sequential treatments. The treatment goal was originally thought to be palliative or, hopefully, moving in advancing in the direction to more of curative or minimal residual disease negativity. Over time, there have been evolving standards of care. In fact, there are only four FDA approved drugs for CLL that include chlorambucil, cyclophosphamide, fludarabine and Campath. Historically, alkaline-based therapy has been the primary mode or the standard of care. Any number of the drugs listed on this slide can now be used as single agents or in combination to treat chronic lymphocytic leukemia.

Campath is a humanized monoclonal antibody which is directed against CD52 antigen. CD52 is expressed on both normal and malignant cells.

Specifically, it is expressed on B and T lymphocytes. It is important to note, however, that CD52 is not expressed on bone marrow progenitor cells.

Campath works by lyses of lymphocytes via complement fixation, antibody dependent mediated cell cytotoxicity and induction of apoptosis. This is clearly a different mechanism of action from the available cytotoxic chemotherapeutic agents.

Looking back at our registrational data, this slide accounts for the three studies that were used in support. CAM211 was our pivotal study; 125-005 and 125-009 were supportive studies for this registration. These three studies were similar in nature. The median age in years in these three studies ranged from 57 to 66 years. The median number of prior regimens for all three studies was three. Interestingly, all three of these studies really looked at a refractory patient population. The one of interest is that only a third of patients in the 005 study actually had seen fludarabine in the past or failed fludarabine.

Disease characteristics in this patient population, most of them, or three-quarters, had advanced stage disease and approximately one third

had B type symptoms upon enrollment into the study.

The efficacy results of our registrational data included response rate from 21-33 percent. Looking at the 95 percent confidence intervals, they were relatively consistent across the three studies. It is also important to note that in CAM211 we did see a complete response rate of 2 percent and a partial response rate of 31 percent. the median duration of response ranged from 7-11 months. The median time to response ranged from 2-4 months. The median progression-free survival was anywhere from 4-7 months.

Also, not noted on this slide, was the overall survival data and it is important to point out that for Campath overall survival in CAM211 the median was approximately 16 months in comparison to the fludarabine data where the median survival of fludarabine failure patients is only thought to be around 10 months.

The safety database of 149 patients really outlined three main safety concerns which, of course, included infusion-related events, the infectious complications and hematolytic toxicity. The most common events seen across all studies are, in fact, acute infusional-related events. These

usually are most apparent on the first infusion and decline with subsequent infusions. We have also seen a variety of opportunistic infections reported and study 005 and 009, in fact, did not require anti-infectious prophylaxis. Subsequent to that, we have utilized anti-infective prophylaxis specifically in the pivotal study and did note a substantial decline in opportunistic infections with the onset of anti-infectious prophylaxis.

I should also mention that this prophylaxis is continued throughout the duration of the study, from the initiation of they to completion of study therapy, and actually onwards after completion of study therapy for a minimum of at least two months after completion of study therapy and until CD4 counts have recovered.

Hematologic toxicity, which can be severe, often emerges on therapy but is thought to be transient. Overall, in this advanced patient population the safety profile is thought to be reasonable and manageable.

Accelerated approval was granted on May 7 of 2001 for patients who had been treated with alkylating agents in the past and who had failed fludarabine therapy. At that time, we were presented with nine post-approval commitments. Five at this point have been completed, four are ongoing to be addressed with the CAM307 study, which I will address. We have one final commitment that will be outstanding at the completion of CAM307 and I will discuss this in a future study that has already been submitted to the FDA at the end of October for review in CAM203.

This slide depicts the five post-marketing commitments which have been completed and actually FDA released. These really revolve around the CMC data, with the exception of the submission of the final study report for CAM213.

The four post-marketing commitments listed on this slide are the remaining commitments thought to be addressed with CAM307. CAM307 was to

demonstrate that alemtuzumab demonstrated a superior disease-free survival as compared to chlorambucil. CAM307 has had enrollment complete. This information will come forward in our clinical study report which is due at the end of next year.

In addition, we were also able to assess the incidence of loss of CD52 expression at the time of relapse or disease progression. In addition, we looked at the development of antibodies in relationship to Campath therapy. The one outstanding commitment which remains is the immunologic assessment of the effect of Campath on the patient's ability to respond to vaccinations after Campath therapy.

CAM307 was a Phase 3 study in front-line patients with B-CLL, looking at comparison with chlorambucil as the comparator arm. The purpose of this study was to verify the clinical benefit of Campath therapy. It was an open-label,

multi-center, randomized, active control trial. The primary objective was to demonstrate that Campath had superior progression-free survival over chlorambucil. You may recall that in our post-marketing commitments it was suggested to utilize disease-free survival. However, with multiple discussions with the FDA subsequent to that post-marketing commitment, it was agreed upon that progression-free survival is the appropriate endpoint.

Secondary objectives were to compare treatment arms with respect to survival, response rates, duration of response, time to treatment failure, time to alternative therapy and safety.

The inclusion criteria are listed on this slide. I will point out a couple of pertinent ones. Patients must have had histopathologically confirmed diagnosis of B-CLL with a positive clone for CD5, CD19 and CD23. Patients were allowed to be enrolled on study if they had Rai stage 1 through IV disease with evidence of progression. They could have received no prior chemotherapies

for B-CLL.

Exclusion criteria are noted here. Pertinent criteria involved that patients, to enroll on study, had to have an ANC of greater than 500 and a platelet count of greater than 10,000. They could not currently have any evidence of autoimmune thrombocytopenia. They couldn't have an active infection or co-morbid conditions at their study participation.

This is the study design that was selected. Patients were randomized on a 1:1 basis to receive Campath at 30 mg a day. This was on our standard dose escalation of 3 mg to 10 mg to 30 mg when tolerated. Dosing was then, after reaching the dose of 30 mg, to be 3 times per week up to a total of 12 weeks. The 12 weeks was inclusive of the dose escalation period. The comparator arm was single agent chlorambucil at a dose of 40 mg/m2 orally, which was given once every 28 days for a maximum of 12 months.

One of the problems with oncology trial design is coming up with the appropriate comparator

arm. We had many discussions with the FDA in regards to this comparator arm and what would be pertinent to the study design. This comparator arm was actually chosen because of the Kanti Rai paper that was published in December of 2000, prior to our approval for this agent. As the sponsor, we had actually gone to the FDA several times trying to utilize fludarabine as the control agent because of the Kanti Rai paper. This Kanti Rai paper looked at fludarabine versus chlorambucil versus the combination. In fact, fludarabine at that stage was actually shown to have superior response rates to chlorambucil. However, since chlorambucil was the only approved single first-line agent for B-CLL at this stage, it was thought that chlorambucil was the appropriate comparator.

Also, the sponsor recognizes that there are many doses and regimens for chlorambucil. This dosing regimen was also chosen because of the Kanti Rai paper which utilized the same dosing regimen in that paper.

At this stage, we have enrolled 297

patients and enrollment is complete, and 149 patients were enrolled to Campath and 148 patients were enrolled on the chlorambucil arm. The last patient was enrolled on July 15 of 2004. The bottom bullet really accentuates the fact that we had a lot of active sites but not as many accruing sites. Overall, we had 68 active sites, however, only 45 were capable of putting a patient on study. Specifically, in the United States we had 20 sites that were active and capable of enrolling, however, only nine were able to do so.

