UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DRUG EVALUATION AND RESEARCH

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ONCOLOGIC DRUGS ADVISORY COMMITTEE

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74th MEETING

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THURSDAY,

MARCH 13, 2003

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The Committee met at 8:00 a.m. in the Versailles Ballroom of the Holiday Inn ? Bethesda, 8120 Wisconsin Avenue, Bethesda, Maryland, Dr. Donna Przepiorka, Chair, presiding.

PRESENT:

DONNA PRZEPIORKA, M.D., Ph.D.	Chairperson
DOUGLAS W. BLAYNEY, M.D.	Member
OTIS W. BRAWLEY, M.D.	Member
JOHN T. CARPENTER, JR., M.D.	Member

PRESENT (Continued):

BRUCE D. CHESON, M.D.	Member
THOMAS FLEMING, Ph.D	Consultant (Voting)
STEPHEN L. GEORGE, Ph.D.	Member
DAVID P. KELSEN, M.D.	Member
SCOTT M. LIPPMAN, M.D.	Member
SILVANA MARTINO, D.O.	Member
MUSA MAYER, M.S.	Patient Representative (Voting)
GEORGE OHYE	Acting Industry Representative (Non-Voting)
JODY L. PELUSI, F.N.P., Ph.D.	Consumer Representative
GREGORY H. REAMAN, M.D.	Member
BRUCE G. REDMAN, D.O.	Member
SARAH A TAYLOR, M.D.	Member
JOHANNA CLIFFORD, M.S., RN, BSN,	Executive Secretary

SPONSOR REPRESENTATIVES:

STEPHEN HOWELL, M.D.	SkyePharma, Inc.
MATTHEW L. SHERMAN, M.D.	Wyeth Pharmaceuticals
CRAIG L. TENDLER, M.D.	Schering-Plough Corporation
DANIEL VLOCK, M.D.	Pharmacia Corporation

FDA REPRESENTATIVES:

MARK AVIGAN, M.D.

PETER BROSS, M.D.

MARTIN COHEN, M.D.

RAMZI DAGHER, M.D.

CHARLENE FLOWERS, Pharm.D.

HUGO GALLO-TORRES, M.D.

STEVEN HIRSCHFIELD, M.D., Ph.D.

ROBERT JUSTICE, M.D.

NAROYAN NAIR, M.D.

RICHARD PAZDUR, M.D.

ROBERT TEMPLE, M.D.

GRANT WILLIAMS, M.D.

C O N T E N T S

P R O C E E D I N G S

(8:08 a.m.)

CHAIRPERSON PRZEPIORKA: Good morning. This is the second day of the 74th meeting of the Oncology Drugs Advisory Committee.

Today we have four more drugs to review plus some discussion regarding the accelerated approval process in general.

And I want to start out by introducing the members of the committee. If we could all start with Mr. Ohye and go around, speak into the microphone and let people know who you are.

Thank you.

MR. OHYE: George Ohye, acting industry rep.

DR. FLEMING: Thomas Fleming, University of Washington.

MS. MAYER: Musa Mayer, patient rep.

DR. PELUSI: Jody Pelusi, oncology nurse practitioner, consumer rep.

DR. REDMAN: Bruce Redman, University of Michigan Comprehensive Cancer Center.

DR. TAYLOR: Sarah Taylor, University of Kansas Medical Center.

DR. REAMAN: Gregory Reaman, pediatric oncologist, George Washington University.

DR. CHESON: Bruce Cheson, Georgetown University Lombardy Cancer Center.

DR. CARPENTER: John Carpenter, medical oncologist, University of Alabama at Birmingham.

DR. BRAWLEY: Otis Brawley, Winship Cancer Institute, Emory University.

CHAIRPERSON PRZEPIORKA: Donna Przepiorka, hematology, University of Tennessee Cancer Institute, Memphis.

MS. CLIFFORD: Johanna Clifford, advising consulting staff, Food and Drug Administration, Executive Secretary to this meeting.

DR. BLAYNEY: Doug Blayney, medical oncologist, Wilshire Oncology Medical Group, Pasadena, California.

DR. GEORGE: Stephen George, Duke University.

DR. LIPPMAN: Scott Lippman, Indiana

University Cancer Center.

DR. MARTINO: Silvana Martino, medical oncology, the John Wayne Cancer Institute in Santa Monica California.

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

DR. BROSS: Peter Bross, medical officer, FDA.

DR. WILLIAMS: Grant Williams, Deputy Director, Division of Oncology Drugs.

DR. PAZDUR: Richard Pazdur, FDA.

DR. TEMPLE: Bob Temple, Office Director, FDA.

CHAIRPERSON PRZEPIORKA: Thank you.

Ms. Clifford will read the conflict of interest statement.

MS. CLIFFORD: The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude even the appearance of a conflict.

To determine if any conflict exists, the

agency has reviewed the submitted agenda for this meeting and all financial interests reported by the committee participants. The conflict of interest statute prohibits special government employees from participating in matters that could affect the personal and imputed interests.

However, the agency may grant a waiver if the need for the individual service outweighs the conflict created by the financial interest. Accordingly, waivers have been granted to the following individuals:

Dr. Douglas Blayney for owning stock in a competitor worth between 25,001 to $50,000;

Dr. David Kelsen for owning stock in two competitors. Each stock is worth between 25,001 to $50,000;

Dr. Thomas Fleming for serving on two data monitoring committees for a competitor on unrelated matters. He received from 10,001 to $50,000 a year;

Dr. Scott Lippman for serving on a competitor's speakers bureau for which he receives

less than $10,0001 a year.

A copy of these waiver statements can 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 George Ohye is participating in this meeting as the acting industry rep. Mr. Ohye would like to disclose that he owns stock in two of the competitors.

In the event that the discussions involve any of the products or firms not already on the agenda for which an FDA participant has a financial interest, the participant should exclude him or herself from such involvement, and the exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment on.

CHAIRPERSON PRZEPIORKA: Thank you.

We're now scheduled to have the open

public hearing. We officially have no one listed to speak at the public hearing. If there is anyone who wishes to make a statement, please come forward at this time.

(No response.)

CHAIRPERSON PRZEPIORKA: Seeing no one, we will continue on to the next item of the agenda for the first presentation by the sponsor, Dr. Matthew Sherman from Wyeth-Ayerst, who will present the discussion of NDA 21-174 Mylotarg for treatment of CD33 positive AML patients in first relapse who are 60 years of age or older and who are not considered candidates for cytotoxic chemotherapy.

DR. SHERMAN: Thank you.

And good morning. I am Dr. Matthew Sherman, Assistant Vice President and head of clinical development in oncology at Wyeth Pharmaceuticals.

On behalf of Wyeth, it's my pleasure to be here today to tell you about Wyeth's progress in fulfilling its post approval commitment for Mylotarg.

Today's agenda is as follows. I will begin with a brief introduction and overview of the regulatory history. I will then highlight the post approval commitment, including both the Phase 1/2 safety combination studies that were needed, as well as the randomized Phase 3 study that is ready to begin.

I will review the post marketing safety surveillance and will update you on the status of the ongoing prospective observational study.

In concluding, I will review the ways in which the FDA's accelerated approval of Mylotarg has enabled Wyeth to provide a novel therapy for the treatment of relapse to AML in older patients addressing an unmet medical need.

Mylotarg is indicated for the treatment of patients with CD33 positive AML in first relapse who are 60 years of age or greater and not considered candidates for other cytotoxic chemotherapy.

Mylotarg is the first in the class of compounds known as antibody targeted chemotherapy.

Mylotarg binds specifically to the CD33 antigen on the surface of myeloid leukemic cells. The complex is internalized, calicheamicin released by hydrolysis, where it binds to DNA, causing double strand breaks, leading to cell death.

Mylotarg received orphan drug designation in November 1999. The incidence of AML in the U.S. population is approximately 10,000 patients per year, and the prevalence, approximately 30,000. This prevalence is far below the cutoff of 200,000 required for orphan drug designation, making Mylotarg an orphan's orphan.

Mylotarg received accelerated approval in May 2000. This approval was based on the results from three pooled Phase 2 studies, which showed a 26 percent response rate in patients with relapsed AML. Enrollment in these studies was continued in order to collect additional data.

We now have treated a total of 277 patients with relapsed AML in support of our accelerated approval in second line patients. These data will be submitted in the near future to the FDA

for review and label update.

Wyeth agreed to a post approval commitment to determine the efficacy of Mylotarg in combination with induction chemotherapy for newly diagnosed patients with AML. This slide summarizes the key features that needed to be addressed for both accelerated and full approval.

Mylotarg was initially developed in second line patients with relapsed AML as a single agent. The dose level identified as a single agent was nine milligrams per meter squared, given on days one and 15.

In contrast, the program now underway is the use of Mylotarg in first line patients with de novo AML in combination with standard induction chemotherapy. This led to a very different dose selection of six milligrams per meter squared given only once on day four.

Another key differentiating feature is the endpoint of survival that will be examined in the post approval study.

In the next two slides, I will summarize

the work in progress towards completing post approval commitment.

New Phase 1/2 studies were conducted in order to establish the safety and maximally tolerated dose level of Mylotarg in combination. Both studies ere designed prior to the receipt of accelerated approval and initiation and enrollment began soon after approval was granted.

Both studies were conducted in parallel in order to minimize the time necessary to start the Phase 3 study.

Study 205 was a two drug combination of Mylotarg and cytarabine and was designed to replace anthracycline in the treatment regimen. This study targeted older patients who could not typically tolerate anthracycline chemotherapy.

Study 206 was designed to incorporate Mylotarg into the standard induction chemotherapy regimen of daunorubicin and cytarabine in young patients who would better tolerate the three drug regimen.

As you can see here, the first patient

enrolled soon after approval and the last patient visit is expected in April of this year. Each study had two parts. The first, to determine the maximally tolerated dose, and the second, to verify the safety in de novo patients and obtain preliminary activity of the combination.

Each study required four dose escalation steps with two months between cohorts followed by an expansion at the MTD dose level.

Enrollment in these studies is now completed. A total of 109 AML patients have been treated. These studies were completed in approximately two and a half years.

In this slide you can see the summary results from the dose escalating Part 1 in Studies 205 and 206. The MTD of Mylotarg was identified as six and four milligrams per meter squared in days one and eight in combination with cytarabine.

As I mentioned, the MTD dose level of Mylotarg was six milligrams per meter squared on day four in the combination with standard doses of daunorubicin and cytarabine. The three drug

combination demonstrated an acceptable safety profile which was a requirement of the post approval commitment, and we decided to proceed to Phase 3.

Last December, at the American Society of Hematology meeting, we reported the preliminary response rate of greater than 80 percent in de novo patients in both Part 1 and Part 2 of this study, giving us the confidence to begin the Phase 3 comparative study.

The Phase 3 study will be a randomized, controlled trial of Mylotarg in combination with standard chemotherapy in de novo AML patients. This study will provide a comparison of daunorubicin and cytarabine given as an established three in seven regimen with and without Mylotarg.

The primary endpoint for this study is patient survival.

In fulfillment of our post approval commitment, the protocol was submitted to the FDA for special protocol assessment in December of last year, and we've received initial comments which we are now addressing.

This study was designed in collaboration with the Southwest Oncology Group under the guidance of Dr. Fred Appelbaum. SWOG has estimated an enrollment rate of 160 patients per year.

The number of patients needed for the study is 684. So the anticipated enrollment will be four and a half years. An additional three years is necessarily for follow-up, and the study is expected to take seven and a half years to complete.

Importantly, an interim analysis will be planned after 36, 56, and 72 months based on early stopping rules.

A study of this slide presents certain challenges. AML is a serious and yet fortunately for patients an uncommon disease. As I noted, SWOG has estimated an enrollment of 160 patients per year. Treatment of AML typically occurs at major medical centers and universities that participant in cooperative group studies. SWOG agreed to participate in this study while the CALGB and ECOG in the United States and the EROTC and GIMEMA in Europe had prior commitments and competing studies,

and both did not accept a request to join.

I will now discuss our post marketing safety surveillance. In the clinical trial experience, 30 percent of patients treated with single agent Mylotarg experience Grade 3 or 4 elevated liver function tests, but most were reversible.

A lot rate of veno-occlusive disease was noted.

In the NDA submission of 142 relapsed AMO patients, three cases, or 2.1 percent, were noted. This was confirmed in a recent analysis of 277 AML patients. In this series, seven cases, representing 2.5 percent, were reported.

Again, these data will be submitted shortly to the FDA for review.

Following approval safety continued to be monitored by our global safety surveillance program. A single center report from the M.D. Anderson Cancer Center of severe hepatotoxicity and a higher rate than expected of VOD was received. At this site investigators piloted the use of Mylotarg

in various chemotherapy combinations and different dose schedules.

The FDA and Wyeth had numerous discussions regarding these reports. Label changes were implemented to strengthen warnings for these observations, and Wyeth quickly developed and initiated a prospective observational study to capture additional information.

The rationale for the prospective observational study was to assess the safety of Mylotarg when used in routine clinical practice in diverse settings, such as community hospitals, academic cancer centers, and others.

Patient eligibility includes both on label and off label use. Enrollment is ongoing, and we are providing the FDA with quarterly reports for this study.

Fifty-seven sites have been activated, and 11 sites are under review. These sites represent academic, community, and managed care and small private practice settings across all regions of the country. One hundred one patients have

enrolled by signing the consent, and 90 patients have received Mylotarg.

The current target enrollment is 500 patients. The study is expected to complete in mid-2004. The incidence of VOD in this observational study as of February 28th has been four cases of 4.4 percent similar to what we've seen in our clinical trial experience.

Site recruitment is difficult. Over 200 sites were contacted, and only one third sites agreed to participate. Again, patient recruitment is difficult in this small patient population. Even major centers treat a limited number of AML patients a year.

In conclusion, patient recruitment and study completion have been appropriate for this uncommon patient population. We have treated 277 patients with relapsed AML to support the accelerated approval and 109 patients in combination with standard chemotherapy.

The FDA approval of Mylotarg under Subpart H has provided older AML patients at first

relapse with a meaningful treatment options for an unmet medical need. Mylotarg is now incorporated into the national comprehensive cancer network treatment guidelines for relapsed AML in the older patient.

Wyeth has demonstrated a commitment to completing its post approval obligation; that Phase 1/2 dose escalation studies were developed prior to accelerated approval, and a new dose level of Mylotarg in combination was established.

The randomized Phase 3 study is currently under discussion with the FDA, and the prospective observational study is ongoing as planned.

Thank you very much.

CHAIRPERSON PRZEPIORKA: Thank you, Dr. Sherman.

The gist of the problem here then is that this is an uncommon disease, and it looks like it will take 7.5 years to complete the Phase 3 study for the commitment. Does the FDA have any comments?

DR. BROSS: I had a first question. Dr

. Sherman, what's the status of this drug in Europe?

DR. SHERMAN: I'm sorry. Can you --

DR. BROSS: What's the status of this drug in Europe?

DR. SHERMAN: This drug has not received approval in Europe at this time.

DR. BROSS: And the second point is a comment, as Dr. Pazdur pointed out yesterday. It is difficult to characterize the safety and toxicity profile in these single arm trials in refractory patients, and this is an example of issues that can arise.