This slide depicts the actual patient accrual distribution worldwide. Out of those nine enrolling sites, the United States was only able to enroll 24 patients. It was imperative for this study to move into Eastern Europe to actually enroll the study in a timely fashion.

Our statistical design--we had patients randomized on a 1:1 basis by interactive voice response system. Our primary endpoint assumption was based upon our sample size of 284 patients and suggested a 50 percent improvement in

progression-free survival.

We had multiple analyses built into this study design. In April of 2004 our first interim analysis was really to look at safety only, and it was conducted after 50 patients per arm had reached four months following randomization. The outcome of this was that, in fact, it was safe to continue and so we went forth.

In August of 2005 we had our second interim analysis which was really to evaluate safety and efficacy. This was completed after 95 patients, regardless of treatment arm, progressed or passed away. At the conclusion of this meeting it was determined again that it was safe to continue and that there were no adjustments in sample size required on the data that they had seen.

Our final analysis is predicted for the second quarter of 2006. This is planned after a total of 190 patients have either progressed or passed away.

Overall, looking at our status and

timelines, we have been on target for the majority of our timelines within a month or two, and we are, in fact, on target to complete that final study report for November of 2006.

We did have a couple of challenges along the way which I would like to address on the following slides. The main difficulty encountered with the conduct of this study was that enrollment was slow. This study was originally opened in the United States and Western Europe. The thought was that the issues that we were having with enrollment were really related to the alternative first-line therapeutic options for patients with chronic lymphocytic leukemia. Enrollment increased substantially following the opening of sites outside of the United States, particularly in Eastern Europe.

We also had some logistical difficulties encountered in looking at the immune functional assessment for patients in regards to response to vaccinations who had received Campath. This assessment was originally put into the protocol but

only 8-10 sites in the United States would actually conduct this immune function assessment. Unfortunately, due to the slow accrual, we were unable to meet this commitment. However, we did try as a sponsor. We actually amended the protocol to allow for the immune function assessment to occur ex-U.S.

Despite all that, we were only able to capture data for four patients on the immune function assessment. It had been predetermined with the FDA that we would try and capture 50 patients' data in this cohort.

Other things to note with this immune function assessment is that in fact this really was allowed for a subset of patients in the study. What I mean by that is that patients with immune function could only have advanced stage disease, stage III or IV disease, and they had to have a platelet count of greater than 50,000 to allow for the tetanus toxoid booster to be administered to follow the study.

So, in recent discussion with the Division

of Oncology Drug Products in July of this year, it was proposed that Genzyme fulfill this commitment in a new trial entitled CAM203. CAM203 is a study that we really gained interest in conducting because of the change in paradigms for the administration of Campath in the United States. In fact, we became aware that a good proportion of Campath use was being administered subcutaneously. We believe that the subcutaneous push was because of the availability for the subcutaneous route of administration to decrease the infusion-related events.

So, we have gone forth to conduct a Phase 2 open-label study, multi-center, to evaluate the efficacy and safety of subcutaneously administered Campath in the exact same patient population as our CAM211 pivotal study, really looking at those patients who had received prior therapy with an alkylating agent and had failed fludarabine.

So, in conclusion, we believe that Campath has emerged as an important treatment option for patients with chronic lymphocytic leukemia. Our

post-marketing commitments will be fully met following completion of CAM307 and CAM203, and these trials will provide further support for Campath use in first-line therapy as well as subcutaneous route of administration. Thank you for your attention.

ODAC Discussion

DR. MARTINO: Thank you. Dr. Perry, do you want to start?

DR. PERRY: Yes, I can't pick on Dr. Pazdur who conveniently has gone--

[Laughter]

--but I will pick on any FDA volunteer. It seems to me that the standard of therapy at the time this trial was initiated was not chlorambucil, which is a drug that only Dr. Cheson and I and those with greyer hair than us still use. It seems to me the company was forced to conduct this trial with one hand behind their back when fludarabine was really the comparator drug rather than chlorambucil. Why did the FDA refuse the company's, I am sure impassioned, plea to use

fludarabine which would have made this a quicker study, a clinically more valuable study because the comparison of the two is really what we want and need to know, and insist on a historically relic of a drug, chlorambucil?

DR. KEEGAN: I think the best I can say at this point, given that we weren't coming in today to debate the design of the original trials, I don't have all the information available. It is correct that there was a great deal of discussion about the comparator arm and the amount of information we had to support fludarabine versus chlorambucil. I do recall that we also had some involvement with SGE, ODAC or consultants on the design of the study, but that is probably about the best I can say at this point in time, that it was discussed; it was a compromise situation; and it didn't appear to us that it had--at least from what the company had said--hinder their ability to conduct the trial. It may have been more informative to have had other controls, that is true as time went on. But the study at that point

was well under way.

DR. PERRY: I am sure it did impact the company's ability to do the study. I would have had difficulty trying to randomize somebody to those two options and that is why many of the patients were not in the United States. So, this is not a U.S. trial. It seems to me that what we want is a trial based on the populations we treat with the drugs we use.

DR. MARTINO: Dr. Cheson?

DR. CHESON: Well, one could make the argument from the company's perspective that comparing two of their own drugs to each other is not in their best interest, that being fludarabine and Campath. But I think the company has to be commended for completing this trial because, as Dr. Perry said, this is really antiquated therapy.

My question is primarily--and it is also wonderful to see that you are doing a subcutaneous study because none of us is using intravenous anymore--we won't tell the FDA that! On the study in which you are looking at vaccinations, and I

can't imagine why they want you to do that, are you comparing something before and after therapy, or is this just measuring response to vaccination after treatment, which wouldn't make any sense whatsoever in a CLL patient?

DR. SIRARD: The way it is in the CAM203 study is to actually look at patients with an antigen and a mitogen stimulation index in advance of Campath therapy, in addition to looking at titers for tetanus prior to study therapy. Six months after patients have completed Campath we are going to give them a tetanus booster and then, after receiving a tetanus booster, two weeks later we are going to do that antigen and mitogen proliferation and do another tetanus antibody to evaluate response.

DR. CHESON: Why do we care? To the FDA I guess, why do we care? Why is this important to you?

DR. KEEGAN: The question that arose, where we have an antibody with broad specificity, this antibody is reactive with T-cells, B-cells and

macrophages, is to what extent can we provide guidance on the duration of the impairment of the immune response that might be drug related, given that, you know, the drugs are in the circulation for up to many months after administration.

Another point, just to clarify the rationale for the subcutaneous administration information, what is not commonly known I think is that, in fact, in certain populations there is a fairly high rate of development of antibodies directed to the antibody itself, approximately 40 percent. What impact that has on the pharmacokinetic profile, the pharmacodynamic profile and ultimately efficacy has not been studied. So, in fact, while the practice may have evolved, the information supporting that practice has not and that was one of the reasons to request that the company determine that.

DR. CHESON: So, you are doing pharmacokinetics in this as well?

DR. SIRARD: We are. The study itself is based upon looking at two questions, the first of

which is do you need a run-in, the 3, 10, 30, or can you go straight to 30? We are looking at patients in two groups there, a small number of patients, and they are going to have what is considered a dense sampling PK assessment. Then, after it has been determined which is the appropriate way to administer Campath, either with or without escalation, the remaining patients will have more sparse sampling but will include time points after completion of Campath therapy at similar time points as the antibody assessments.

DR. CHESON: As Pat alluded to, subcutaneous administration was first published by London et al., and Karolinska did it without any knowledge whatsoever as to the absorption or pharmacokinetics. Although they subsequently published in Blood last year, it would be nice to validate that. And, I think if we didn't need that run-in it would certainly save a lot of nuisance; I am glad you are doing it.

DR. SIRARD: Thanks.

DR. MARTINO: Dr. Eckhardt?

DR. ECKHARDT: Yes, I just wanted to say that I actually think we are here to discuss some of the clinical trial designs that went on because

we are here because of the lack of delay in completing commitments after accelerated approval, and I think what we have heard today is that there are various categories that could include rare diseases and difficulty with accrual. We have looked at trial designs that have placebo arms, leading to difficulty with accrual. And, I think that this is a good example of having arms that include antiquated drugs and that also lead to difficulties with accrual. I think that these are some of the issues that we need to start thinking about as we look back at some of the difficulties.

You know, the corollary to that is that the longer it takes to complete the commitment, the less relevant the results are coming out of this program. I can see that this is a real problem because you have comparisons to antiquated drugs. You have the fact that accrual is taking so long that sometimes you have changing disease supportive

care paradigms. So, I think that all of these things are important and we can't really exclude any of them in our discussions.

DR. MARTINO: Go ahead, doctor.

DR. PRZEPIORKA: One comment and one question for the FDA, my comment being that we are in a good news-bad news situation right now in oncology in that many drugs are coming up very rapidly and, unfortunately, the paradigm for care is changing very rapidly and it can be very difficult for drug companies to fulfill their Phase 4 commitments in such an environment. If the design of this particular protocol was at a time when fludarabine was not yet totally accepted as first-line therapy, then I can understand that there might be some quandary on the part of the FDA not to move ahead with fludarabine. On the other hand, I did hear the sponsor say--and I will paraphrase it--we were required to use this by the FDA because it was the only FDA approved drug at that time.

Dr. Pazdur earlier today asked that we

move forward and we learn some lessons from the experience. So, I just want to get some clarification from the FDA. Is your requirement for the control arm to be only an FDA approved drug or something that has a compendium indication or something that is approved by the literature?

DR. KEEGAN: I would say that it has to be an acceptable comparator. Having FDA approval for an indication certainly would meet that bill but there are other ways to get there. It would require that one have confidence that the body of information is compelling.

DR. CHESON: But I think you also need to consider what is standard of care and, as you know, more than 80 percent of oncology drug use is off-label. For example, you would be hard-pressed in some places to even consider fludarabine as a standard of care any more for previously untreated CLL with the combination therapies. You have to think ahead. You have to have expert input into the design of these trials, knowing what is likely to be relevant and important, not necessarily on

day one since it takes a year to get these protocols going, but what is still going to be important two or three years from then so that people will still be interested in putting their patients on study. Fludarabine was well ingrained as the standard treatment when the study got going.

I am amazed that it ever got completed because we thought it was ridiculous to use chlorambucil as the standard therapy. But that is this example. There are lots of other examples where you have to say what will be the standard of therapy in a year or two. You can't predict five but you can certainly predict changes that are going to take place in a year or two in many diseases. And, this would have been a good example to think ahead because this is really, you know, ho-hum. But you did it and, hopefully, the results will be as you want them but ho-hum.

DR. MARTINO: Are there other comments or questions? Yes?

MS. MAYER: Well, perhaps this is for discussion later but I wonder if FDA and perhaps

Dr. George could comment on the potential or lack of potential for adaptive randomized, controlled trials as a way of addressing some of the issues that we have been talking about, with making trials perhaps a little more--well, certainly finish sooner and be more acceptable to patients. I am jut thinking out loud here, this might be a setting in which this might be tried.

DR. GEORGE: Well, I think a more general point might be is are there other creative design issues that might save time and effort. The answer is yes, to some extent, but it has been my experience that they won't overcome these basic problems of accrual, for example, in this trial if it was an issue of the comparator group that was causing any kind of slow accrual. I doubt that that would really help that much. But I think it is a good point. We have to be a little more creative in these situations where we are not liable to get information like we would like, such as some adjuvant study in a very common disease where we can get very large numbers of patients

easily onto trials. So, I think in that sense it is certainly worth exploring these other ways to look at the design of studies.

DR. MARTINO: Anything else from the committee? If not, we thank you, doctor. The last part is a more general discussion and we need to read a conflict of interest again for this.

Conflict of Interest Statement

MS. CLIFFORD: The following announcement addresses the issue of conflict of interest with respect to this portion of the meeting and is made part of the record to preclude even the appearance of such. Based on the agenda, it has been determined that the topics to be discussed in this portion of today's meeting are issues of broad applicability and there are no products being approved.

Unlike issues before a committee in which a particular product is discussed, issues of broader applicability involve many industrial sponsors and academic institutions. All special government employees have been screened for their

financial interests as they may apply to the general topics at hand to determine if any conflict of interest exists. The agency has reviewed the agenda and all relevant financial interests reported by the meeting participants.

The Food and Drug Administration has granted general matters waivers to the following special government employees participating in this discussion who require a waiver under Title 18 USC Section 208: Maha Hussain, Michael Perry, Gail Eckhardt, Dr. Steven George, Pamela Haylock, Dr. Silvana Martino and Dr. Maria Rodriguez.

A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

Because general topics impact so many entitites, it is not practical to recite all potential conflicts of interest as they may apply to each member and consultant. FDA acknowledges that there may be potential conflicts of interest but, because of the general nature of the

discussions before the committee, these potential conflicts are mitigated.

With respect to FDA's invited industry representative, we would like to note that Dr. Antonio Grillo-Lopez is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Grillo-Lopez is employed by Neoplastic and Autoimmune Diseases Research.

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants' involvement and their inclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

ODAC Discussion of Accelerated Approval

DR. MARTINO: Thank you. The FDA has provided us two questions that they want us to

address, but I am assuming that we are at liberty to deal with the process as a whole because, in all fairness, I think that is really how I would like to handle this.

The accelerated approval process I think you are all familiar with. We have spent more than today dealing with this topic. It remains, at least I would say in my own gut, the most controversial element of what we do, which is dealing with drugs when there is limited amount of information. So, the question is what advice do any of us have to provide either to the sponsors or to the FDA that relates to how the process needs to be improved. With that, I am hoping that you all will be free to just say whatever is in your gut. This is your opportunity so go to it. I will start on my left.

DR. ECKHARDT: Well, I am going to out on a limb here. I mean, I think a lot of what we talked about today, we have spent a lot of time on what I would think of as exceptional disease states, and this isn't the whole accelerated

approval strategy or process but I think we need to have categories for looking at data in a different manner, and one of them, I would say, is in the rare diseases or exceptional disease states that are a much smaller patient target. I think one way to proceed towards approval of those agents would be to not have them necessarily on this other track because I think, again, we are finding that for some of the randomized trial designs with placebo control the accrual is so slow that we never get there.

So, one could envision setting up a body of data requirements for full approval of these agents, and that could be a constellation of data that doesn't necessarily have to be randomized but needs to be done in a high quality manner that could be partnered with the FDA. Because I think, clearly, what you see with these diseases is that you are bringing in data from various sources and I think if you had an idea about how you wanted to maintain quality, those would really be in a category so that they aren't sort of, again, in

this fugue state of approval for years and years and years with never meeting their commitments.

So, I think one way to think about some of those diseases is as sort of an exceptional approval strategy or exceptional diseases because they are exceptions in terms of the numbers of patients.