You've all heard about the Iressa situation. In the single arm trials submitted to the FDA, we saw one patient who had a fatal liver event, but it was difficult to characterize because it looked as if he had sepsis and other things, and so Dr. Giles called our attention to the reports of veno-occlusive disease in this case.

And we met with the sponsor, and I must say that Wyeth was very cooperative in coming up with a plan to keep an eye on this veno-occlusive

disease, and we came up with several responses to this.

I might call your attention to the first page of the label, which is under Tab 1. You will see the black box warning, and the second arm of the response was the observational study that Dr. Sherman described.

However, in the first stage of the observational study the accrual was less than dramatic. The last quarterly report I had seen before this was 50 patients had been accrued, 47 as of October 31st, and you'll see that there's been a remarkable jump in approval. I'm sure it had nothing to do with scheduling of this meeting, but we need to characterize the veno-occlusive disease with respect to the incidence, true incidence of veno-occlusive disease.

A second way we had of characterizing this, as Dr. Sherman pointed out, you had enrolled 277 patients in the expanded Phase 2 trial and came up with approximately an incidence of three percent of veno-occlusive disease.

In addition, we have our AERS database, and in the AERS database we received 125 reports of liver toxicity associated with fatal outcomes. Now, this has not been reviewed, and there may be duplicative reports. It's very difficult to come up with an incidence on this, but it's just illustrative of some of the challenges when you approve a drug. It's sort of like opening Pandora's box.

And I wondered if Dr. Sherman would like to comment on how we could improve post marketing surveillance because this is a challenge faced by both FDA and the industry, and also if the members of the committee would like to make any comments in terms of the adequacy of our response and any other suggestions that they might have.

DR. SHERMAN: Well, if I can answer briefly first, this question relates to the observation of hepatotoxicity and perhaps specifically veno-occlusive disease observed initially in the clinical trials that were submitted in the initial NDA.

And I think overall the system from both the FDA and the sponsor's perspective has worked in this regard. There was a very small signal in the initial application of approximately 2.1 percent. This was also confirmed with another point estimate of 2.5 percent in our nearly expanded cohort size of 277 patients.

And the ongoing observational study with now additional sites and more vigorous enrollment in approximately 90 patients has a 4.4 percent incidence of VOD. So these are all very similar.

A bit of an outlier here was the publication by Dr. Giles from M.D. Anderson, and in reviewing that publication it is noted that several of those patients had received Mylotarg, some as a single agent, but also many in combination before any Phase 1 combination studies were done, both with approved and unapproved agents.

So it adds, I think, a complexity, but overall the reporting system both from the sponsor and from the post marketing site, I think works in providing this information.

CHAIRPERSON PRZEPIORKA: I'd like to ask what percentage of those patients had fatal VOD.

DR. SHERMAN: The majority of patients with VOD in the clinical experience or I should say about two thirds of those patients -- I don't have the exact numbers -- had evidence of fatal VOD.

What's complicating in these patients with relapsed AML is also many of them had refractory AML, too, and complications of therapy. So whether or not their death was a direct result of VOD or a combination of VOD in the setting of progressive AML and sepsis is not always clearly ascertained.

CHAIRPERSON PRZEPIORKA: Well, VOD is not a common complication of AML treatment, and in fact, we like to take care of these patients as out-patients as much as possible. Clearly, in the relapse setting there are other things that can occur, but now we're moving this drug up in Phase 3 or Phase 4 to the de novo setting.

In the first Phase 2 studies that you have performed, what was the incidence of VOD and

how many were fatal?

DR. SHERMAN: The incidence of VOD was very uncommon in the 205 and 206 Phase 1 safety combination studies. In the dose escalation parts of those studies, at the lower dose levels there was only one patients with VOD out of approximately 20 or 30 patients. And in the expanded cohorts, there was also one additional patient with VOD.

So, again, in a carefully controlled study setting with appropriate dose levels, we expect that there will be a very low incidence of VOD.

Also, in other studies not presented today being done in Europe there is a very low report of VOD in the clinical trial setting using lower doses of Mylotarg in combination with induction therapy.

CHAIRPERSON PRZEPIORKA: The numbers seem to still pan out to the two to four percent range in the post marketing studies. Given the fact that those all had lower doses, is there any reason to revisit the dose that's currently in the label?

DR. SHERMAN: Well, that question would go back to, you know, addressing the safety and efficacy data that was presented as the initial NDA, and it is the believe that the response rate of 30 percent overall and 26 percent in the elderly patient population with the approved dose level of nine milligrams per meter square was a positive benefit-risk assessment.

But there has been no other studies done. Maybe I'll ask Dr. Jay Feingold from our Global Medical Affairs Group to talk about VOD in the context of additional studies.

DR. FEINGOLD: All right. Good morning. My name is Jay Feingold, and I'm from Wyeth.

Just one correction to what Dr. Sherman said. In the Phase 2 part of the 206 study, several of those patients went on to receive stem cell transplant at Dana Farber, and there were four patients that developed VOD, none of which were fatal, but they did develop VOD, biopsy proven following the bone marrow transplant or the stem cell transplant, which obviously came after the

induction of remission with Mylotarg contained regimen. It was unclear there.

But the investigators at Dana Farber thought that that was a higher incidence of VOD than they would normally expect to see in their stem cell population, based on what they had seen in the previous couple of years with the same induction regimen without Mylotarg.

In terms of post marketing surveillance and the incidence of VOD, we have a very active surveillance program, and in fact, because of the observational study, many centers, particularly larger centers that are participating, we hear about these things right away, and I think that many physicians who are using Mylotarg are very sensitive to hepatotoxicity, particularly VOD.

We have not had a tremendous number of reports of VOD from the post marketing spontaneous reporting setting in patients who are receiving the drug within this label indication and label doses or really even outside indication and doses, but I can't tell you what percentage are actually being

reported to us, as was your question.

The issue of whether we have the right dose or not, of course, obviously is a significant issue because we only -- once the dose was established in the pivotal studies in Phase 1, we only used that dose in the Phase 2 studies.

We have studies ongoing looking at Mylotarg at lower doses to see if they induce remissions or responses at the same rate as they did at nine and nine on day one and 15, but we don't have the results of those studies yet.

CHAIRPERSON PRZEPIORKA: Dr. Cheson.

DR. CHESON: Have you been able to characterize the mechanism by which this agent causes VOD, and is there anything that can be done to prevent it rather than treating it once it occurs?

That's the first of several questions.

DR. FEINGOLD: Two good questions.

With regard to the first question, we're working closely with George McDonald at the Fred Hutchinson Cancer Center and Laurie DeLeve

in Southern California on both preclinical and clinical models to try to figure out what's going on.

Dr. McDonald's theory, and it is a theory at this point, is that the Kupffer cells are CD33 positive and are taking up the antibody, internalizing it, and releasing the calicheamicin and causing activation of stellate cells, which in turn is causing matrix deposition and VOD in liver.

But that's totally theory. He hasn't done any of the work yet, is not finalized, I should say, but Dr. DeLeve is looking at this in a preclinical model.

With regard to the second question, I can tell you that at least in the Dana Farber experience, they actually used defibrotide, and the four patients recovered. However, that's not preventive, although they're now talking about using it empirically. But I don't know that they've started that trial yet.

So I don't know of anything that does prevent it, but I do know that at least in a non-randomized fashion several patients did respond to

defibrotide.

CHAIRPERSON PRZEPIORKA: Dr. Williams.

DR. WILLIAMS: My question relates to the actual indication, if I can read it here. I'm not admitting I need glasses. Mylotarg is indicated basically in patients who are not candidates for other cytotoxic chemotherapy. And as I recall, this was determined because there wasn't a good comparison with standard therapy, and so therefore, it should only be indicated for patients who should not get standard therapy.

And my question, it seems to me based on chance or history that your Phase 3 study is not likely to be successful, that is, over the past 15 years nobody has improved on the current two drugs we have.

So if that's negative, then you're going to be asking, well, are there patients for whom we should still do this, patients who can't get standard therapy.

Do you have any experience at this time -- and if you don't, I would hope that you would get

some -- in the actual patient population for whom this was approved of both the safety and efficacy?

DR. SHERMAN: Well, I'll start by first saying, again, that was the FDA's request at the time of labeling, to do the follow-on study in a different patient population than the first line patients.

DR. WILLIAMS: I'm not at all disputing that. That would be adequate.

DR. SHERMAN: And understanding that though, there are actually studies going on in the Medical Affairs Group to look at Mylotarg in the indicated patient population.

Again, Jay may answer that.

DR. FEINGOLD: There are several studies, one of which has actually been completed by the EORTC, which is a study in 61 to 75 year olds, although now that I'm saying it, I recall now that it's a de novo population, not a relapse population.

But there are other studies in which we're looking at changing the dose of Mylotarg, as Dr. Przepiorka mentioned, to see if it's less toxic.

Most of these studies right now are Phase 2, non-randomized, and again, it's very difficult with small populations of patients to get multi-center, large studies done. But we do have some studies looking at the variation of dosing and in looking at different combinations, both in relapse and in de novo disease in patients over 61.

DR. WILLIAMS: Let me elaborate just a little bit. We've only done this on maybe two occasions, and we've been very hesitant to do it, that is, to label the drug for a patient population that hasn't been studied, which are patients who should not get chemotherapy.

Obviously everybody in the study was a candidate because it was a randomized study to one or the other. So I think it's important to determine also the safety and efficacy in the actual label population, and I just wondered. I didn't understand whether any of your studies actually looked at people who could not or had criteria for ones who could not get chemotherapy, basically were not candidates for chemotherapy and for whom a

reasonable CR rate would certainly be evidence of clinical benefit and probably support for approval.

DR. FEINGOLD: Certainly not yet in a randomized fashion.

DR. WILLIAMS: Well, but you couldn't randomize them. The question is have you actually studied the population who were not candidates for chemotherapy.

And I think it seems to me that would be a good second track to be pursuing.

DR. FEINGOLD: I think it might be hard to define who's not a candidate for chemotherapy because I think that different physicians would view that differently. For instance, in Europe that might be an easier place to come to than in the United State where physicians generally speaking will try to devise some regimen for a patient.

So I think that would be a difficult study and, no, we haven't tried that.

DR. WILLIAMS: To follow one more time, I guess if these studies are not positive or if they have to be stopped because of toxicity, then you

think there's basically no other option here. I think you've told me that you don't think this population can really be defined that it's approved for.

DR. SHERMAN: Well, we have to probably go back and give more thought to perhaps the population that could be studied in extension of the initial indication. It may be a very elderly patient population. It may be, again, looking in that group of patients, whether or not a study could be done to satisfy --

DR. WILLIAMS: And in the spirit of yesterday though, I think it's to think about doing that up front, not after the other study phase.

DR. FEINGOLD: There are 277 patients that were entered on the Phase 2 trials. Supposedly those were patients for whom other physicians didn't feel had other choices for chemotherapy. I'm not sure I understand the question.

I mean, there's 277 Phase 2 patients, 180 of which or so were over the age of 60. So those patients were not considered candidates for

other chemotherapy by their physicians. So they were entered onto the Mylotarg clinical trials.

DR. WILLIAMS: So these clinical trials, you're talking about the single arm study.

DR. FEINGOLD: Yes.

DR. WILLIAMS: Right. Okay. Well, I would assume that there could be criteria. Agreeing upon criteria would be helpful in supporting that these patients are not candidates for other therapy, and I think could make a stronger argument that efficacy demonstrated is basically clinical benefit, but it could not be obtained in any other way, such as standard therapy.

DR. BROSS: Dr. Feingold, I understand you expanded the cohort of your Phase 2 trial and accrued a total of 277 patients, and the last about 150 of those were pretty much, as much as possible, in the indicated population; is that correct?

DR. FEINGOLD: I'm sorry. In which population?

DR. BROSS: The expanded cohort of a total of 277 patients, that was your Phase 2

population. So maybe we can ask for that data and see if any further revisions of the label --

DR. FEINGOLD: Right. That data is coming to you.

DR. SHERMAN: If we could show Slide 23, that would just be one summary of the data. That compares the initial NDA submission in the 142 patients versus the expanded group of 277 patients.

Now, of course, we should ask where do these patients come from. These are patients who were enrolled in clinical trials from the time of the NDA submission to the time of approval, which was approximately seven months.

So from October of 1999, when the NDA was submitted, to May of 2000 studies were kept open to provide access to the product. There was obviously a lot of interest, and those additional patients were enrolled. The studies were closed when the drug became commercially available.

Overall the total response rate remains similar from 30 percent down to 26 percent, and when you look at the data for patients less than 60 years

of age, a similar overall response rate, and for patients for the approved label, 60 years or greater, again, a similar overall response rate.

CHAIRPERSON PRZEPIORKA: Dr. Martino.

DR. MARTINO: A question actually to the FDA. Once a drug is approved can you describe what techniques you have to capture toxicities that are reported subsequently so that we all have a general understanding of that?

DR. BROSS: Well, we have now a whole division of post marketing safety, and they are very much involved in this. And I think this is a good example of the different options that you have for capturing safety, and it's an important issue.

The first signal that we may get or spontaneous reports from physicians, I think it was actually Jesse Goodman who reported by E-mail the first case of fatal pulmonary toxicity, and Dr. Giles, I think, contacted Dr. Pazdur directly.

Subsequent to that, we received spontaneous reports from the AERS database, and I'm not sure. Julie Beitz and Charlene -- is Charlene

here? Do you want to say anything about the post marketing?

Charlene Flowers is one of the safety analysts in the post marketing safety arena.

DR. FLOWERS: Good morning. My name is Charlene Flowers, and I do work with the Office of Drug Safety at FDA.

And when a drug if approved, whether it's approved full approval or approval from Subpart H, all post marketing drugs are surveillanced at the same level. So we receive reports from the sponsors, and we look at them and analyze them in the same fashion.

So, I mean, there is no differentiation. We receive the periodic reports and non-serious and serious reports are looked at.

Does that answer your question?

DR. BROSS: And if there's a problem or an issue that emerges, as in this case, then we ask for a formal report. In the Center for Biologics, I unfortunately don't have the luxury for having a whole safety division; so the medical officers have

to do their own reports.

And as it turned out, the pulmonary toxicity is probably analogous to that seen in Herceptin, and so I had a chance to look at the safety reports from the Center for Biologics.

But that's the mean arena. Spontaneous reports, AERS database; we look at medical meetings, and so forth.

DR. FLOWERS: May I just add one more point?

In fact, when drugs are approved either through Subpart H or full approval, those are products that we categorize as new molecular entities, and in fact, they get a more scrutinized surveillance than our older products because we would suspect that you'd see serious unlabeled events for most drugs in the first three years of marketing, and that's marketing of either of the products.

CHAIRPERSON PRZEPIORKA: I think it's a great idea that with new molecular entities that there's more intensive surveillance, but, Dr. Bross,

I think I heard you say that there were 225 reports, but you're still not clear whether they were duplicates or not duplicates. So I have to ask: what is the procedure for them actually doing something with the reports now that we have so many?

DR. BROSS: Well, I call up Charlene and said, "We need a report on this," and we actually did the first preliminary report prior to meeting with the company. I think it was in 2001 to get a handle on the reporting rate, but the actual incidence is difficult to derive from the reporting rate because you really don't know what the denominator is, and we can ask the company for distribution data and what their estimated rate of use of this product is.