I think the other hairy issue though goes towards the accelerated approval process, and I sort of agree that this may not be the best term for that. I do like the idea of conditional approval, and I think there some of the strategies that we need to think about are almost going to be disease specific. You know, what are the various diseases where we would allow single-arm data to at least get the process started and I like the idea of thinking about it as a conditional process of going forward. You can think about single-arm data but I think then the question is for those types--and I can think of things like, you know, second-line pancreatic cancer is very different than second-line breast cancer, and first-line

hepatocellular cancer is different from colorectal cancer first-line. And, what I would like to see is that we still allow the ability to get in there with the single-arm data within a disease where that is appropriate and then it becomes a question of what supports full approval.

One thing I wanted to ask the FDA again is about this issue of being able to use relevant control-arm data because I can tell you that one of the reasons that people aren't developing drugs, for instance in hepatocellular carcinoma, is that the only approved drug is Adriamycin and no one knows how to get from step one to step two, and that is an active drug that has activity, single-arm data. How do you design that Phase 3? Can you design the Phase 3 with clinician's choice?

So, I like the idea of some liberal thinking about how to take something that has its initial conditional approval with single-arm data into Phase 3, and whether there is a way to get over those stumbling blocks. So, that is a lot but that is free thinking.

DR. MARTINO: Dr. Hussain?

DR. HUSSAIN: I echo Dr. Eckhardt's remarks and I would go back and say that assuming

that the accelerated process or the legislation was written in a vague way on purpose, I would imagine--and Rick is shaking his head that that is true--we have a ten-year experience with it. It seems to me it is time to revisit the benchmarks, if there were any benchmarks, and if there aren't, perhaps establish some benchmarks.

It would seem to me some process of education for all those who will serve on this committee or who participate in the voting process becomes important because I am impressed by the arbitrariness of the burden of proof for a vote of a yes or a no, and it is really in the eye of the beholder. In a study that had 21 patients, one of six had a response; seven of 16 had a response and, all of a sudden, that is accelerated approval. It seems to me that the bar has to be set where there is a bare minimum that has to be satisfied. It may, in fact, require the FDA to convene structured

meetings to actually set some standards and then look at that and in the next five years perhaps re-evaluate. Otherwise, I think the process seems to be fairly arbitrary and there is some experience that I would imagine has to go with it in terms of the vote process.

DR. MARTINO: Dr. Perry?

DR. PERRY: Well, my colleagues to my right are not only smarter than I am but also better looking. I agree with what they had to say.

Let me pose a potential picture for you. A new drug is available that offers a response rate of 50 percent in cholangiole carcinoma. So, I will take away from hepatoma and make it even rarer. So, 40 percents are treated and 20 of then respond with partial responses--none of this stabilization of disease or this quasi stuff but real partial responses with duration of responses considerably longer than the six months we would have said is historically accurate. The median response is 18 months.

If you were to say to a company this is

great. I want you to do a Phase 3 trial now to randomize between the best available drug, first the company would say, okay, tell me what is the best available drug. As you, of all people, know there is no best available drug. It might be Adriamycin if you believe in Adriamycin data but, as I recall, it is 15 percent response rate. So, you are asking the company to design a trial between a drug with a track record of 15 percent and new drug with a record of perhaps 50 percent, and by the time they had 40 percent they would have a pretty good view I think of the safety profile of the drug. I think that would be a very difficult drug to accrue to, and I don't think even if you allowed a crossover patients would want to go to the Adriamycin arm and have to get two cycles of that and get further prolongations of their proton and elevations of their bilirubin which would make them ineligible for the other drug.

So, I think you have to have a new paradigm, a new way of getting around some of these artificial burdens that we have put up. The kinds

of diseases we are treating now are not the simple ones like breast and colon cancer where there are lots of patients, lots of points along the way that they can be treated. If you are going to treat some of these people with first-line therapy for a bad disease you would like to get it at least partially right at least out of the chute.

DR. MARTINO: So, are you then suggesting that we ought to set the bar of what we require for accelerated approval a bit higher? I mean, is that what I am actually hearing from you?

DR. PERRY: What you hear from me is subject always to interpretation. What you are hearing from me is that I endorse what my colleagues have said. That is, first I don't think accelerated approval is any longer an acceptable term. It ought to be conditional approval. Accelerated approval implies something that is not being delivered and I think that is very, very wrong and needs to be stopped.

Second, I think that we do need to set a bar that says if you have a Phase 2 study with X

level of expectation done by a responsible group, with the data audited, I think you might be able to proceed from there without having to go through a Phase 3 trial.

DR. MARTINO: I think I actually understand you.

DR. PAZDUR: Magnitude is everything obviously, and the point that you brought out of a very high response rate obviously is something that we generally don't see in many of these applications.

I would like to remind you that many times what we are looking at with these applications are response rates that are either hovering around 5 percent or 15 percent. For those of that have been in the business long enough remember if the drug didn't have a 20 percent response rate it wasn't worth not of approval but even of further developing that drug.

So, where you set the bar--and we have always been asked this question, you know, what is the lowest response rate that you will accept--is

almost an impossible question to answer because, obviously, it is in the context of the risk/benefit relationship. We would accept a lower response rate for a drug that had fewer toxicities. If we are dealing with a toxic drugs there are issues of a different risk/benefit relationship.

But magnitude is everything. I think, you know, when we have these endpoint discussions it is very important to realize that if we have a refractory disease situation and we have a very impressive response rate, that is much different than the usual turn of events here that we have when we are dealing with either getting a barely perceptible response rate or a response rate that, you know, many people would question.

DR. MARTINO: Rick, I want to deal with this issue of the actual choice of words of accelerated approval. There are many of us who dislike that. Okay? We feel it is misleading. It gives really the wrong impression. Everyone assumes that it means that this is such a wonderful drug that no one should be denied it, even those of

us who have no disease to start with. Okay? That being the case, is that choice of words changeable? Because I actually see that as a crux to many of our arguments.

DR. PAZDUR: I think we would have to get some counsel on that from the FDA lawyers here. That isn't a Dr. Pazdur term or an interpretive word. It is actually written into the regulations and, hence, that would have to be substantially changed in the regulations here.

But, remember, what you are talking about here with conditional approval, you are implying here that you will have the authority then--not just the authority that is written in the regulations but the real authority and the motivation by ODAC to actually take these drugs off the market. Let me address that issue. That is a very, very painful procedure here because if we do have a drug that has been approved with an X percent response rate, it is a very difficult issue then after the drug is out there for a year, two years to decide and say, well, maybe this drug

doesn't have the benefit that we would like it to have. Okay?

So, conditional approval may serve you at this point, but I think you have to look down the pike here. By conditional approval you are really saying to the FDA that, yes, the ODAC will have the motivation to really address the hard issue that if other studies don't demonstrate the clinical benefit, or if subsequent studies show other issues with the drug, then there will be a clear message to take the drug off the market. And, I don't know if that exists. We know, obviously, for safety issues--the American public is very clear that for safety issues they have accepted this paradigm. But to have a drug that is on the market for several years and then to say, well, let's readdress this issue after people have used it, and this drug should come off the market is something that is a very ambiguous situation.

DR. MARTINO: Well, but I guess in my own mind I don't think of it as a decision that necessarily ODAC ever makes. Remember, we are

advisory to you--

DR. PAZDUR: Correct.

DR. PERRY: You used the term ODAC and authority in the same sentence, without a negative--

DR. MARTINO: Yes.

DR. PERRY: I hope that was just a mis-statement.

DR. MARTINO: We appreciate the point but, speaking for the committee, our concern is does the FDA have the guts to withdraw drugs for something other than toxicities? That really is the issue here. Okay? You know, we have some concerns as to whether you folks do have that level of courage in you.

DR. GRILLO-LOPEZ: Can I comment on that?

DR. MARTINO: Yes, doctor, you may.

DR. GRILLO-LOPEZ: Thank you. That is one extreme. The other extreme is that the FDA might decide to withdraw the requirement for a confirmatory study. Today we saw an example with Doxil of a situation where that might be possible

and, in fact, justified for a variety of reasons.

I understand that the FDA is in a bind in a situation like that because the FDA has in writing required those confirmatory trials and it is hard to pull back from that. It is also hard because it would be setting a precedent. That hasn't been ever done before. Right? So, it is difficult for the FDA to do that. However, should this committee recommend to the FDA that a requirement for confirmatory trials be withdrawn, I am sure the FDA would give that very good consideration.

So, we need to talk about those two extremes, and with Doxil as an example where it is already a regular approval for ovarian cancer, where two other major indications are being looked at for approval studies, where there is ample evidence of the decline in the incidence of KS and so on, you know, that may be a reasonable way to proceed.

DR. MARTINO: I still have the feeling that from a drug company's point of view, as long

as you have given me approval I am actually pretty happy. Even though I asked the question earlier of what did it really mean if you had full approval or provisional approval--and I did get answers to that question but the answers that I got implied to me that if you have accelerated approval only, well, there are some nuisances; there are some problems you have to tend to in terms of doing other things. But I still suspect that either approval is really quite satisfactory to a drug company. So, I am not sure that there is always an appropriate level of intent or commitment on their parts to deal with what, in fact, are rather complicated trials where they have to reach around the world, and one does recognize that it is not easy to do those things. But it is in doing that which is difficult which I think bespeaks of someone's commitment. The things that are easy, are easy. Those are hardly ever a challenge.

So, I am still concerned with the fact that I am not sure there is enough of a bite if something isn't produced and isn't done in a timely

fashion; that there is a certain leisureliness with which they are allowed to view the process. The bottom line here is not making life difficult for them. The bottom line is that as a physician, and I know that there are people in this audience who assume that the only people who understand any of this are people who are not physicians--I think you are quite wrong about that. I think those of us that are physicians actually understand the patient's perspective better than pretty much anybody else, not only because we are physicians but also because we are human beings ourselves and our families deal with these same issues of cancer. So, this is not an issue that somehow is not understood by those of us.

The key again gets down to the fact that I have to have a certain trust in the data before I am willing to give it approval. It is not true that placebo effect is zero. That is not correct. That has been shown many times over. There is a placebo effect, especially if you are looking at toxicities and especially if you are looking at

quality of life issues. So, a placebo is a potential therapy. So, it isn't a zero therapy.

But I do have the feeling that there is a certain lack of rigor that is allowed to the companies even in diseases where it is very difficult to get patients into certain trials. They don't lose a whole lot if they don't do those things in a timely fashion. Yes, doctor?

DR. PRZEPIORKA: First and foremost, I was struck today by the presentation in comparison to the presentation in 2003. The previous presentation pretty much revealed a lot of foolishness and foot-dragging on the part of the pharmaceutical industry which was definitely not present here. There are some very serious design considerations that held up Phase 4 completion here, and I think the FDA has to be applauded for everything they put together to make sure that the pharmaceutical company understands that it really means what it means. It is sad that we have come to the point right now where we need to deal with the very tough stuff but, on the other hand, to get

here so quickly I think is something good for the FDA.

The first question I actually put down this morning is how long should it take to complete Phase 4 commitments. By the end of the day, the best I can tell, is that it depends on what the outcome is. Clearly, if you are doing a trial in advanced disease a short outcome and a short expectation for completion is going to be what I would expect, as opposed to an adjuvant trial or a prevention trial. So, unfortunately, I don't think we can answer that question much more specifically.

In today's presentations there were two themes that came out for what actually prevented Phase 4 commitments from being completed. One was bad control arms. I think that you have a potential here to really have some serious problems in the future if the details of the control arm are not really assessed appropriately at the time of trial design. As much as Dr. Cheson would like you to be able to predict the future, I am not sure we can actually do that unless we call him on every

case, and if he is willing we will do it!

The other issue is the rare diseases and there just aren't enough patients out there to do two randomized, controlled trials in those situations. I liked the terminology "exceptional circumstances" although, in my mind, it meant something different than what the EMEA meant. This is probably a situation where, are sitting on a review committee, I would probably accept a single-arm trial as long as approval was conditional, and it was conditional on the fact that use of the drug was restricted and could not be used off-label. Because what I would be concerned about is having a drug approved for a specific use, i.e., low-hanging fruit, and then everybody go out and use it for everything else for which it was never studied. I absolutely detest having drug out there being used without good science and for no reason.

Dr. George mentioned his desire to see more registration studies as a Phase 4 commitment and I think that is a nice way to go for these rare

diseases.

DR. PAZDUR: In all fairness, Donna, you are presenting a picture here that is far outside of even the FDA's mandate. It involves, you know, not only the drug approval process but reimbursement issues, etc. Some people may think you are right, however, obviously this is a very complicated to portray, you know, a change in events that would involve what physicians can use off-label, etc. This is really kind of outside even the purview of the FDA and involves a major change in drug reimbursement, etc.

The point that I do want to bring up because I sense a very negative tone to this conversation, and I kind of want to change it in a sense. You know, we presented basically applications that did not meet their expected accrual, and I think that people have to understand that there are drugs that have fulfilled the requirements, and drugs that have demonstrated clinical benefit, and have resulted from successful development plans after our discussions of 2003.

One great example of this is Velcade that basically had a Phase 3 trial in place; was approved on response rate criteria; and went on to

demonstrate a Phase 3 trial. So, you know, there are successes here. Here, again, it is kind of taking a look at a school and all you are presenting are people that failed the entrance examination or failed their first test, or something. There are examples of success and perhaps in doing this program maybe we should have spent a little more time in going over the successful applications.

One of the reasons, however, we wanted to spend some time on the applications that did not meet their accelerated approval commitments is that we want you to have an understanding when these applications come to you the potential problems that they can have. They can have problems obviously with completing their Phase 4 commitments, and we may be left in this quandary for a period of time here. So, here again, it is a mixed issue here of successful applications that we

perhaps did not, in all honesty, give a full picture of but, you know, time was limited in a one-day meeting.

DR. MARTINO: Dr. Cheson, you are next.

DR. CHESON: Most of what I was going to say has already been said, including some premonitions. But one theme that I guess that I have been strongest about over the last couple of years is that I think the bar is set way too low. We have had drugs like Iressa and others which just were obvious to some of us were not going to pan out like they were supposed to with a five percent response rate, and other drugs which have kind of limped along because--

DR. MARTINO: [Not at microphone; inaudible].

DR. CHESON: Well, if you look at the confidence intervals, the lower limit of the confidence interval was 5.4 percent which, in the protocol, was designated as a negative study. Be that as it may, there are other drugs for which there was more emotion than anything else pushing

them through the system. That is the first point. I would really put a plea in for putting our heads sometimes ahead of our hearts although it is difficult to do.