But it's not a very scientific way, and so another example of safety database collection was the observational study that we asked the sponsors to initiate, but I think that this was fairly challenging.

I've seen information from the sponsor saying that you canvassed 100 medical centers, and I

got a few nibbles, and then you canvassed them again and finally got, I think, 80 centers to agree, but at that point there were only something like 47 patients who had enrolled in this.

So I think it's a challenge to accomplish the observational study, and I can't really criticize the sponsor for lack of effort on this part. But it's a challenge how to characterize the safety database, and the Iressa situation is another example.

And we had information from Japan which has a lot more complete reporting on the use of drugs than we do in this country, but it's a real problem.

CHAIRPERSON PRZEPIORKA: Dr. Pazdur.

DR. PAZDUR: Yeah, I wanted to address this issue, and I'm glad Silvana brought it up because I think oncology represents a unique situation to take a look at observational studies once the drug is approved if one wants to get a better idea of toxicity.

Let's face it. Post marketing, trying

to find side effects or toxicities in the population once the drug is out there relies on multiple factors, people's willingness to cooperate in reporting these; what's the denominator; how many patients have used it for a specific indication. It's a very difficult situation to get one's hands on, especially if it's an unusual toxicity.

The issue here though in oncology, unlike other therapeutic areas, other therapeutic areas when a drug goes out, it's used by everyone. You know, an anti-hypertensive, an antibiotic, it's widespread use. However, in oncology and specifically in the treatment of acute leukemia, this in a sense is a restricted use, not imposed by the FDA, but imposed by how patients are treated in the real world. You don't have people treated with Mylotarg by a general practitioner as an out-patient basis. You know, it's a very defined location that these people are treated.

So that the aim here, what we wanted to do was to see how we could better utilize, you know, this aspect of oncology. If we wanted to ask

specific toxicity questions, the drugs are being used in select institutions. Could you get select institutions to report a denominator of their entire use of the drug with the reports of safety?

And I'd like some discussion on this because I think it is a unique aspect of oncology that we do have cancer centers, cooperative groups that could aid in this, but again, it would provide us also a denominator that is frequently missing in these widespread usage.

As Bob mentioned also, you know, we do have a study here that we're doing. We're not only relying on the post marketing experience, as well as the clinical trial database, but I think oncology does give us a unique situation to study this because it is a specialized group of people, physicians that are using the drug.

CHAIRPERSON PRZEPIORKA: Dr. Temple.

DR. TEMPLE: I just want to make the point that the spontaneous reporting system is best at being a signaling system for events you don't know about, and it's spectacularly good at

discovering hepatotoxicity where you don't know about it, and to some extent that worked here, although the mechanism was telephone calls to Rick.

Once you already know the rate and it's two to four percent, you don't need spontaneous reporting systems to work further on that. The very studies and observational data will give you a denominator and help you characterize the patient population and see if there are people at greater risk or lesser risk.

And at that point the spontaneous system is not the usual way you do it. I guess what I noticed is that very few hospitals signed up for this observational study, and we're curious why. I think that's what Rick is asking. It shouldn't be that burdensome. So that's a little disappointing.

CHAIRPERSON PRZEPIORKA: Dr. Feingold, could you address that?

DR. FEINGOLD: Sure. And I'd also like one other issue as well. The other difficulty, I think, in this particular case is VOD because if you ask George McDonald, it's a clinical diagnosis where

you prefer to get a biopsy. If you ask hepatologist at Dana Farber, it's absolutely a biopsy diagnosis or you don't have a diagnosis.

So while in the spontaneous environment, we as a company always accept the investigator's report at face value. If one looks at some of those reports, I'm not so certain that they're all VOD, not so much in the Giles case, but some of the others.

The additional question as to why it's so difficult to recruit centers, we've had IRBs that many major medical centers tell us that this was not a scientifically meritorious study and they would not approve it even though we told them clearly that it was an FDA mandate.

We've had other centers saying that they didn't want to spend their scarce resources on trying to do a study that they thought had limited scientific merit.

And then in going out to the community settings, the physicians didn't want to get involved because they didn't have the infrastructure to be

able to complete the CRFs even though it's electronic and all of that sort of stuff, and so it became a real hassle.

Basically what we did with the centers, a lot of the bigger centers that did sign up was we basically twisted their arm real hard and kept using Dr. Pazdur's name as the major reason why they really wanted to do this.

(Laughter.)

DR. FEINGOLD: And that actually did help in a few places.

DR. PAZDUR: I'm really sad not that you mentioned my name by any means.

(Laughter.)

DR. PAZDUR: All publicity is good publicity.

The issue tough is that there wasn't a concern, and granted this is not obviously the -- we're not asking a rip-roaring question here, but it is a relatively minor as far as time and energy to fill out basically a form report on an individual institution's experience capturing all patients that

received the drug.

So maybe we need to talk more about this in a different forum with the institutions, the IRBs, et cetera, because we do have an opportunity here that is unique, and if we have drugs going out in an earlier fashion, in some situations we're going to want to see these toxicities.

Usually on toxicity and oncology trials, as I've repeated numerous times, are not the limiting factor of whether the drug should be approved because we've accepted generally severe toxicity and even in certain circumstances a percentage of deaths related to the therapy.

But in specific situations where we're uncertain about a toxicity, where we're going to have to have a large patient population, Bob is right. Our current mechanism of doing that picks up signals, but it really doesn't give us the comfort of a large, controlled experience, and again, you could do a large clinical official trial, a randomized trial or whatever, but again, these are a time consuming effort, and we're looking at other

alternatives here.

CHAIRPERSON PRZEPIORKA: And I just wanted to think/remember that we talked about the potential of requiring registration for all physicians who use Mylotarg, just like we do with thalidomide. And I could tell the folks out there who are unhappy to cooperate to look at the thalidomide experience and think of all the paper work they could possibly be filling out instead of just one form.

And I'm not certain because we know the incidence is 2.5 percent and we're getting that information now, I'm not sure if we need to go down to that onerous burden at this point.

Dr. Redman.

DR. REDMAN: Just a comment to Dr. Pazdur. As Medical Director of a comprehensive cancer center clinical trials office at the University of Michigan, this is not a trivial matter. We are under funded, overworked, and to add on another burden, though appropriate, is a major concern across the country.

DR. PAZDUR: Here, again, we would expect that there would be compensation for these forms to be filled out, et cetera. So it's not goodwill that we're asking for.

Here, again, I understand that everyone is overworked, but if we do have a commitment to get these drugs out, there may be instances where we want additional information, and it really is a shame that we don't try to optimize our control situation that we have in oncology because it is a very special environment when we're approving these drugs compared to other therapeutic areas, such as cardiology or infectious disease for the most part.

CHAIRPERSON PRZEPIORKA: Dr. George.

DR. GEORGE: I have a question from a little different angle, a couple of issues. One is on the randomized study, I don't remember you stating if there were any age restrictions on that study. Is it all ages?

DR. SHERMAN: The current proposal for the SWOG study is age population eligibility from 18 to 55 years, and this was proposed, in fact, because

there are other competing studies for the 55 and older patients by SWOG that would limit accrual onto this study.

DR. GEORGE: So it's for the younger patients. My question has to do with, I guess, where this is going, the logic of it.

If this work, if Mylotarg improves survival in this setting, what does that say about the indication or how would that work?

This may be a question for the FDA, as for the sponsor, and conversely, if it doesn't appear to do a thing, how does that affect the accelerated approval?

DR. BROSS: Could I just make a comment about that? I think that my bosses want to answer that, but I would just like to recall that this is one of the challenges of making that a confirmatory study when you have a drug approved when there's no other medical option, and as Dr. Feingold pointed out, I think, that one option for confirming the clinical benefit would be to do a randomized study of Mylotarg versus our best supportive care.

But I think as was pointed out by Dr. Brawley yesterday, the patients don't really like to be randomized to no care or what they might perceive as inferior care, and we really felt that it was not a practical study to accrue. And so it was a challenge as to how to confirm clinical benefit in the original indication.

Now, one possibility would be just to review the expanded Phase 2 study data information, which is incomplete, of course. It's not a randomized study, but that's one option.

But as you pointed out, the confirmatory trial is in an entirely different indication, and the combination of standard induction chemotherapy plus Mylotarg, I think, was perceived to be too toxic in the indicated population, and so we allowed this to go through.

But you have pointed out one of the challenges of a confirmatory study when a confirmatory study is in a different indication, and maybe Dr. Pazdur would like to say something about this.

DR. PAZDUR: I mentioned this in my opening comments yesterday. We have allowed the trials to be done in an earlier or less refractory setting, and that has been in several of these applications. There are several advantages of this.

Number one, I think it promotes efficient drug development moving these agents rapidly into a population where they're going to get maximal benefit.

Number two, frequently if we approve a drug, as you've seen over the past day, there may be difficulty in enrolling patients in the exact indication that you approve the drug i. After all, who's going to go on a randomized study and not get the most recently approved drug?

I think if I was in a patient situation, I'd have somewhat of an uncomfortable feeling. So it makes some sense to do that.

Nevertheless, it is a problem that we have this kind of hanging indication there that has not have clinical benefit exactly demonstrated in that indication.

Now, one of the things as Bob alluded to yesterday is to encourage perhaps other drug development in this area, is to let other people get accelerated approval in that indication until one drug does prove clinical benefit in that specific indication, and that is undergoing discussion at the present time internally at the FDA.

But that is a problem. We recognize it.

DR. GEORGE: I guess it is a problem, but do you have any thoughts right now about how this might work? I mean, if this appears to have clinical benefit in the de novo population, that would be very good. Would that mean that the indication then would be for de novo -- would there be a full approval for the --

DR. PAZDUR: It would have to depend on the strength of the evidence. Obviously they would send it in. Depending on what the database looks like, there could be a consideration for an indication as a first line therapy.

DR. GEORGE: And if it didn't appear to do anything?

DR. PAZDUR: Then we're back to where many of the other discussions were yesterday, and I think one of the reasons Grant expressed some pessimism, one of the aspects that I presented yesterday in my opening comments is that we would like sponsors to have carefully sought out alternative back-up plans.

You know, here again, I think we should be realistic. The regulation says "reasonably likely to predict clinical benefit." Well, that isn't certainty that these trials or these endpoints are going to predict clinical benefit. Just by the luck of things or just by the fact that there may be some drugs that come into the area that there isn't clinical benefit or may not be able to easily demonstrate clinical benefit. I think we need back-up plans to look at more carefully the indication would be another situation of a back-up study for Mylotarg to do a randomized study, for example, looking at dose that Donna alluded to as far as what is the dose in an elderly population. That might be another plan that could be entertained.

Here, again, I think this is something we'd like to discuss with the sponsor to give them time to think about alternative plans, but I really do emphasize that I think even though we're doing one trial here, at lease some discussion should be occurring and some thought on the company's part of what could be back-up plans always.

CHAIRPERSON PRZEPIORKA: I just want to echo what he stated about the need to go back and look into that original population because if, in fact, the randomized trial is negative and all you have to deal with is the patients who can't otherwise get chemotherapy, you're still left with the burden of proving clinical benefit.

And getting a CR in an elderly individual that lasts four weeks may not be what the patient or we, the physicians, would perceive as clinical benefit when the standard of care for treatment of leukemia is multiple cycles and getting a long term remission.

And if you can't give nine mgs. per meter squared on days one and 14 for more than one

cycle, then the patient clearly hasn't had a clinical benefit.

Dr. Cheson.

DR. CHESON: Good segue. This is an example of creating new response criteria to fix the toxicities of the drug, which has troubled me since the drug was initially approved. In the most widely used of the response criteria for AML, those published about 1990 by the NCI sponsored working group, there wasn't any CRp. So there are two parts to this.

One is a question, and that is: have you had enough time now to distinguish the CRps from the real CRs and to see if there is any difference in their eventual outcome?

The CRps, for those of you in the audience who aren't familiar with it, is patients who have fulfilled most of the criteria for CR. The only other one they didn't fulfill is they remained thrombocytopenic.

Now, whether this says something more about the drug or more about the patient would be

determined by the long term outcome of the two cohorts. That's the first part, and maybe you can answer that and we'll get to the second part.

DR. SHERMAN: Dr. Cheson, that's a very good question, and there was a lot of discussion in the field by leukemic experts at the time that the initial NDA for Mylotarg in relapsed AML was discussed, and in fact, in front of this very committee nearly three years ago to the day when we presented the NDA, Dr. Appelbaum presented, you know, his thoughts on the concept of remission and relapsed patients.

And in fact, this has really never been fully studied. So the criteria for remission always applies to first line de novo patients and not the relapse patients, who not only receive more and more intensive therapy and first line treatment, including high dose ara-C.

So the question of recovery of platelets now, you know, is more timely and also made the analogy even in Europe the research council doesn't even look at platelet recovery in their diagnosis of

remission.

But having said that we clearly identified these two patient populations. We believe that they behave similarly and like the 28, we can show a comparison, well, actually not a comparison, but an update of the 277 patients' long term survival on the Kaplan-Meier plots, and these are the data, you know, in the final status of analysis, but to break out the CR/CRp patients from the non-responders, from the 277 database and share that over the long term, these patients seem to behave similarly in terms of their overall survival.

The follow-on question to that though is not --

DR. FLEMING: Just before we leave this, this might be the best you can do, but this certainly doesn't establish whether the induction or achievement of a CRp and the achievement of a CR is causally influencing a better outcome. It could be the characteristics of patients who are, in fact, going to achieve such outcomes. They might have intrinsically done it differently.

I'm not sure how you could answer the question ultimately we'd want to have answered, but this doesn't establish that the achievement of a CRp is of equal clinical benefit as the achievement of a CR.

DR. SHERMAN: Right, and then to go back to Slide 14 -- actually, I'm sorry -- Slide 11, which is the TR-6 preliminary de novo patient data, and although we didn't emphasize this point, these are all de novo first line patients who were treated in the Study 206, the three drug combination, Mylotarg plus standard seven in three chemotherapy. Part 1 patients were on the dose escalating phase, but receiving the dose level that was expanded in Part 2, but we break these out separately.

But you can see here of these patients, of the seven patients who went into remission, using all of the standard criteria for remission, all had a complete response using the formal criteria for first line patients without any consideration of CRp patients. All had full recovery, up concentrated in 100,000.

And of the 43 patients in Part 2 in the expanded cohort for whom we have data, 365 have a complete response, including one CRp patient. So we can include that patient right now for an 83 response rate.

If we drop that patient, the response falls somewhat, but still greater than the 55 to 60 percent response rate the SWOG has seen using the standard induction regimen. So this is the data that we believe would be useful for the Phase 3 randomized controlled trial.

DR. CHESON: Thank you.

Those are interesting data, and hopefully will see the light of publication.

Speaking of seeing the light of publication, just as a point of information, there are a new set of the response criteria recommendations developed by an international working group that are about ready to be submitted for publication. So before one embarks on a missive trial, one might get their hands on them and consider them as a possibility for including in the

protocol.

DR. SHERMAN: Those were the results from the meeting in Madrid last year, yes. We actually had some early discussions of those results, and we'll be incorporating them. I'm not sure if Dr. Feingold can handle the questions or comments about these.