The other point is that what we heard today was some really crappy study designs, as people have recapitulated over and over again. I don't know the entire process by which the FDA and the companies go through their deliberations, but it seems to me there should be some more outside, uninvolved consultants participating. This is a huge effort. It is taking a decade, 15 years, who knows how long to get some of these studies done and you might benefit from some additional input from people out there who are involved in the clinical trials; involved in the cutting edge research that have no investment either with you all or with the companies, to say this is really a stupid idea, or this really has some likelihood of working. That might help us with some of these problems that we observed today.

And, I am not so sure that today should be

viewed as a show place of ugly ducklings. I think that we saw some companies that really are trying hard, doing the right thing. I have really learned a lot of good lessons here. And, they are moving in the right direction. We saw some from which we can learn a lot about how not to do things, like the Doxil story, a drug that obviously has activity. And maybe we need to rethink why we keep them on the market or don't, depending on what sort of evidence. I think we need to tailor our appreciation of the evidence to the individual clinical scenario, and I don't think that we can have one global way we look at things. But I think we need to be very, very specific and very, very careful and have a lot of informed opinion because everybody puts a lot of work into this, particularly the FDA and the companies, and it is a shame when resources are wasted, and the worst resource to waste is a patient going on a clinical trial that never gets completed.

DR. MARTINO: Dr. Grillo-Lopez?

DR. GRILLO-LOPEZ: The FDA now has ten

years experience with accelerated approvals. We have recently learned about that experience and have expanded on it today and, clearly, we need to learn and we need to be able to fulfill the FDA's request that the committee make recommendations on how to improve that process and learn from what we have heard today. In order to do that, I think we need to reflect not just on the drug development process but on the cancer treatment development process. We start with a single agent but what is really at the end of that road is the incorporation of that single agent into some combination therapy that, hopefully, may be curative. We have precious few, but we do have some combinations that are curative today.

As I said earlier, in my view, the FDA regulates the earlier part of that process, the single-agent part but, again in my view, it is the oncology community that is responsible for that end point, that objective of finding the optimal combination, hopefully curative, within which that agent works best. There are multiple examples of

how long that process takes. If you take, for example, nitrogen mustard, it took perhaps around 20 years for DeVita and others at the NCI to find that incorporating it into the MOPP regimen was curative for Hodgkin's disease--20 years. Adriamycin, doxorubicin--it was at least ten years after the FDA approval for the oncology community to find in another indication, in lymphoma, in another combination, in the Chopp combination, that it was curative and that for lymphoma within the Chopp combination that was the optimal use of that agent.

One need not wait the 20 years for nitrogen mustard or ten years for doxorubicin to approve. One needs to get these agents early on to the patient via a single-agent approval based on reasonable safety and reasonable clinical activity. So, again, I think we need to keep things simple. We are looking at the early stages of what is a very long process and one needs to keep it simple at that stage and say what is the minimal amount of data that we need to confirm that clinical benefit

that has been seen on an early basis, on a preliminary basis when you give accelerated approval.

What I have seen today in a number of the presentations by the sponsors is that there is a definite opportunity to do things in a more simple way. I have seen some very complicated study designs, study designs where you could forecast that the studies were going to take years to complete, with problems with accession, with placebo arms, with the wrong control drug on the control arm, and so on. Beyond that, also the requirement as a commitment, as part of the confirmatory studies for the generation of data which is of very high scientific interest, but I would question if it is critical to confirming clinical benefit, like HAHA studies and so on. I mean, not that that doesn't need to be done, but does that have to be part of the requirement, I would question that. It certainly makes things a lot more difficult.

The FDA, in their internal deliberations

with the sponsor, has to define what things, once a drug gets an accelerated approval, are going to be the responsibility of the sponsor and the commitment required by the FDA versus what is going to be done by the oncology community over the next couple of decades in research.

DR. MARTINO: Dr. George?

DR. GEORGE: I would like to make a few perhaps obvious, I hope not trivial, comments and observations on accelerated approval. The first one is that it seems that it is inherently a very difficult process almost by definition or by its nature. The purpose of the accelerated approval process, as I understand it, is to get therapies out there earlier to patients who might benefit from them. Now, to do that, what you have to do is look earlier in the process than you normally would, and in this case something that has shown an effect on some putative surrogate that is reasonably likely to predict clinical benefit and, therefore, you give it accelerated approval. This is akin to moving earlier in the process of any

kind and being forced to make a prediction.

So, what is happening is we are making a judgment about an agent or a therapy in some indication where, just almost by its nature, we are going to make more mistakes that way, and we are doing it deliberately. In other words, I think it is not a bad idea, to me, but we just have to face up to that fact. If you think of the whole population of possible therapies we might approve, and we approve some and don't approve others, we are going to be wrong if we are making that decision earlier in the information gathering process. We are going to have a higher error rate, if you want to think of it that way.

So, then the problem comes down to how do we distinguish when we have made an error, I mean, what is an error? Is it an error to say we gave accelerated approval to one indication and then we tried to do a so-called confirmatory trial in a completely--not completely different but a different indication, earlier disease, say, and combination therapies and it doesn't work out in

that setting. Does that mean it is wrong to have given that accelerated approval in the advanced situation or not?

So, I think that is why it is a very difficult process. It is that we have set ourselves up to have a higher error rate, just by the definition of the process. We have also gotten into a situation where it is very hard to determine what success or failure is, that is, whether we really made the right decision when we gave that accelerated approval. And, all those things together make this a really, a really difficult process. I mean, we could always just way any agent that comes along, we ought to just give it accelerated approval. That seems to be the attitude of some. That seems not in the best interest of the public or the regulations. But we have moved things earlier and that is going to increase the error rate.

DR. MARTINO: Dr. Rodriguez?

DR. RODRIGUEZ: Actually, just a brief comment that the article that was included in one

of our booklets that talked about the accelerated approval, I think it was published a year ago in the Journal of the National Cancer Institute, to me, I read that article and it sounded like the sum experience was that this is a positive process that has made available to patients drugs that otherwise would not have been made available so quickly. But today my experience is that we have seen, as you said, the ones that didn't work out or that possibly maybe we should consider did work but for obvious reasons didn't quite meet the pattern of the others. I wonder if maybe as a segue to this article would be when it doesn't work, why doesn't it work and how can we change it.

DR. MARTINO: Mrs. Mayer?

MS. MAYER: There are several points I would like to make. I think we heard rather passionately earlier this afternoon how some among the public respond to the threat of withdrawal of drugs for the maintenance of high standards in terms of levels of evidence. Really, the law, as it is currently written, in order to work depends

upon all parts of the process, including the part which enables FDA to mandate the withdrawal of a drug for lack of efficacy, as well as for lack of safety.

I was very intrigued early on to hear about how EMEA is planning to address that issue. I guess no one knows at this point how practical their way of making their conditional marketing authorization expire after a period of time. But it strikes me that that way of proceeding, whether it is a year, two years or whatever, where marketing approval simply ends and all of the issues are reconsidered at that time is a way of addressing unanticipated issues that come up in changes in treatment and many of the other issues that we have talked about today. So, I hope that FDA will think about that as one possible approach.

Another thought about very small magnitude of responses, I think we need to find a way to address the issue that magnitude of treatment response is directly proportional to appropriate patient selection for drugs. That is an issue I

think that needs to be addressed as well.

Finally, I wonder if it might make sense for FDA to commission an analysis of the successes and failures of accelerated approval to look to see in a more systematic way than we are able to do sitting around the table, and perhaps in a more impartial way than FDA can themselves do, a real look at the characteristics that identify the successes and that identify the real problematic issues.