DR. FEINGOLD: I think you answered it.

DR. SHERMAN: Okay.

CHAIRPERSON PRZEPIORKA: Actually, that first slide you showed was for the refractory or recurrent patients rather than the de novo patients, and I believe Peter Thall and Eli Estey have published an evaluation of platelet recovery and its importance in the response criteria.

And in fact, in their analysis, patients who did not get a platelet recovery by three months had a poorer response than patients who did.

And so like Dr. Cheson, I have some questions about the reality of the CRp in the de novo population, and I hope the protocol actually will predefine some sort of an analysis to take that

into account.

Mr. Ohye.

MR. OHYE: Just a small observation, if I may. I think Mylotarg represents sort of a poster child for why we have accelerated approval and how it works, and I'm only sorry that we didn't have this drug as our kickoff for the discussions because it represents all of the challenges that are involved in accelerated approval.

You're trying to do studies in Phase 4 and partner with FDA and cooperative groups, and you still have a study that's going to take seven years, and I don't think anybody can criticize, you know, the company's diligence.

I also think it shows the real world challenges in terms of safety surveillance and what companies have to do and what they're faced with in trying to gather valid data so that FDA and patients and practitioners can have good data.

And I'd like to compliment the sponsor for presenting a very succinct and very illuminating presentation.

And I'd also like to point out in jest that American Home Products is one of the few corporations whose stock I do not own.

(Laughter.)

CHAIRPERSON PRZEPIORKA: Dr. Blayney.

DR. BLAYNEY: Thank you.

I mean, I wish to echo Mr. Ohye's comments. I think this represents a good faith effort and a nice development plan in hopes that not only refractory patients, but de novo, you know, newly diagnosed AML patients can benefit from this therapy. So I think this is, I think, a nicely drawn out plan for Phase 4.

Having said that, one thing on that Kaplan-Meier plot that you showed earlier, I think as I remember the discussion three years ago, many of these patients then went on to use Mylotarg for a while and then went on to stem cell transplant; is that correct?

DR. FEINGOLD: Yes.

DR. BLAYNEY: So that the Kaplan-Meier plot represents not only the effect of the agent

here, but also the effect of adding a stem cell transplant in.

DR. FEINGOLD: Or chemotherapy.

DR. BLAYNEY: Or other therapy. So it may be somewhat misleading to attribute all of that 25 percent survival to the agent.

Thirdly, I think it's worth using the word passive surveillance to describe what the Medwatch and the AERS database is. As a practitioner, this is one more albeit minor, but one more burden that we have in reporting adverse events. It's in contradistinction to the active surveillance that SEER data, which I think is very good in terms of incidence and survival data; the Medwatch is a passive surveillance and only, as you say, provides a signal, and then as we've heard, it's somewhat confused because there's really no analysis. There could be double reporting and the vocabulary that's used is not well controlled.

So I think, Rick, I do agree this represents a nice opportunity, but I would encourage you all to do some thinking about how to make this

easy and reliable and not burdensome because this clearly is restricted in the small R sense of the drug because it is used by a small number of practitioners. So it does, I think, represent a good opportunity.

CHAIRPERSON PRZEPIORKA: Dr. Kelsen.

Dr. Pelusi.

DR. PELUSI: Actually, I want to echo what Dr. Blayney said in terms of using this drug in the community setting and what does that mean for reporting.

I come from a one physician practice, and we have used this drug on two different patients and actually have had very nice results, and when I think about the reporting and stuff, we are lucky enough to have two research nurses, which is not the usual in a very rural practice, but we do, and so, again, your comment about there may be some assistance really needs to be taken very seriously.

But, again, I think many times we assume that all of these patients are treated in big inner city settings, and the reality in many of our rural

states is that that doesn't happen, and we do the best that we can.

And so I think it is important to capture that data of how it's truly being used, but does bring up the whole thing that we've been talking about is for accelerated approval. Once it gets out there, people do see it as approval, and so this setting up, if you will, of the practitioners using the drug, I think, becomes a real pertinent issue that we need to look at very critically so that we can begin to see how it's being used and if many of these side effects or maybe because it's being used out of protocol.

And just one quick question for Dr. Reaman actually. Is this a drug that would ever be thought about being used in a pediatric population?

DR. REAMAN: Absolutely, and I was going to ask the pediatric development plan, but there are studies that have been proposed actually begun using Mylotarg in combination with chemotherapy.

CHAIRPERSON PRZEPIORKA: Dr. Feingold.

DR. FEINGOLD: So if I could answer Dr.

Reaman's question second, Dr. Pazdur's comment first with regard to observational studies. You have to be very careful here because most of the patients on the observational study is using a commercial drug. That means somebody is paying for the drug. So if we offer them help, however you want to frame it, to fill out the case report forms for the observational study, it can be seen as inducement. So we have to be very, very careful there, as we've discussed in the past.

But I think that the FDA may have a different method that we possibly as sponsors could still help, and those are the cooperative groups. Dick Larson and Marty Tallman aren't here. So I can say this, but if the cooperative groups -- or Fred either -- if the cooperative groups would agree to be part of that because, after all, their institutions probably represent most of the institutions who are going to be using this drug other than small practices, we could probably get a pretty good indication.

So I would say that maybe if we could

somehow get cooperative from the cooperative groups, that may be a method.

In terms, if I may, of the pediatric development, COG has just started a trial in the multiple relapse kids with AML in which Mylotarg is being used at two different doses, I believe, in combination with chemotherapy in a non-randomized fashion as a dose binder before going onto a randomized study.

That follows an international Phase 1 study, single agent.

CHAIRPERSON PRZEPIORKA: Dr. Pazdur.

DR. PAZDUR: I'd like to follow up on one of Jody's comments, and that is the use of this drug. We went to great lengths in seeing that this drug is for an unmet medical need here in a patient population that is greater than 60 and basically cannot tolerate conventional chemotherapy. In fact, I was the author of that paraphrase, "cannot tolerate chemotherapy," because we wanted to make sure that people understood that obviously not all elderly people, patients, are the same.

Somebody might be 75 and very frail with other medical conditions, and the other person might be 65 and have just run a marathon, and one might have wanted to be more aggressive.

The reason I'm using that preamble is we obviously understand that there's a great deal of off label use of a drug. Could the company give us -- because I understand obviously you have reps. in the field, and you probably have some understanding of how this drug is used after we approve it for accelerated approval, and also perhaps some of the hematologists on the committee could comment how it is being used in their practices.

DR. FEINGOLD: I can answer. Of course, everything is based on market research which is a limited number of places, patient chart or things like that. We believe that currently about 40 percent of the use is strictly within the label, first relapse over the age of 60.

We don't really know a lot about the others. We put, as you know, a very strong warning in the label not to us it in combination outside

clinical trials, and what we hear is that most institutions are adhering to that.

DR. BROSS: Maybe I could make one comment just on the basis of the AERS database reporting.

CHAIRPERSON PRZEPIORKA: Cr. Cheson had the microphone.

DR. BROSS: Oh, I'm sorry.

DR. CHESON: That's all right.

DR. BROSS: You're our guest. Please go first.

DR. CHESON: No, I was just responding to your question.

We do not use it in combination, not outside of a clinical trial. We do use it occasionally in patients under the age of 60, but generally those who have failed -- who are CD33 positive and who have failed, you know, first, second, third line therapy and really don't have anything splendid left other than, you know, if we have a clinical trial we'll do it. If not, then we'll use Mylotarg.

CHAIRPERSON PRZEPIORKA: Our experience is that the drug does have substantial hepatotoxicity, and so we have limited it also to the labeled indication and also patients below the cutoff age who also have no other reason to be getting chemotherapy in the interim. For example, patients with persistent infections who just can't get more chemotherapy right now, but we need a bridge.

DR. PAZDUR: Peter?

DR. BROSS: I was just going to say from the AERS reporting database, of 35 patients who appear to have veno-occlusive disease, and again, these are very challenging reviews, out of 125 patients with some kind of liver event associated with death, the 35 patients, of these we had 13 out of 35 were in patients 60 years of age or older, but most of these also appear to have had other chemotherapy.

So out of 35 patients, normally two of those 35 patients with veno-occlusive disease reported that appeared to have used the drug as part

of the labeled indication.

Again, most of these are reports from M.D. Anderson, and they were most likely patients on protocol, but we do have some indication that the drug is being used off label hopefully on protocol.

CHAIRPERSON PRZEPIORKA: Dr. Martino.

DR. MARTINO: Let's make the assumption that the SWOG trial is negative. At that point, which is potentially seven years from now, what is the FDA likely to do about that?

I guess I'm trying to understand, and it's the same issue I had yesterday, is once you have given a drug an accelerated approval and it now has acquired pretty much a life of its own within the practicing community, though I realize that you have the option of withdrawal, I still don't have a sense of the vigor with which you might entertain such a thought.

DR. PAZDUR: Well, I think we've addressed this, but probably not your satisfaction. Okay?

(Laughter.)

DR. PAZDUR: One of the reasons why we're having this meeting is to draw attention to the concept of timely completion and the concept that clinical benefit has to be demonstrated. Okay?

I don't want to get into that situation, and I'm trying to avoid getting into that situation, and that's why we're starting these dialogues. I made it quite explicit in my opening comments that in addition to having these trials initiated, being early on, we should start thinking of alternative back-up plans.

Most drugs, and very successful drugs, basically have multiple clinical trials that are being done. They're widely used in groups. The confirmatory studies are one of many trials that are being done.

Take a look at successful drugs, such as Taxotere, Taxol, et cetera. There are many trials that were done after those drugs were available that could have potentially served for clinical benefit confirmation.

So what we're trying to do is bring

attention to this and start working with sponsors. Okay. You're doing this study. Maybe we need to start taking a look at other indications.

One would hope, here again, during this seven year period of time that there would be multiple trials that would be undertake specifically in the indication, okay, that they have received, and that's the reason why we're contemplating putting a carrot out there that other sponsors could come in and get accelerated approval in the exact same indication Company X did until you prove clinical benefit in that indication. That would be an extra incentive in addition to a first line trial.

Here, again, I emphasize to the sponsors, and again, one of the reasons why we wanted to have this meeting is not only for their clinical people to hear this, but also to send a clear message to their management that this is an important part of the drug development process and adequate resources have to be allocated to it. We're going to be taking a very careful look at

these post approval Phase 4 commitments.

We don't want to get into that situation. Obviously we have the ability of taking the drug off the market, but you can imagine, Silvana, that that would be a very difficult situation to be put in.

I think if we faced an unrecognized toxicity or severe toxicity, the agency is clearly committed to taking drugs off the market. But then to say that a drug has been on the market for seven years and, by the way, now it doesn't work and we're taking it off the market, that probably represents a failure to many people, not only to the company; to the FDA; but most importantly, to the patients.

I wish I could give you a specific answer. I can't. It's a hypothetical question. Yes, if push comes to shove, we could take it off the market, but then it becomes a highly I don't want to use the word "politicized issue," but highly emotional issue of the past experience with the drug.

I made the point yesterday that the drug

should not only be viewed in connection with the confirmatory trial. That's one aspect of the drug, but once a drug has been out for seven years, there should be adequate other clinical experience that one could draw on, and one would hope that we would have other studies done, as well as recognition by clinicians, et cetera, or other users of the drugs, patients, cooperative groups that could give us evidence of how this drug works.

Confirmatory trials are very important. That's why we're having this meeting, but for us to take a very, very strong sense and say this is the only data that we will look at I think would be somewhat misguided.

In approving the drugs, we take a look at the totality of data that is out there, both for safety and for efficacy. Therefore, in this consideration we would do a similar thing.

DR.L MARTINO: Well, it's because I see the difficulty in this practicality that it concerns me, and with all due respect to the present group that is presenting, but I've been struck with the

limited data that has been accepted to which accelerated approval has been given. It concerns me that I see almost what I would call hints of success as adequate for such approval. Yet once the cat is out of the bag, it cannot be retrieved easily, if at all.

DR. PAZDUR: Criticism is well accepted, and I understand exactly where you're coming from, and here again, this is the reason for this meeting.

We specifically also wanted to educate the committee regarding accelerated approval, and several of you have come up to me and expressed that you've had an education by being here. We have been faced in many situations where we have brought an application to the committee for consideration, for full approval, and then during discussion it was stated, "Well, let's consider accelerated approval for this application."

As I stated before, this should not be a second thought. It should be a well thought out program, and the people that are the applications' indications that were successful, those four have

been well thought out programs. It wasn't, "Well, let's see if we could get accelerated approval and then we'll consider a confirmatory study."

Here, again, we understand your concern. that's why we're having the meeting, to draw attention to this, to ask sponsors to give this careful consideration, their management to allocate appropriate resources to completing this.

As Tom pointed out, and I do want to spend some time on this, we do expect the same vim and vigor for these studies to be completed as one would complete a registration trial. You could answer the question yourself if these attempts -- and here, again, I'm not mentioning any specific drugs -- have been done with the same vim and` vigor that one would expect for a registration trial.

So we hear you.

CHAIRPERSON PRZEPIORKA: So to sum up, we have a Phase 4 commitment in an uncommon disease with some toxicity going on, and we have to come up with a plan if the Phase 4 study is negative, and just to address the question, sine I'm the

discussant for this drug: has accrual to the ongoing trials been satisfactory?

And I think those sponsors made an incredible effort to get as many centers as they can for both the randomized trial, as well as the observational trial, and so I don't think we need to address number two at this time, although adding the cooperative group to the observational trial is actually a very good idea.

And then have changing circumstances impeded the planned trial or what alternative designs should be considered? And I don't think we've had any changing circumstances to deal with at this point in time.

And I would like to actually suggest that Mr. Ohye is right on board, that this is the poster child of all the problems that can happen.

On the other hand, it seems like Wyeth has come to the forefront to come up with as many solutions to those problems as you possibly can, as well.

Dr. Blayney, did you have other

comments?

DR. BLAYNEY: Right. I just didn't want to leave this rest. I think, you know, the goal of accelerated approval is to get drugs that may have activity into the hands of practitioners as soon as is safe and effective, and it is the will of the people through acting through Congress and their elected representatives that this happen, and it's our challenge to help the regulatory FDA and other regulatory people to make that as scientific as possible and to, if you will, hold their feet, as Rick has said, hold their feet to the fire of the developers to get these trials done.

Because you know, the marketplace will sort it out, not only the marketplace, but the cooperative groups and other things that we've heard today.

So I think we can't in all of these comments lose sight of the fact that the goal here is to move therapies into as wide a patient population as will benefit and make them safe, and I think we're sort of struggling with the construct

that was ginned up 15 years ago in the field. As we've heard, the ground has shifted and now we're trying to deal with that.

CHAIRPERSON PRZEPIORKA: Any other -- oh, Dr. Reaman.

DR. REAMAN: This isn't specifically for Mylotarg, but just to go back to the issue of post approval toxicity assessment, and I'm concerned that we sort of raised the issue, but we haven't effectively dealt with it, and is there a possibility to require post approval observational studies where commercial supply of the drug wouldn't be used and it wouldn't appear as an inducement from the sponsor to actually have those kinds of trials?

I would see a real opportunity within the cooperative group setting for these kinds of studies, and I would certainly echo Dr. Redman's statement that the resources are scarce and there's no difference in the amount of resources that would be required here.

But I have real difficulty with approval and no obligation for assessing toxicity in the long

term.

DR. PAZDUR: The answer to your question is yes.

CHAIRPERSON PRZEPIORKA: Dr. Fleming.

DR. FLEMING: I was waiting for the end of the discussion to raise an issue which was exactly what Silvana raised, and that is I'm pleased to see the design of the Phase 3 trial here that could provide us considerable insight about what the role of Mylotarg could be in first line, and truly hope that we see a positive result, truly hope that we achieve a survival advantage.

Nevertheless, it's a very real possibility that this, in fact, will not be a positive study, and we will have taken ten years.

And also understand in this setting why it is, in fact, going to take a considerable period of time to design and conduct the trial. So the ten year aspect is understandable.

The concern is if, in fact, and Silvana was getting at this; I just want to echo this. If, in fact, this is negative, we're left with a number

of uncertainties, and just returning to something that Rick was talking about earlier, I kind of think of it as a philosophical issue, and that is in oncology we certainly accept serious AEs and even some fatal toxicities, and that makes sense because in agents that we have that have been established to provide benefit in a life threatening disease setting, benefit to risk could still be very clearly favorable even in the context of serious AEs or even some fatal AEs.

Well, we haven't established benefit. We have in accelerated approval a marker reasonably likely to predict clinical benefit, is the terminology, and certainly it's not out of the realm of likelihood that such agents don't provide clinical benefit.

So now we've had ten years of exposure to an agent that, in fact, hasn't provided clinical benefit in that scenario. What specifically is the strategy?

I guess what I'm troubled by is what appears to be a very open ended situation here. My

understanding was the principle behind accelerated approval was if there is adequate plausibility of benefit, then we would try as best possible to provide earlier access to provide broad opportunities for benefit, but in a manner that didn't meaningfully influence our ability to reliably determine whether we have favorable benefit to risk.

We want to benefit the public by getting early access to potentially effective interventions, but at the same time we want to protect the public from being exposed to interventions that, in fact, may be more toxic than effective. And a biologically active intervention could still conceivably be toxic and not clinically effective.

So we're at the end of a ten year period. Do we now step back and say, "Well, we still haven't actually proven whether in the indication of patients over age 60 who can't tolerate chemotherapy, is it beneficial in this setting?

It's troubling me greatly here in the

realization over the last two days that while we are striving to achieve something that is intrinsically very good and potentially in a number of settings such as this one, if this, in fact, is an effective agent and it is a good thing. It seems to me like we have dropped the safeguards for the opposite situation, which is still very plausible, and that is that we are in a number of settings approving toxic interventions that may not be effective, may be preventing patients from getting access to other interventions that could have a better benefit to risk without a clear, understood plan for at what point do you say the evidence of benefit to risk is no longer adequately favorable; that the continuation of the accelerated approval or access should be provided?

CHAIRPERSON PRZEPIORKA: Dr. Kelsen.

DR. KELSEN: I think Dr. Pazdur has made the point a couple of times that one of the messages at least I've gotten this morning is that we should be much more careful in our thinking about accelerated approval than we may have been in the

past because of the difficulty of removing a drug once it has reached the market.

I think in the AIDS population, which may have been one of the driving forces for accelerated approval, there are very good surrogates. I mean, we heard all about that yesterday, a drop in the viral load, et cetera.

In oncology, we're approving on surrogates which don't have that power at this point in time. They may in the future. That would be wonderful, but right now the surrogates we're approving are really relatively weak compared to the AIDS population, and we all feel the need to bring drugs to the market, as Dr. Blayney pointed out, that may help people, but as you just said, "may" is the big operative word.

So I find it very sobering to think about whether we will move to acceleration or not, and particularly the point that Rick made about the drug comes for a full approval, and there's a discussion, well, maybe we ought to make it accelerated approval.

DR. PAZDUR: I think just to follow up to Dave's comment, remember also in AIDS one has a much more extensive database as far as safety, as far as patient exposure than we generally have in oncology, and that is, I think, something else that the group here has to look at when these applications come through.

Again, I share your concern. There is a tremendous amount of tension that exists not only in the FDA, but also in the oncology community regarding getting drugs out faster, sooner, and making sure obviously that they are effective and safe.

And there is this delicate balance that we have to walk on a tightrope so to speak. How to address every issue and how to do every clinical trial in a sense has to be done on a case-by-case basis. Do you demand that a sponsor do five leukemia studies in case one of them fails? Do they do two? Do they do three? Do they do one in the indication? Do they do one in a more advanced disease?

Here, again, this is something that I think as we gain more experience with the accelerated approval process we, and including yourselves, have to come to some terms with, but we have not really had usually with the ODAC members over the past decade experience careful discussion with you at the time of accelerated approval on what the studies would be.

And I think that this is demonstrating that before we okay let's vote for accelerated approval and then go to the airport, that we need to have a very careful understanding of what we're doing here, what the database is, what is the potential toxicity, where does this fit into other therapies.

So I think this is a sobering experience. This is, again, not something that I have not thought about, and this is one of the reasons why I brought this whole issue to an Advisory Board meeting, to hear this and to have public disclosure of this.

CHAIRPERSON PRZEPIORKA: More

importantly, I think you may be getting the feeling from the committee that if in the future the Phase 4 studies are negative and you bring that information back to this committee, this committee would be very willing to say pull the drug.

DR. WILLIAMS: One issue that I think relates to whether or not you would accept first line evidence maybe as an argument for it is the fact that oftentimes you have a refractory setting; you have second line; you have first line. That all potentially could be the same patient. So that if you approve it for first line, there's no longer a need for refractory setting, and it becomes a sort of "who cares" kind of thing whether or not you show a benefit.

But this is a different setting, where these are two different patient populations. One is an older population, and then up front is a very different population, and you know, knowing that there's benefit in each place, I guess the extrapolation is a little less obvious and perhaps provides a little more support for also examining it

in your population.

CHAIRPERSON PRZEPIORKA: Dr. Cheson.

DR. CHESON: Just a couple of practical questions. As far as getting the information quickly, the way you do that is you get the studies completed quickly, and to have two of the cooperative groups doing Mylotarg studies at the same time, competing with this sort of idea, we could have some better coordination of that.

The second point is for Dr. Fleming or Dr. George. We have these things with this O'Brien and what's his name, stopping rule things --

(Laughter.)

DR. CHESON: -- for success, but there are also these futility rules that I don't see incorporated into statistical sections as frequently as they might be, which would stop studies for absence of the apparent likelihood of clinical benefit.

What's your thinking on that?

DR. FLEMING: Well, it's a very good point, and actually, I think it is, as we are moving

ahead and the science of clinical trials is becoming more and more refined, the procedures for monitoring trials are becoming much more refined; the presence of data monitoring committees, the presence of monitoring boundaries, and I call it the lower boundary for lack of benefit.

In my experience, the majority of trials that I at least see in the design stage now do incorporate exactly what you're talking about, Bruce, which is not only an upper boundary to say if, in fact, you clearly established a mortality benefit, then there could be an early termination so that you're not continuing to randomize people when you've already established benefit.

Similarly, if there is lack of benefit, if you have an unfavorable trend and you're well into a trial, you can rule out targeted levels of benefit so that generally speaking if you are 60 to 70 percent of the way into the number of events in a trial and you see no difference, you have evidence that's quite strong against the targeted level of benefit.

So I'm presuming actually even if it wasn't stated that the monitoring committee will, in fact, have such guidelines, which would mean that in this trial if it's a seven and a half year trial, we might be, if there is, in fact, no effect on survival, we might be able to see a few years in advance, two or three years in advance that there is no such benefit.

That at least cuts this ten year period to seven, but it still leaves all of these other issues lurking out there that we've been talking about for the last period of time.

DR. GEORGE: Just a quick follow-up on that. I think all of the groups now, I think, are including these kinds of rules in every trial, including futility analyses. So I think for the cooperative groups anyway it's a deal.

CHAIRPERSON PRZEPIORKA: Any other questions from the FDA, from the sponsors or the committee?

(No response.)

CHAIRPERSON PRZEPIORKA: If not, we are

now scheduled to take a break. I'd like to take a 15 minute break, and if possible go through the next two presentations before the lunch break.

So if the sponsor for the first session this afternoon could be ready for 11, that would be appreciated.

Thank you.

(Whereupon, the foregoing matter went off the record at 9;45 a.m. and went back on the record at 10:02 a.m.)

CHAIRPERSON PRZEPIORKA: Okay. If we could start out.

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 the evidence or appearance of conflict.

To determine if any conflict exists, the agency has reviewed the submitted agenda for this meeting and all relevant financial interests reported by the committee participants. The conflict of interest statute prohibits special

government employees from participating in matters that affect their person and imputed interests.

However, this agency may grant a waiver if the need for individual service outweighs the conflict created by that financial interest.

Accordingly, waivers were granted to the following individuals to permit them to participate fully:

Dr. Blayney for owning stock in a competitor worth between 25,001 to $50,000;

Dr. Kelsen for owning stock in a competitor worth 5,001 to $25,000.

A copy of these waiver statement may be obtained by submitting a written request to the agency's Freedom of Information Office.

We would also like to note that George Ohye is participating as the acting industry rep. Mr. Ohye would like to disclose that he owns stock in one of the competitors. In the event that the discussion involves any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participant should

exclude himself or herself from such involvement, and the exclusion will be noted for the record.

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

CHAIRPERSON PRZEPIORKA: Thank you.

And could the new colleagues from the FDA please introduce themselves?

DR. HIRSCHFIELD: I'm Dr. Steven Hirschfield, Medical Officer, the Division of Oncology Drug Products and also in the Office of Pediatric Drug Development. I'm a pediatric oncologist by training.

CHAIRPERSON PRZEPIORKA: Thank you.

The first presentation for this session will be from Dr. Stephen Howell from SkyePharma on DepoCyt, indicated for intrathecal treatment of lymphomatous meningitis.

DR. HOWELL: Madame Chairman, ladies and gentlemen, my name is Stephen Howell. I'm a

Professor of Medicine at the University of California, San Diego, and it's my pleasure today to present the information on NDA 21-041, DepoCyt.

I need to disclose that I stand in conflict of interest with respect to this product in that own stock in the company that has developed the drug.

DepoCyt is a sustained release formulation of a well known cytotoxic compound, cytarabine. This sustained release formulation was developed in 1987. The cytarabine is encapsulated in the chambers of 20 micron particles made up of phospholipids and cholesterol, and when these particles are suspended in a vial of saline, the product has the consistency of skim milk. When injected intrathecally, then these particles spread out reasonably well throughout the neuraxis and ara-C is slowly released from the particles over a period of two to three weeks.

The indication for which this product is approved is lymphomatous meningitis. Accelerated approval was obtained on April 1st of 1999, and the

total drug development time for this product was 11 years.

The product was approved on the basis of a high response rate in patients with lymphomatous meningitis in a randomized, controlled, prospective trial which accrued 17 patients to the DepoCyt arm and 16 patients to the ara-C arm. The FDA analysis indicated a response rate of in seven patients a response rate of 41 percent in the DepoCyt arm and one response out of 16 patients on the ara-C arm, for a response rate of six percent with a P value in the difference in the response rates of less than 0.04.

At the time the NDA was submitted, these were the clinical trials that were in the NDA. The Phase 1 trial with substantial pharmacokinetics had been conducted in 19 patients. The trial I just discussed, lymphomatous meningitis, prospective, randomized trial included 33 patients.

A study in solid tumor neoplastic meningitis patients had accrued 61 patients, and this was a prospective randomized trial.

Prior to the accelerated approval, the company had initiated an open label confirmatory trial in patients with solid tumor neoplastic meningitis that at the time of the NDA submission and review had accrued 89 patients; subsequently recruited a total of 110 patients.

There were five patients accrued to a prospective randomized trial in leukemic meningitis, and there were two confirmatory pharmacokinetic trials, one conducted in the United States, and one conducted in Europe.

The post marketing commitment that was made at the time of accelerated approval consisted of conducting a controlled randomized trial to determine the patient's benefit and safety of DepoCyt in the treatment of both solid tumor and lymphomatous meningitis. This trial was to include a pharmacokinetic sub-study. The trial was to be initiated within six months, and the total planned elapsed time was approximately 4.5 years.

So the approval was obtained in April of '99. The trial was to start in September, and the

expected total lapsed time until study report completion was 4.5 years.

The purpose of this post marketing trial was to confirm the clinical benefit of DepoCyt in the treatment of patients with both lymphomatous and neoplastic meningitis and to provide additional evidence to support approval for solid tumor neoplastic meningitis. The design was prospective, randomized, and controlled. The controlled endpoint is time to neurologic progression, which is the goal of treatment in this disease.

This is not a surrogate endpoint. This is the actual goal of treatment. Secondary endpoints included survival, improvement in neurologic symptoms present at the time treatment was started, quality of life, cytologic response rate, and safety.

And in an initial plan for an interim analysis was subsequently dropped in further discussion with the agency after trial initiation.

The eligibility criteria include biopsy proven lymphoma or malignant solid tumor elsewhere;

a neoplastic meningitis diagnosed on the basis of either a positive CSF cytology within 21 days prior to randomization or a set of characteristic signs and symptoms on neurologic examination in combination with an MRI or a CT scan showing meningeal tumor in age greater than 18 years.

This is the trial schema. Patients are randomized to either DepoCyt given once every two weeks or standard therapy, that is, methotrexate or cytarabine given twice a week.

There are a total of six two-week cycles of induction, and if the patient continues to do well, they're candidates to remain on study and receive an additional four cycles at a monthly interval of maintenance therapy.

The stratification is for lymphoma versus solid tumor and USA versus European study sites. Patients on both arms of the trial are to receive dexamethasone, four milligrams twice a day through days one through five, with then a rapid taper over the subsequent two days.

This is the schema for the solid tumor

trial. It is identical to the lymphoma trial, with the exception that patients on the solid tumor arm receive ten milligrams of methotrexate as their standard therapy. This is followed by leucovorin starting 24 hours later to limit systemic toxicity. The only difference in the lymphoma patients are that they're receiving 50 milligrams of cytarabine as free drug twice a week as opposed to methotrexate.

The patients are to undergo a neurologic evaluation prior to the treatment and at the beginning of each two week treatment cycle, plus at each follow-up visit, and there is very detailed documentation of the basis for concluding that neurologic progression has occurred when the investigator makes that ascertainment.

CSF cytology and chemistries are obtained at the start and end of each cycle, and adverse events occurring from 21 days prior to the start of treatment through 21 days after the last dose are accrued to the case report form.

There are two primary analyses planned

for this trial. The first analysis is directed at satisfying the post marketing requirement, and it will compare all patients randomized to DepoCyt versus all patients randomized to the comparator, that is, either methotrexate if you're a solid tumor patient or ara-C if you're a lymphoma patient.

Because this trial is also directed at obtaining approval for solid tumor neoplastic meningitis, the second primary analysis will compare all solid tumor patients randomized to DepoCyt versus all solid tumor patients randomized to methotrexate.

The trial is powered to detect a 50 percent reduction in the hazard function for time to neurologic progression in patients with solid tumor neoplastic meningitis, and the estimated number of events needed to make that ascertainment is 75.