DR. MARTINO: Dr. Perry?

DR. PERRY: I was going to suggest that the public members of ODAC write a summary of this meeting that we could submit to the FDA as our opinion if we could come to some consensus. I think what we have discussed today is important enough that I want to make sure that we have some sort of paper trial rather than a vague corporate memory that goes away when those of us on the board are no longer here, so that we have a written record and someone else could refer back to it and say, yes, that is what they thought back at this

point in time and we don't want to make the same mistakes again.

DR. MARTINO: I actually think we are televised and can actually be viewed.

DR. PERRY: But that is not the same thing as a summary.

DR. MARTINO: I will grant you that.

DR. PAZDUR: Are you planning on coming up with a consensus? Because, remember, we are hearing varying opinions here.

DR. PERRY: I think at least parts of the table here have some elements of consensus and elements where we might disagree, but I think the way we report this meeting might be different from the way somebody else reports this meeting and I would like to have at least our opinion, to the degree we share it, put together on paper so you could have it and you could say, yes, this is what ODAC was trying to say to us and we will listen or we won't, depending on our own good judgment.

DR. MARTINO: Are you volunteering to write such a paper, which then would be circulated

and which some of us might care to sign and others not?

DR. PERRY: No--

DR. MARTINO: Because I tend to agree with Rick that I am hearing various opinions around the table also.

DR. PERRY: I would not consent to write it. I would consent to help start it with input from everybody else. I am not foolish enough to think that I could put the thoughts of this group together in a coherent way and that everybody would agree with. But I would like to start the letter out and let everybody else add or amend it as they wish.

DR. MARTINO: I don't think any of us would object to that, at least on the committee. I mean, it is an exercise that certainly is worth doing and, again, some of us will want to do it and others not. Some of us will sign the final product, etc. The issue is will that be of any use to the FDA?

DR. PAZDUR: We are always interested in

hearing what people's thoughts are after they kind of digest everything but, here again, I think one of the issues that I want to bring up is we are presenting really a select group of applications here. And, for us really to get a picture of the whole program we would have to go into a lot more detail of the successful applications. You know, it is hard to judge the success and the failure of the program if all you are looking at are applications that have not fulfilled the requirements for, you know, three or four years, five years or whatever arbitrary period we selected here. I have no problem if people want to write down their thoughts. however, to label it as a consensus of opinion of ODAC is something that I think would be very difficult to do without having everyone sign off on this.

Here again, this is the reason we are having this meeting. It is recorded. It is published basically. We give copies to people of it. It is on the web site. So, here again, if people want to give us their opinions after the

meeting we are more than willing to hear them, but for a document to come out and say that this is a consensus of ODAC we would really have to have everybody sign it, not just the people--well, I don't want to sign it, or how carefully did I read this? This kind of is another vehicle which we have not explored under the advisors and consultants rules, etc., and really I would have to get some additional input from the AC people on this.

DR. MARTINO: So, can I summarize to say that if there are individuals who would care to summarize--

DR. PAZDUR: Their own opinions.

DR. MARTINO: --for you their opinions, then you would be happy to receive them? Is that what I am hearing?

DR. PAZDUR: yes, but I think it would be dangerous to say that this is a consensus of ODAC. We welcome people, after the meeting, thinking about this problem. We have thought about it for weeks, months and years here and have had many,

many meetings with sponsors, internally, with ODAC members, etc. So, if people want to go home and think about it, and digest what they have heard, we would be more than willing to read carefully and consider any individual's comments.

DR. MARTINO: Dr. Mortimer?

DR. MORTIMER: I think if there is anything that I could take home from today it is what an incredibly difficult job this is, and I think all of us felt a little maligned and it was hard not to come to your defense, Rick. I mean, it is our job to protect the public. But I think the problem with the pace of new drug development, as we so wonderfully saw today as we had the wrong control for CLL, as we had the altering of the incidence and the natural history of the disease, new ways of diagnostics for meningeal carcinomatosis, it is really hard to know what the standard of care is. I know that everybody is aware that we need new markers of efficacy, whether it is biomarkers or new functional images, but this paradigm is changing.

As I sit here, I was thinking about if I was going to conduct a trial of a new drug in metastatic breast cancer, something near and dear

to my heart, I am not sure what the control arm is. So, unlike Bruce, I don't really feel so strongly that I know what the standard of care is anymore. It changes too quickly.

DR. MARTINO: Dr. Grillo-Lopez?

DR. GRILLO-LOPEZ: I would like to make a couple of comments. First, a word of caution about the possible withdrawal of accelerated approval. Although this is allowed in the regulations, it is very dangerous ground, particularly if the drug has some evidence of activity, and unless there is clear-cut very dangerous toxicity that has been identified post-approval, or there is some definite evidence that the drug actually does not work at all, the danger is that for a perceived lack of performance on the part of the sponsor you might actually be punishing the patients rather than the sponsor. So, just a word of caution there.

Secondly, my good friend, Dr. Bruce Cheson

and I have complete agreement on one subject and that is fine writing instruments, fountain pens, and today I may have found another area where we are in agreement. That may be one of the concrete recommendations that we can make to the FDA, that is, getting a third party, maybe the ODAC committee maybe not the ODAC committee, maybe someone else that is a third party or, at least the investigators that may be called on to do the confirmatory trials to participate in those early discussions. Now, there is something that I have called the "oops" factor, and that is that after the agreement has been reached between the FDA and the sponsor, when you go to the investigators and say could you please do this study, the investigator might say that study? It is not feasible; it can't be done. No one can do this. To hear that after the fact is painful. So, the early involvement, again, of third parties, experts, the cooperative groups or investigators I think is very important in the process.

DR. PAZDUR: Yes, I wanted to comment on

that because we are doing that now with the special protocol assessments, and many of you that are on the committee have been involved, as well as experts that we have that are not on the ODAC committee. Here again, we are taking a look at trials that were initiated many years ago before we routinely set that up, but I would say for the vast, vast majority of cases now of protocols that are coming under special protocol assessment and I would say all of these confirmatory studies are coming under special protocol assessments now, we are actively pursuing really getting people's opinions that are the "thought leaders" in these disease areas to assist us and discuss with us and we are very open. And, also the sponsors are bringing in these people also.

Remember, we don't set standard of care in a sense. That is set by the community here. In a superiority trial you have to demonstrate that you are better than something and, here again, that is something that every investigator, every sponsor faces not only in their confirmatory trials

shifting standards but also when they are developing their drugs. Things change over the course of one year, two years, three years, and that is the reality of medicine. What one has to make sure when they are developing a drug is that they have an acceptable standard and, here again, if this is widely accepted in the community, even if it is not an approved regimen or not an approved drug, we would allow that to proceed, especially in a superiority trial where you are beating something.

But the reality that, well, these things change so fast maybe is a reflection more of the point that you were bringing up, that these trials are taking a long time perhaps there may not be a serious commitment. Let's be quite honest here to all of the members of the committee, if we were talking about a clinical development plan and we were talking about the approval of the drug to complete a clinical trial, would it take ten years or would they have multiple trials that are ongoing, banking on if one fails another would

supplement that failed study?