The trial is powered at .8, and because there are two primary analyses, the alpha level has been adjusted, and the alpha will be 0.038.

The trial was set up immediately after the approval was obtained. Investigator selection,

IRB approvals, contracts were completed, and the trial was opened in October of 1999.

However, at that same time, all DepoCyt was recalled from the market. No product was available for clinical trial execution for a period of 17 months. The agency reapproved the introduction of DepoCyt in March of '01, and trial reinitiation began immediately on receipt of that letter.

This included investigator selection, site requalification, IRB reapprovals, contract renegotiation, and because we had been through it all before, we were able to get the first patient entered in a period of just four months. The first patient entered the trial on July 1st, 1991 -- I'm sorry -- 2001.

So here's the original time line as it was planned. Because of the 17 month loss of clinical product available, the whole time line is shifted by 17 months to the right. The first patient was entered on July of '01.

The expectation is that we'll actually

be able to complete this trial in slightly less elapsed time than had originally been planned, approximately 4.1 years versus 4.5 years.

The basis for the product recall was that in October of 1999, some of the lots of DepoCyt that had been manufactured were found to release free cytarabine at a slightly higher rate on stability testing. In careful review of what was going on, it turned out that the raw material supplier had made an unannounced change in the manufacturing process for one of the lipids that are used to make this product that eliminated a small amount of EDTA.

When that was discovered, after a great deal of investigation, EDTA was replaced, and the product went through another review with the agency and was again available in March of 2001.

New assays were introduced to assure the quality of the raw materials, and that has not subsequently been a problem.

The current patient accrual to this study from a total of 37 open sites, there are 16

sites that were open initially in the United States. An additional 19 sites have been opened over the past six months in Europe. Total accrual to date is 57 patients. Of these, 43 are solid tumors. Thirty-two percent of the total accrual is lymphoma, or a total of 14 patients.

Looking at the accrual rate across the whole study, that is, from the time the study was opened to date, it's 2.4 patients per month. The accrual rate over the past six months is approximately 4.7 patients per month, and just as a point of reference, the accrual rate of the prior pivotal study at a time when the product was not on the market as 2.9 patients per month for this rare and orphan indication.

The accrual by site is 38 patients in the United States and Canada, and a total of 19 patients thus far from Europe. The distribution between lymphoma and solid tumor is as shown.

Now, there are some challenges to the completion of this trial. First of all, there are a very limited number of cases per year in the United

States and Europe, and unfortunately only a limited number or a small fraction of those cases are actually available for participation in a clinical trial. Most of these patients have extensive disease elsewhere in their body, and there are a variety of reasons having to do with the disease elsewhere in their body and their systemic treatment why they may not be available for participation in a randomized trial.

The second challenge of course is the problem of randomization reluctance. This drug is a once every two week dosing regimen via an intrathecal injection. That's difficult to do even once every two weeks.

The alternative is twice a week intrathecal injections, and in disclosing this difference in schedule to patients and the available data, it turns out that there's a lot of reluctance on the part of patients to be randomized on this trial.

And of course, there's competition for patients. There are three other clinical trials now

open at the major cancer centers in the United States testing new intrathecal therapies, and we have to compete with those trials for patients.

I'd be pleased to answer any questions.

CHAIRPERSON PRZEPIORKA: Thank you very much. Dr. Hirschfield, do you have comments?

DR. HIRSCHFIELD: I just want to first of all commend Dr. Howell on engaging on a trial that has a clinical benefit endpoint and one which is a symptomatic endpoint, and this is something which has already been discussed in this meeting, but something which we hope will establish a new standard and paradigm for approving oncology drug products.

Some years ago we had a visiting fellow, Dr. Fumitaka Nagamura, and he and I decided to look at some of the issues regarding oncology drug approvals, and we looked at the broad issues of endpoints. We looked at trial designs, and then we began looking at systematically accelerated approval with the understanding that accelerated approval would accelerate something or another, hence the name, and the understanding was that the

acceleration would be, as Dr. Blayney and Dr. Pazdur and many others have pointed out, the availability to a broad population of patients of the product during the course of its development scheme with, and again, this is the important point, I think, of this discussion, with a well developed schema in place.

And as Dr. Howell pointed out, and as we noted in our review of the applications that had come for accelerated approval, there were some which had a schema in place, and what seemed to be the intent of the program was met in that a short period after the accelerated approval then could come the full approval.

And we also noted at the time and has been pointed out in this meeting by Dr. Dagher and others that there was a selection of the submissions which were single arm studies based on response rate and some on others.

But what we also noted was that if one compares accelerated approval with standard

approvals and asks the question how long has this product been in clinical development, the answers had quite a wide range; and that if the intent was to accelerate the clinical development program somehow, that there was some questions that could be raised.

And one of the, again, themes that has emerged from the discussions over the last two days is that accelerated approval was not intended to be an alternative for a product which would not fulfilling the criteria which has been established for full approval coming through an alternative mechanism.

And as Dr. Howell pointed out, it was 11 years from the filing of the IND to the submission of the NDA, and the approval of the NDA in this case was approved on a relatively modest number of patients, and that's just for the public record because it has been discussed in front of this committee.

There were various scenarios that the data took, and if one followed the protocol

initially, on protocol criteria the response rates were two versus zero in one of the four scenarios.

In another of the scenarios the response rate was three versus one.

In the third scenario, which Dr. Howell noted, which was the one that was ultimately used to form the basis for the accelerated approval, it was seven to one.

But in the fourth scenario, and all of these scenarios varied according to how much of the protocol violations one was willing to relax. So the first scenario, two versus zero, was if one followed the protocol, and all other scenarios was a question of relaxing criteria one way or another.

And then the last criteria, it was 11 to seven, which were no differences. So because there was a suggestion that there was potential utility in this particular product, the committee recommended that the product receive accelerated approval, which we endorsed.

But I would submit we still don't know what the utility is for this particular product, and

it's approximately 16 years since the filing of the first IND.

So in examining the issues surrounding accelerated approval, I would ask the committee to also consider addressing specifically not just the development plan with regard to the link between the accelerated approval and the standard approval or full approval, but also to offer any comments or thoughts on accelerated approval as an alternative mechanism when standard approval ought to perhaps be pursued.

CHAIRPERSON PRZEPIORKA: Okay. Dr. Reaman, do you have comments?

DR. REAMAN: I have some questions. In the initial study, was the schedule of ara-C the same as the schedule of cytarabine that's used in the post approval study for lymphomatous meningitis?

DR. HOWELL: Yes, the schedule for the comparator drug, whether it was methotrexate or cytarabine, is the standard schedule used in the clinic, and it has been constant throughout all of the clinical trials.

DR. REAMAN: And I guess I would question the praise of Dr. Hirschfield on designing a study with a clinical benefit endpoint because I'm not exactly sure what the clinical benefit endpoint is, time to neurological progression.

In looking at your presentation, there's a detailed assessment of what neurological progression is at the time of progression, but the eligibility criteria include positive CSF cytology or a positive CT or MRI scan, or both, and how does one make that leap from a variable eligibility criteria to a defined, well documented investigation of progression?

DR. HOWELL: The nature of this disease is that the most problematic result of the meningeal component of the disease is a fairly rapid degradation in neurologic function. These patients often present with cranial neuropathies, diplopia, speech --

DR. REAMAN: Isn't it very much dependent on where? Sot here's tremendous variability, I would imagine, in what would be

called a neurological progression.

DR. HOWELL: Yes, there is, and that is perhaps the single greatest challenge in trying to design these clinical trials. A great deal of effort went into the attempt to define a standard set of criteria as to what would constitute progression of neurological symptoms and signs.

In fact, we made an effort to develop a consensus document on this among the neural oncology world. However, after major efforts, it turned out because the number of clinical parameters that are involved and the fact that the these patients often have the symptomatology related to their systemic disease which overlaps with the symptomatology and signs generated by the neurologic component of their disease, we were unsuccessful, and when I say "we," I'm speaking broadly of the community of physicians who are interested in these trials in coming up with such an algorithm driven or even consensus endpoint.

So in the end we have to rely on the judgment of the investigator as to whether neurologic progression in any given particular

patient has occurred.

However, what we have asked is in this trial when the investigator makes that ascertainment, concludes that neurologic progression has occurred, that we document the basis for that decision in great detail so that we have a clear understanding of what that patient was felt to have accomplished, why that patient was felt to have undergone neurologic progression.

Does that answer your question?

DR. REAMAN: Sort of, yes. Can I ask the background for the use of methotrexate in the solid tumor neoplastic meningitis patients rather than cytarabine?

DR. HOWELL: Well, cytarabine is not known to have any activity in patients with solid tumor neoplastic meningitis when given as a free drug. The half-life in the CSF is very short. So methotrexate in this country and in Europe is the standard therapy used for most patients with solid tumor neoplastic meningitis.

There is only one other drug that's

available for intrathecal administration, and that's thiotepa. Thiotepa is occasionally used as well.

In patients with lymphomatous meningitis, occasionally all three drugs are used, but the vast majority of patients with solid tumor neoplastic meningitis receive only methotrexate or thiotepa.

Let me point out that the whole rationale behind this formulation was that when you maintain cytarabine in the environment of any tumor cell for a period of as long as two to three weeks, then the vast majority of all kinds of cancer will respond with a substantial log tumor burden reduction.

DR. REAMAN: And I want to go back to your original trial and the timing of the completion of that trial and when the lots of DepoCyt were recalled because of excessive ara-C activity. Is there a chance that some of that drug was actually utilized in the initial trial to possibly explain the difference in response rates?

DR. HOWELL: My understanding is that

the answer to that question is no, that the problem arose in the manufacturing of batches in anticipation of approval of the drug in commercialization.

DR. REAMAN: Thank you.

CHAIRPERSON PRZEPIORKA: Dr. Martino.

DR. MARTINO: A question as to the two presentations of patients with meningeal carcinomatosis. There is a group that is allowed to have cytology positivity, and I'm assuming that those are patients who actually have symptoms because that would be the clue that you would want to actually assess their CSF.

You also have another group where it is actually an MRI or some radiological technique that shows you meningeal involvement. Now, in my personal experience that patient population does not always have symptoms. Sometimes it actually is an X-ray diagnosis, and I personally view those as really two clinical behaviors, one which can be remarkably indolent and have practically no symptoms and the ones with CSF positivity which invariably

have symptoms because it is the symptoms that have been the reason why you did the spinal tap.

Do you view those two as different or is that just my own peculiarity of understanding?

And if you agree with me that they are biologically different, are they somehow stratified for in your randomizations?

DR. HOWELL: I disagree with you. The vast majority of patients are brought to attention with respect to the suspicion for neoplastic meningitis by virtue of the fact that they present with a symptom or a sign in the context of having disease elsewhere in their body that could have metastasized to the CSF of the meninges.

We do two things when a patient presents in that situation. One alternative is to do a lumbar puncture and confirm the diagnosis based on cytology. However, more and more over the past several years, the response is to get an MRI or a CT. It's easier. It doesn't cost you the patient time and pain of doing a lumbar puncture, and the technology and refinements for making the diagnosis

of meningeal involvement, particularly on MRI, have now dramatically improved.

So approximately 30 percent of all cases are currently diagnosed on the basis of an MRI or CT rather than on the basis of a lumbar puncture. But the vast majority of both of those came to attention because they developed a sign or a symptom in the context of a disease that could metastasize. There is a --

DR. MARTINO: And then I think that's actually my question, is: are these predominantly or exclusively patients who have some symptoms?

Because it's my experience that sometimes you get an MRI because you're thinking that there might be metastatic disease, and it is at that point that you see that there is meningeal involvement, but you don't really have a patient who has much in the way of symptoms.

Do you understand what I'm getting at?

DR. HOWELL: The last sentence that I was about to complete is that there is a small subpopulation of patients who are incidentally

diagnosed with meningeal involvement because they had an MRI or CT scan done for concern about a brain met. or something of that nature.

That represents a very small fraction of the patients in these clinical trials.

DR. MARTINO: Would they be included in your studies?

DR. HOWELL: Yes, they could potentially be included in the study. That is correct.

DR. MARTINO: Do you have a sense of how many those might be in the studies related to --

DR. HOWELL: I apologize. I don't have a hard number for you, but I am -- my estimate is that that would be something less than one or two percent of all the patients in these trials.

DR. MARTINO: Thank you.

CHAIRPERSON PRZEPIORKA: Dr. Howell, I just want to point out that as a member of the medical community, we don't want the public to think that we're using MRIs or CTs solely as the means to diagnose CNS disease or meningeal involvement. LP spinal tap is still the gold standard, and the place

where MRI alone would come into play for diagnosis is those with a spinal tap that is negative, especially solid tumors which sometimes don't float freely in the spinal fluid.

But clearly everybody with any sort of CNS problem should probably get a spinal tap, and we would probably never lower that standard for our patients.

Dr. Reaman, did you have more comments?

DR. REAMAN: I was going to address that issue, but also with respect to standard of care for these patients, I would think that external beam radiotherapy would also play a role in the management of lymphomatous meningitis.

And was that considered in patients entered on this trial or on the previous trial?

DR. HOWELL: No, it was not considered. Total cranial spinal radiation would be a way of managing diffuse involvement of these neuraxis by lymphoma, and there are substantial complications from that procedure.

All patients entered in this trial, if

they have visible focal, lumpy-bumpy disease, in other words, if you can see nodules, the recommendation for both solid tumor and lymphomatous patients is that they receive focal cranial radiation or focal cranial radiation of the cauda equina, if that's indicated, but not total cranial spinal radiation.

And I don't believe that the committee broadly would consider total cranial spinal radiation for lymphomatous meningitis as the standard of care.

DR. REAMAN: I don't think I mentioned the total cranial spinal. We have done that in the past in children with leukemic meningitis.

My question really related to focal radiotherapy in the situation of lumpy-bumpy disease and how is that --

DR. HOWELL: You're absolutely right. The standard of care for focal disease is that radiotherapy should be used, and that is actually specified in all of these clinical trials, both the previous ones and the current trial. If the patient has evidence of focal disease, then that patient

is to receive radiation therapy prior to receiving intrathecal therapy.

DR. REAMAN: And then how does that relate to the determination of therapeutic effect and time to neurologic progression?

DR. HOWELL: The patient completes radiation therapy prior to coming on study, and so a new evaluation is done of the eligibility criteria, and that patient is reassessed prior to study entry.

So the radiation therapy is not given as part of the study. If the patient needs radiation therapy, they are to receive that prior to randomization.

DR. REAMAN: Is there a stratification then by eligibility for those patients who are pretreated with radiation versus those who were not?

DR. HOWELL: No, sir, there is not. We have in the past looked at association between whether the patient received either prior or concurrent radiation therapy because it's conceivable the patient on study may subsequently

develop focal disease, and there appears to be no association.

But I would caution that it's a small set of patients, and such associations would normally require a much larger number of patients to be evaluable.

CHAIRPERSON PRZEPIORKA: I think Dr. Cheson has some more comments along this line.

DR. CHESON: Several. I agree that the standard for patients who have solid parenchymal disease includes radiation, whereas for those who have meningeal involvement, intrathecal therapy is generally used, but that raises several other issues.

I guess we can do these one at a time so that I remember what they are. One, is there a difference or was there a difference or should there be a difference in how these agents are instilled into the spinal fluid?

In other words, lumbar puncture versus a reservoir technique.

DR. HOWELL: There are some differences

in the pharmacokinetic behavior.

DR. CHESON: Right.

DR. HOWELL: One of the challenges we faced in developing this product in the first place is that there are two real problems with the pharmacology of intrathecal therapy. One is that the three drugs that were available, methotrexate, ara-C, and thiotepa, all have relatively short half-lives in the CSF. So they're very rapidly cleared.

And the second is that if you inject them in either the lumbar sac or in a lateral ventricle, they don't spread out very well throughout the neuraxis because, in particular, cytarabine is cleared so rapidly that it never gets a chance to equilibrate throughout the CSF.

One of the goals of developing this particulate encapsulated material is the idea that the particles would spread out much more effectively than the free drug because their residence time in the CSF is very long and they have an opportunity to flow with CSF flow.

And in fact, in studies of the particle

pharmacokinetics, that is, when you inject this material in the lateral ventricle and sample from the lumbar sac, the equilibration occurs in 12 to 24 hours. So the number of particles at both ends of the neuraxis, the concentration of particles at both ends of the neuraxis is equivalent by 12 to 24 hours, and thereafter, in the limited number of cases in which we were able to leave a needle in a patient and sample repeatedly over the next two weeks, we saw absolutely identical kinetics in the particle clearance.

If you inject in the lumbar sac and look at drug concentrations and particle counts in the lateral ventricle, what you find is that they are about half a log to a log lower than they are in the lumbar sac. So the distribution from the lumbar sac to the lateral ventricle is not quite as good as distribution from the lateral ventricle to the lumber sac, but it's pretty good.

And the concentrations attained are still several orders of magnitude higher than concentrations which kill three to four logs of

tumor cells in the NCI 60 cell panel screen.

So we're reasonably confident that we're obtaining good pharmacokinetics at both ends.

In the analysis of response rates and time to neurologic progression, there's absolutely no difference as a function of route of drug administration, and the agency looked at this at the time of initial approval, and also looked at it in detail by the CPMP during the European approval process, and there was absolutely no evidence of a difference in response rate or clinical outcome as an function of route of administration.

DR. CHESON: Thank you.

Next, in those patients whose diagnosis was made by an imaging study, when you stick the needle in there to give them one medication or another, in general we take some out and send it off for cytologies. In what proportion of those patients that were pure imaging diagnosis did the cytology confirm the diagnosis of meningeal involvement?

DR. HOWELL: I don't have that

information because in all the prior trials, we did not use imaging as an eligibility criterion. Only in the current trial do we use that as an eligibility question.

So that will be one of the analyses that will be done with this study, but I do not have any data on that point at the present time.

DR. CHESON: And my final point for now. a lot of these patients develop a central nervous system disease alone, but others develop it in concert with the development of progressive systemic disease. Are the latter group excluded?

And if they are not, how do you account for the potential effects of systemic therapy on the central nervous system control?

DR. HOWELL: They are not excluded from this trial. If we had excluded patients who needed systemic therapy concurrently, we would never be able to complete any clinical trial because the vast majority of these patients require systemic therapy.

Systemic drugs don't cross the blood-brain barrier in meninges and then the CSF is behind

the blood-brain barrier. So as you know, the standard of approach of getting drugs from the systemic circuit into the CSF has been a high dose strategy.

High dose methotrexate given intravenously, high dose ara-C given intravenously do, in fact, generate reasonable levels of drug. However, it's very often difficult to integrate a high dose IV strategy into the standard chemotherapy regimen that that patient is already receiving for their systemic lymphoma.

So if the patient is on rituximab and CHOP regimen, trying to factor high dose methotrexate or high dose ara-C regimen on top of that for the meningeal component of disease gets very complex.

So the bottom line is that we have a difficult challenge because we are focusing on the meningeal component of disease, and we're asking can we improve that component of the disease in the face of patients who are also having symptoms and signs and problems from the systemic chemotherapy that

they're getting for the rest of their disease.

That's the fundamental challenge in the disease. We have not been able to figure out a way around that. The obvious way to do it would be isolated meningeal relapse when there's no other evidence of disease anywhere else, and I wish I had enough patients to do that trial.

CHAIRPERSON PRZEPIORKA: Dr. Fleming.

DR. FLEMING: Just following up on some earlier discussion, it wasn't clear to me, since I don't have a definition exactly of the neurological progression criteria. In what fraction of these patients that would have neurologic progression would there be progression of symptoms, would it be symptomatic?

DR. HOWELL: These patients are going to have symptoms, in part, from the neurologic component of the disease. They're going to have symptoms from the systemic component of the disease. They're going to have symptoms from the meningeal treatment and the systemic treatment.

That's part of the complexity of trying

to determine when neurologic progression has occurred. For example, is increasing headache evidence of neurologic deterioration?

Well, in one patient it might be, if that patient had a clear history of having headache associated with the onset of the meningeal component of the disease.

On the other hand, another patient who has a long history of migraine headaches and headache reactions to systemic therapy, headache may be totally irrelevant.

And so the answer to the question is no. No one symptom, no one sign definitely constitutes progression of neurologic disease. It is the constellation of symptoms and signs and how they change relative to everything else you know about that patient, the complexity of that patient's clinical situation that you have to make that judgment.

And it is a difficult judgment to make, and not all neural oncologists agree on how to make that judgment, which is the challenge that we faced

and the reason that we have relied upon the individual investigator's assessment to determine the endpoint.

DR. FLEMING: Well, do you have a slide that formulates the exact criteria for neurologic progression?

DR. HOWELL: There are no exact criteria for neurologic progression. There is no algorithm.

DR. FLEMING: And so remind me then. In the protocol, what algorithm do you follow in defining whether the primary endpoint has occurred?

DR. HOWELL: There is no algorithm. We rely on the global assessment of the investigator to determine whether neurologic progression has occurred in that particular patient, and then we ask that investigator to document in great detail the basis for that decision.

DR. FLEMING: And so it's entirely possible that patients could have worsening or improvement of symptoms that wouldn't, in fact, translate into a definition of neurologic progression, worsening of symptoms, and conversely,

a patient could, in fact, be characterized as having neurologic progression without any tangible change in symptoms?

DR. HOWELL: In symptoms, yes, but the physician may pick up a sign. The patient may not be aware of a particular neurologic sign that the physician on his neurologic examination picks up.

DR. FLEMING: So you have as a secondary endpoint improvement in neurologic symptoms, quality of life, survival, et cetera, but those are all secondary endpoints. It's possible that we could see a statistically significant difference in time to neurologic progression without being able to conclude from that that there, in fact, is a difference between the two treatment arms in actual symptoms the patients have that are related to neurologic phenomena?

DR. HOWELL: That is technically correct. One of the most important measures of how well you're doing with these patients is if the patient presents to you with a complex of symptoms that are really bothering the patient, loss of

bladder and bowel control being an example, and you can improve that. Then you've really done something for the patient.

And we're trying to capture that as a secondary endpoint to determine what fraction of the patients who present with a problematic symptom, things actually get better.

The challenge, of course, is that because neurologic damage does not heal very well, the most neurologic deficits that the patient presents with at the time of study randomization are fixed deficits. A few of them will improve, but usually not very much.

The goal is really to prevent things from getting worse, from delaying this degradation of neurologic function going forward rather than fixing the things that are already there.

DR. FLEMING: But if I understand what you're saying, because of the multi-dimensionality of the ways in which neurologic symptoms could occur, and because of the frequency of occurrence of symptoms that may not be specifically driven by

neurological processes, the study is likely to be under powered to be able to statistically show differences in these kinds of direct symptoms related to this neurological process?

DR. HOWELL: I don't know whether it will be under powered or not. It is not powered on the basis of the frequency of improvement of symptoms. It's powered on the basis of time to neurologic progression.

DR. FLEMING: One other question, and that is as we've heard earlier today from the FDA, when you look at the data upon which the accelerated approval is based, there are some encouraging trends in the response, although as I understand, if you characterize the response in several different ways, it becomes a little less clear how strong the signal is.

So I think in your words, it was you still don't know how likely it is that this product has utility. And obviously hopefully this study, in fact, establishes clear evidence of benefit.

In the setting in which this study would

establish lack of benefit, what is the strategy? Is there a strategy for other studies, or is that something as yet that hasn't been thought through?

DR. HOWELL: Is that a question to me or to the agency?

Perhaps I can introduce the answer from our vantage point. You recall that the rationale behind developing this product in the beginning was that we have a rare but very devastating and difficult medical problem to treat. We don't like doing lumbar punctures or OMI reservoir penetrations twice a week.

The hope was to develop a product which would be easier on the patient by being able to deliver it once every two weeks. The whole rationale behind developing this product was the fact that we could have a kinder and gentler schedule of drug administration.

And in our initial discussions with everybody involved in the development program, it was the advantage of the schedule of administration which was perceived to be the major benefit of this

drug.

DR. HIRSCHFIELD: I'd like to address that, too, and I also want to thank Dr. Przepiorka and Drs. Cheson and Reaman for pointing out the difficulties and the nature of using radiologic evidence in this condition and why we would not accept radiologic evidence as either eligibility criteria or as an endpoint.

And I would like to answer Dr. Fleming's question by just discussing a little more of the history of the development of this product and how we got to this point, and that would also address Dr. Reaman's question of why would we want to use time to neurologic progression.

The initial DNA for this product was submitted prior to the accelerated approval NDA, and it was discussed publicly in front of this committee, and the committee voted at the time seven to three that the clinical studies were not adequate and well controlled and voted ten to nothing -- that's zero -- that the data did not represent substantial evidence of efficacy.

The sponsor maintained that the endpoints that were submitted and analyzed and discussed were perhaps not the appropriate endpoints, and they felt that they had data that supported time to neurologic progression.

Because there were no predefined criteria and because we had limited and incomplete information, we were unable to confirm that assertion. So when the second submission came in and we looked at the lymphomatous meningitis circumstance, there was this difference in response rate, depending, again, on how one relaxed the protocol violation criteria. There were no differences in survival between the two study arms, but it was a woefully under powered study with 16 and 17 patients, respectively.

But perceiving that we didn't see a signal that survival might be impacted, we were willing to explore with the sponsor this issue of time to neurologic progression.

Philosophically and globally we were interested, and Dr. Temple has commented as well as

Dr. Pazdur, on our interest in looking at a symptom benefit, quality of life type endpoint for product approval for cancer patients, particularly if the possibility of prolonging life didn't seem to be a likely outcome.

So we work with the sponsor to evolve strategy in, in essence, uncharted territory, and in this particular case, we're doing an experiment in that we, from the way this protocol was developed, would act as a type of neutral observer or judge in the case, providing that thorough, complete, and adequate documentation is given to us so that one can make this type of assessment.

Subsequent studies without in any way, I believe, revealing any proprietary information, but in further reflection on a strategy of how to approach this problem for other types of agents which might be addressing this issue, we are now recommending a strategy of having, during the course of the study, a neutral observer at each site, a neurologist who would examine the patients without awareness of what treatment they were assigned to

and without awareness of what the primary physician's assess might be, but just to make an unblinded, systematic assessment.

And we would hope through such a strategy that we could advance the field and be able to allow products on the market with a claim that it can be a benefit because this was the first one in this exploration.

And correct me if I'm mistaken, Dr. Howell, but the protocol that will involve DepoCyt does not have that feature, and therefore, we are assuming the burden.

DR. HOWELL: Dr. Hirschfield is correct. It does not have that feature and for an excellent medical reason. If we had a blinded neurologist evaluating these patients, how long if that neurologist was doing his job correctly would it take for the neurologist to discover which arm of the trial the patient was on when one arm is twice a week dosing and the other arm is once every two week dosing and when there are reasonable symptoms and signs associated with the dosing itself?

Defending that blind in front of these gentlemen I surmise would be impossible, and therefore, although it was discussed with the agency and discussed with experts in the field, the consensus was that there was no real way to involve a truly blinded, independent evaluator in this assessment.

So I think Dr. Hirschfield is correct. This is a bit of an experiment, and to be honest, we don't know whether this endpoint of time to neurologic progression is going to be a robust and solid endpoint on which to demonstrate the clinical benefit of this product.

DR. HIRSCHFIELD: I didn't answer the last part of Dr. Fleming's question. What if the study is uninformative?

We certainly hope that every study by intent will be informative. Otherwise it would be unethical. But if we find that we cannot tell the difference in treatment arms, I believe that the committee would be revising this application as soon as those data became available, which would be, by

my rough calculation approximately somewhere between 18 to 20 years after the IND was filed.

CHAIRPERSON PRZEPIORKA: Dr. Hirschfield, on the basis of what we've heard today, I think we already have some concerns about the protocol design with regard to the eligibility being very heterogeneous with regard to prognosis, with regard to stratification not based on prior radiotherapy, with regard to the lack of an objective outcome.

And I could probably predict that no matter which decade this comes back to the committee, the committee is going to say why did the FDA allow this protocol to go on.

DR. HIRSCHFIELD: That's a fair question, and sometimes I think that question could be posed for many, many of the studies which are executed in the field of oncology.

At the time, it was our best attempt in consultation with our consultants as to how to proceed, and we're all learning with time, and one of the reasons to bring this discussion before this

committee is that before we reach that point in some time in the future, that we would have to revisit all of you collectively.

If there's a chance for adaptations or other changes in the protocol, I think now would be the most appropriate time because the enrollment is still at a relatively early stage.

CHAIRPERSON PRZEPIORKA: Dr. Redman.

DR. REDMAN: Just not for the committee, but for myself as a practicing solid tumor oncologist, just to respond to some, there is no gold standard that I'm aware of other than did the patient deteriorate, and so I accept that as an endpoint as a practicing oncologist.

I don't think there's too many oncologists that practice that see this disease in solid tumor patients that cannot determine when the patient is no longer responding to therapy in that regard.

We may wish that they continue responding. That's another problem, but as a clinical investigator.

We do treat patients with negative CSF. We've done the CSF, but in the appropriate study, neurological deterioration and appropriate MRI, we will accept or I will accept negative CSF. I'm assuming most will.

A survival endpoint in meningeal carcinomatosis is really irrelevant because the patients ultimately, again, in solid tumor patients die of their systemic disease, though some do die of a neurological disease.

In this subgroup, in this very much orphan, you're going to end up with five patients in seven subgroups. I think what the sponsor has done I find to be appropriate.

CHAIRPERSON PRZEPIORKA: Dr. Carpenter.

DR. CARPENTER: I would echo Dr. Redman's comments. This is a complex situation, and the vagaries of presentation are nearly infinite, the variation in the individual presentation.

One of the things that leads one to suspect meningeal involvement with a solid tumor is the lack of a coherent pattern to the neurological

loss. I think the idea of having some algorithm or some standard way to do this just doesn't fit the clinical situation in adults, and it probably is possible, at least in most instances, to show some time when there's clear neurological worsening, though that's not going to follow a distinct pattern anymore than the presentation of the disease is.

I think they've made every effort to do the best you can at this point in defining this situation, and while it's an equation that has an incredible number of variables, if you're able, it's not going to be possible to standardize all of those things and get any number of people into a study. I think they're doing the best they can in this situation, which is uncommon, and which is very hard to study.