The rigor with which people approach this needs also to be addressed here. You don't need only one trial. You know, you have a marketed drug here. Two trials, three trials could be done looking at different disease states and many sponsors do this. A beautiful example of this, even though we had a problem with it, is the drug Iressa. This drug had a beautiful clinical trial design, a portfolio. It had two first-line trials. It had a placebo-control trial in a third-line setting. It has a study with radiation therapy. It didn't fail because of a lack of trying here. It had a beautifully designed program. In fact, I wish more of our drugs were as beautifully prescribed in their development plan as Iressa was. They had a great development plan.

DR. GRILLO-LOPEZ: May I comment on that?

DR. MARTINO: Not quite that, doctor. Mrs. Mayer?

MS. MAYER: I want to I guess give a different patient voice. It seems as if every time

the point is made about what is good for patients that is somehow associated with lowering the bar or increasing access with lesser evidence. I work with women who have metastatic breast cancer and, as you know, although there are many treatments available for them, there are not enough and not effective enough. But it is not necessarily a benefit to a woman who is trying to make complex treatment choices for an advanced cancer to have very minimal evidence and to have an already crowded field become even more crowded. I think we can look forward over the next few years, despite the decline in the pipeline of many more drugs being approved.

It is one thing to talk about rare cancers or cancers where there are very few treatments but the majority of patients with advanced cancers are not facing that situation. They are really facing a situation in which there is increasing confusion about which drugs will work for them, and to simply say, well, that will all be worked out in post-approval research is I think to be a little

bit naive about that. I think we need to know that the drugs that are approved do work and that that information needs to come from well designed studies.

DR. MARTINO: We couldn't agree with you more and we thank you from our heart for that because I do see that there is this constant pull. There are people who think that anything should be put out there, but you have to decide what is one's responsibility. Is it to make anything available, or does it have to be things that actually do something more than once in a lifetime in the universe? So, that is another major issue that we all struggle with. When is something good enough that someone should be given that something? I often think of Iressa being the perfect example. If I were to say to someone I am going to sell you a car and 90 percent of the time it won't start, who would buy that from me? Yet, somehow we think that that is what patients want, therapies that work occasionally. Dr. Grillo-Lopez?

DR. GRILLO-LOPEZ: If we were making

mistakes with accelerated approvals we would have more than 1/25 agents that were a problem and some of them would have been withdrawn already, and they haven't. So, I think the accelerated approval mechanism is important. It is worthwhile, and we should be doing more of it. But that is not what I wanted to comment on.

I wanted to ask Dr. Pazdur a question about the experts that you are using in the discussions concerning confirmatory trials. Are these members of ODAC or, if not, do they have regulatory experience or have been members of ODAC in the past? Because I think that is an important component.

DR. PAZDUR: There is a vast array of people that we have as consultants. They include members of ODAC, past members of ODAC, people from the NCI, investigators on other trials previously, in the past year, etc. We do try to have people that really have an understanding of the disease. Okay? That is our major criteria. When we are looking at a lung cancer study we want to have

somebody that has done lung cancer studies and that has an understanding of the disease. We are not choosing somebody necessarily for their regulatory experience.

DR. GRILLO-LOPEZ: But that part is important because eventually that may come to ODAC.

DR. PAZDUR: Could I just mention one thing because I want to go back to both you and Ms. Mayer's comments. I think it is very important that we concentrate and distinguish between two different issues. One is access to drugs and then approval and drugs. They obviously are the same thing in some situations, and I will be the first to say that the best form of access is to have the drug approved. However, they are different concepts.

I think the other thing that people have to understand, especially when they are voting on something here at ODAC, especially for rare diseases, that there are other alternative mechanisms that we have available for patient access. These include single patient INDs. They

include exceptions to the protocol. They include treatment INDs. All of these can bridge a situation while we are looking at an ongoing trial. Here again, I am the first one to say, however, that the best form of access is the approval of a drug but, here again, they are not necessarily the same concept.

DR. MARTINO: Did you have something else, Dr. Grillo-Lopez, or were you done?

DR. GRILLO-LOPEZ: I am done.

DR. MARTINO: Rick, while we are on this topic, it occurs to several of us on the committee that it would not be a bad idea if, when new members are brought on, if they were schooled a bit more on what exactly the responsibilities are; what these distinctions are between full approval, accelerated approval, what is required for one and the other. As with anything, you sort of learn as you go along and then you acquire a certain experience and, hopefully, with that comes a little bit of wisdom. But I think that because we all have a limited time that we serve you, it really

would be better if a little more understanding were given, and perhaps even having members sit here just to observe the committee before they actually become part of the committee. I think that would be useful. There is a learning curve but I think many of us have felt that if it were made shorter we might serve the process a bit better.

DR. PAZDUR: I am thankful for your comment. We will take that back to our advisors and consultants. Obviously, we might be able to bring people in even for the audience. We have brought people into the division as visiting professors before they come onto ODAC to try to give them some indication of what we are looking for, for accelerated approval and other regulations that the FDA commonly uses. We are always interested in improving the process.

Here again, you do have a short snapshot here and it is a learning process. For somebody who had no regulatory experience before, I assumed this job in my previous job as division director it was a sharp learning experience. As my wife always

says, it is your third fellowship.

[Laughter]

DR. MARTINO: The other issue relates to when we add to the committee experts on a disease. If they have served on the committee previously they have an understanding of what the committee does and why and how. But if they haven't had that experience previously they really are sort of thrown in here. We appreciate their expertise and would love to have them for their expertise to add to our own already is. But having them vote in those circumstances I actually think I would like to have you reconsider.

DR. PAZDUR: And we will have to discuss this with the advisors and consultants.

DR. MARTINO: Are there other comments or questions? Yes, Dr. Grillo-Lopez?

DR. GRILLO-LOPEZ: It is possible that some people today may go away from this meeting believing that some pharmaceutical companies are not diligent enough, dragging their feet, not making all efforts to meet their commitments. I

would assure you that there are many reasons why it is to a company's benefit to actually meet these commitments. The requirements and the restrictions that are imposed on the companies by the accelerated approval guidelines should not be minimized. We talked about them on the surface about marketing materials, review and so on. There is a lot more detail to that, and it is something that tends to be onerous, time consuming, consuming of resources to the company and they do want to get beyond that, and the way they get beyond that is by getting full approval.

There are a number of other reasons why completing the confirmatory studies is an advantage to a company and, beyond showing that it is due diligence, it is good relations with the FDA, good relations with the investigators and the oncology community. Such studies--and, in fact, we saw some examples today--might even be useful in order for the company to obtain additional indications, which is much to the company's benefit. If not an additional indication, at least to get some

additional information into the package insert which is also very much to the company's benefit.

So, there are a number of things to say that it is advantageous to the company to actually get these studies done, and I think most companies do actually make their best effort to do this. And we should understand and not minimize difficulties that are faced in implementing and conducting those studies. There is an unpublished study that I have recently come to know about where these people have found that in the pharmaceutical industry setting a Phase 3 trial on the average takes nine months to implement from concept to first patient entered. That is fast. Because I have also heard that in the cooperative group setting a major Phase 3 trial may take up to two years--I am getting the signal from Dr. Cheson--to start.

So, some of the things that we have seen here in terms of problems that these people face are very real and as an oncology community we have to try to deal with that, identify those obstacles and try to change and try to overcome all of that

because we are falling behind. There are other countries in this world that don't face those obstacles and are able to get clinical research done faster than we can. So, we need to address those issues.

DR. MARTINO: Are there any other issues? If not, I thank you all and the committee comes to a close. Thank you.

[Whereupon, at 4:35 p.m., the proceedings were adjourned.]

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