CHAIRPERSON PRZEPIORKA: Dr. Reaman.

DR. REAMAN: I think it's been answered.

CHAIRPERSON PRZEPIORKA: Okay. Dr. Lippman.

DR. LIPPMAN: You know, I understand that this is a difficult disease. The endpoints are

hard to put into an algorithm, but I'd like to sort of follow up on Dr. Fleming's point.

If we're using time to progression and things like headache, could it be time to progression from the meningeal disease or other issues?

I guess the concern I have is that the ascertainment, the control arm is seen much more frequently than the actual treatment arm. So the time to progression or the concern about headaches could really affect statistical interpretation of this study.

I don't know, Dr. Fleming, if you have thoughts on that. Even with the fact that we don't have a firm endpoint, the fact that we don't have a firm endpoint makes me more concerned about the interpretation given the more frequent assessments.

CHAIRPERSON PRZEPIORKA: Dr. Martino.

DR. MARTINO: I think that is a key point here. Those of us that practice oncology appreciate the complexity of all of this, and there is no way to make this easy, but I completely agree

with those that have said that as a clinician you generally know when your patient is doing worse with meningeal disease because it rarely is a subtle event. It usually is fairly obvious that they're going downhill, and these patients invariably go downhill.

The only variable is the rate at which this happens, but I share, you know, the issue that Dr. Lippman brought up, which is that if you're seeing patients more frequently, you have the opportunity to assess whether they're getting worse much more quickly. And so that biases this whole observation against the standard arm.

There's one other point I'd like to make, and that is for me this drug does not have to demonstrate that it actually, in fact, is better than anything else. Okay? For me it purely has to demonstrate that it is not worse than anything else.

The very fact that I can give it less often is an exceptional advantage. It is not a trivial thing in this case. It's an important thing.

So the standard to which we hold this for me is key here.

DR. HOWELL: Madame Chairman, can I respond to the two points made?

CHAIRPERSON PRZEPIORKA: Yes.

DR. HOWELL: On the issue of frequency of evaluation, it is a fundamental problem because of the difference in schedule in the two arms. We didn't have a choice of how to deal with that. So it's not something that we can engineer around in the clinical trial design.

To the extent that we have been able to accommodate that though, the patient is evaluated neurologically only once every two weeks at the end of the cycle, and that is the data that is captured in the case report form. So that is the data that will be used in the analysis, not any information that's obtained at an intervening dosing point in that two week cycle.

Now, is there still some bias there? Yes, because you know, if I see the patient on a Thursday and I'm worrying about it and I don't get

to record something until the following Thursday, I'm going to be even firmer in my belief the following Thursday.

We've done the best we can in dealing with the challenge of having different schedules on the two arms. It remains a problem, but I think by capturing only the evaluation at the end of each cycle we will have at least partially addressed that issue.

CHAIRPERSON PRZEPIORKA: Ms. Mayer.

MS. MAYER: Absent from the discussion of criteria used to evaluate this agent, it seems to me, are two kinds of input, one from patients themselves who could self-report their own quality of life, their own subjective experience around neurological variables.

On the one hand, I realize that there are problems with standardizing this, but on the other hand, we're talking about physician evaluation. To do that independent of what patients are saying themselves about their experience is to sort of dilute a direct route to getting information

from patients.

And the other is the input of perhaps other professionals who might be useful. I'm thinking specifically of neuropsychological evaluation that could be done throughout, perhaps prior to treatment, throughout treatment. That might yield more objective information that could, in fact, be quantified.

DR. HOWELL: Can I respond to that?

We did an experiment, madame. We actually collected all of that data in the first two randomized controlled trials and both our analysis and the agency's analysis, I think, were concordant in discovering that they were totally useless.

There is a challenge here, and that is that these patients and the fact CNS questionnaire was the quality of life tool used in addition to the Karnofsky Performance Status and a variety of other types of quality of life evaluations.

The problem is that these patients are often so neurologically impaired that they cannot report easily using any of the available, the

validated tools in the field, and our experience was that there was so much missing data, despite a real attempt to collect that data, that we could not make a useful evaluation of it.

So in the current post marketing trial that effort, recognizing that we had failed in the experiment that was conducted in the first two randomized trials, that effort has been dropped.

It's not for any lack of interest or lack of paying attention to that component of patient well-being. It simply is an issue of do we have a tool that has a dynamic range and a sensitivity and specificity adequate to the job of collecting that kind of information.

MS. MAYER: I understand. Have you looked into having reports from family members?

DR. HOWELL: No, ma'am, we did not in the post marketing trial.

MS. MAYER: I think that anybody who does end of life care and looks into what methods are useful in late stage disease knows that there are generally care givers in the environment who can

provide very useful feedback as to how the patient is doing.

DR. HOWELL: Your question raises an important component of this disease or an important issue around this disease, and that is, as Dr. Hirschfield has pointed out, the physician sponsored IND was filed in 1989. Part of the reason that we're facing some of these challenges is that a lot of things have changed since 1989.

The implication of filing an IND in 1989 was that we didn't get things done very quickly. That's not correct. There was not a single pharmaceutical company that wanted to touch this product. It was developed under a physician sponsored IND all the way through Phase 1 trials.

We had to go out and set up all of the support, all of the mechanisms for conducting the development of this drug. So although the IND was filed a long time ago, the drug actually has progressed through this orphan and rare disease at a reasonably good clip, but you made an excellent point that a lot of the things that we pay attention

to now and the information we would like to capture now is somewhat more refined and different from what we started with in 1989.

MS. MAYER: Just one more follow-up. As far as patients' ability to be evaluated because of losing neurologic functioning, my husband, who is a neuropsychologist, does quantitative evaluations of patients in coma. It can be done. The scales are there, and I think more attempt needs to be made to gather information from other sources to measure something which is so difficult to quantify.

CHAIRPERSON PRZEPIORKA: Dr. Blayney.

DR. BLAYNEY: Steve, when somebody dies and does not have neurologic progression, is that counted as a response?

DR. HOWELL: No, it's counted as neurologic progression. It's either neurologic progression or death.

DR. BLAYNEY: Or death?

DR. HOWELL: So death is counted as a neurologic progression.

DR. BLAYNEY: You know, this looks like

a non-inferiority trial to me, and I'm surprised. Is that how you view this as powered?

DR. HOWELL: No. It's powered for superiority endpoint, and that is a 50 percent reduction in hazard rate. The non-inferiority trial would have required an even larger number of events.

DR. BLAYNEY: So whenever this comes back, this is, I guess, the record should show that this is not a non-inferiority trial; that this is designed as a superiority trial, and you know, the fall-back position is not that, gee, this is not worse. The primary endpoint is, yeah, this is better.

DR. HIRSCHFIELD: Doctor --

CHAIRPERSON PRZEPIORKA: I have just one quick question. We're talking a lot about trial design problems in this particular patient group, and of course, Dr. Pazdur introduced the concept of maybe the Phase 4 commitment could be in a slightly different patient population. There are far more patients receiving prophylaxis intrathecally.

Have you considered a randomized trial

in that group?

DR. HOWELL: Yes, ma'am, we certainly have. We would love to do a prophylactic clinical trial. We have had extensive discussions with the old pediatric oncology group and now the children's oncology group. We've had extensive discussions with the AIDS related malignancy group. We've had discussions with some of the members sitting around the table about how to execute those trials with the assistance of the NCI. They were cooperative groups.

Unfortunately, not a single team has stepped forward with a willingness to undertake that trial for good reasons. A lot of the therapy for the systemic components of those diseases has evolved very quickly. There are important and urgent questions that need to be asked in randomized clinical trials about appropriate systemic therapy for patients with lymphoma, and many of the groups have seen the issue of prophylaxis as being a somewhat less important issue to be addressed in randomized clinical trials.

But this has been a bit of a crusade for me, and I would certainly welcome the opportunity do such a trial.

CHAIRPERSON PRZEPIORKA: Dr. Lippman.

DR. LIPPMAN: I was just wondering on your design. You talk about a 50 percent reduction in the time to neurologic progress. What did you assume for the control arm in the time to progression?

DR. HOWELL: The control arm in the prior solid tumor randomized controlled trial, a median time to progression was 38 days.

So what we're looking for is a 50 percent improvement in time to neurologic progression.

DR. LIPPMAN: So just if I could ask Dr. Fleming this, and I do feel you've done everything you can within this trial to try to control for the more frequent potential evaluation, but obviously as you said, if someone comes in for their drug and they have a headache the first week after, you're not going to wait three weeks for the formal

evaluation.

So there is that potential. If we have this three week difference, let's just hypothetically say, how will that affect the interpretations of the results, given that the control we're figuring 38 days to progression?

DR. FLEMING: Let me just make sure I understand. So you're saying if the control is 38 days and you have in the intervention a three week improvement? Is that what you -- could you restate the question?

DR. LIPPMAN: So if you assume in the control it's 38 days and we assume that the control patients are seen more frequently per the schedule, and even though the formal evaluation is scheduled at one month, still if someone comes in one week into that with a bad headache, I assume as you point out you can't wait three weeks to do the formal neurologic evaluation.

So the time to progression endpoint could be earlier by a few weeks. How do you sense that will affect the interpretation of the results

if that happens?

DR. FLEMING: It's a valid point. It's hard for me to answer that, to get a good sense of the extent to the bias, and I intend to give an answer, but, Bob, it looks like you have something you want to say.

DR. TEMPLE: Well, a complete but perhaps over conservative solution is just to attribute the event to the next scheduled meeting. So if it's two weeks versus every week and you see something at one week in the more frequently observed group, you just attribute it to the two weeks.

I mean, that might be overdoing it, but it certainly more than accounts for it.

DR. HOWELL: I would like --

DR. FLEMING: Of course, we're assuming that, that everybody would be assessed at exactly the correct periodic time point. My own sense about this is the best way to handle it is to do the best we can, to have a fairly comparable time frame for making assessments between the two arms.

Other biases exist here, and that is my understanding is we aren't able to correct for the unblinding aspect, and there is judgment implemented here. So that, too, creates some considerable bias when you're using clinical judgment about whether an event has occurred and you're unblinded as to the intervention someone is receiving.

Let me just comment on a couple of related points that have just been mentioned. You had said that this study is powering for a 50 percent improvement. In fact, I understood that it's powering for a 50 percent reduction in rate.

So that's actually powering for a doubling, not a 50 percent, but a 100 percent improvement in time to progression is what you're actually powering for.

DR. HOWELL: No, I apologize. I may have made a mistake in that.

DR. FLEMING: Okay.

DR. HOWELL: It's powered for a 50 percent improvement in time to neurologic progression.

DR. FLEMING: If it is, then you're under powered in terms of sample size. If you're targeting a 50 percent reduction in rate, which is what I thought the protocol, your materials indicated, then you're properly powered.

DR. HOWELL: That's probably an error on my part, and I apologize for that.

DR. FLEMING: Okay. I have some related comments, but I'm going to quickly redo some calculations here, and if you could come back to me in a couple of minutes, that would be great.

CHAIRPERSON PRZEPIORKA: Dr. Reaman, can you take a moment here to address the questions?

DR. REAMAN: Well, I think the sponsor has been vigilant in the design and conduct of a post approval trial. I think there was early difficulty because of problems with the product, and that has certainly delayed the eventual time line.

I think there have been some accrual difficulties in the past. That does appear to be improved by the addition of a number of European studies or centers.

I think the fact that the study has been extended to European participation will also help in that the agent is not approved for use in Europe. So that the issue related to inability to enter patients on trial because of the availability of this agent shouldn't be as much of a problem.

I'm a little bit concerned, however, about the claim that there's randomization reluctance in the solid tumor patients if methotrexate is the drug that has been historically demonstrated to be beneficial. Whether or not someone gets a single intrathecal injection or multiple intrathecal injections over a period of time, if they're not getting an agent which has demonstrated efficacy, then it's hard for me to imagine that just how many times they get that agent is really what they would be concerned about.

I have some concerns about the design of the study, as they've obviously been discussed, and it's hard for me to really grapple with the issue of thorough, complete, and adequate documentation of response in a setting where there are no defined

objective criteria for the endpoint that is being used.

And I would certainly also agree with Ms. Mayer that I think we've lost an opportunity or the sponsor has lost an opportunity to use patient and/or family caretaker reporting in assessing symptom improvement in quality of life, and that's certainly something that should be and could be perhaps in the future considered.

CHAIRPERSON PRZEPIORKA: Dr. Martino.

DR. MARTINO: I guess I need to be polite right now. This is not a diagnosis where it is difficult to know if your patient is getting worse, and I'm sensing that some of you have this concern that a doctor can't tell that a patient -- I want to remind you of one simple fact that was stated, which is that the methotrexate arm, which has been our standard, the time to progression or to death is 38 days. I want to emphasize that point: days, not weeks, not years, days. Okay?

This is a rapidly progressive disease. It is actually pretty obvious when your patient is

going downhill. Okay? You know, the idea of trying to get patients to make their own assessment and getting families to do it, all of that is well and good. There probably is no physician that I know of who doesn't talk to the patient or the family in reaching the conclusion of is my patient getting worse.

So it isn't that those other extremely valuable human beings aren't brought into this equation. You know, a physician treats patients and families. That is the reality of medical practice.

So they are not excluded from this issue, but I think we're making this more complex than it really is. I don't think it is half as complicated as we're trying to make this assessment.

CHAIRPERSON PRZEPIORKA: Dr. George.

DR. GEORGE: Well, I don't want to keep beating the same horse perhaps, but it seems to me we are in a difficult situation here. We've got what sounds like to an outsider anyway or one who doesn't treat these patients, you know, a difficult

to assess situation due to variable presentation and no clearly articulated definition of the endpoint. Basically you know it when you see it.

I guess that's fine, but I find it rather troubling in a regulatory setting.

I was wondering. You do have response rate as one of the secondary endpoints; is that correct? That was in the earlier trial in lymphomatous meningitis response rate.

DR. HOWELL: That's correct.

DR. GEORGE: And I was a little trouble by, I guess, what Dr. Hirschfield said on the -- I wasn't here when that was presented originally, but the differing numbers we seem to get depending on adherence. What was going on there?

It sounded like the seven to one we have in the slide here seemed to be the maximal split, and then there were other things. What were the considerations there?

DR. HIRSCHFIELD: Well, I'll comment, and then I think Dr. Williams will make a comment on that also.

We all acknowledge that certainly when the studies were initiated in the late '80s and early '90s, the field was without a paradigm on how to conduct these studies and how to assess them, and what we received were data which were essentially from studies initiated in 1992 when, as several people have pointed out, there were no particular standards.

And I'll also point out that in our assessment of how to proceed, there is no -- although there's a standard of care in the literature, it's very difficult to find evidence to support what could be considered an active control.

Just because methotrexate is used doesn't mean we know either (a) that it benefits patients or (b) the magnitude of that benefit, which is why the study has to be a superiority study.

And just the last point in that regard is the estimate of 38 days are based on one study, but in surveying the literature, there's a large range of what can be considered the time.

So now to go back to how we came up with

these various scenarios, if we would become very strict about these things, then we find it's almost impossible to do an evaluation, and we became flexible and brought that flexibility to the committee to have a discussion on if we would take a series of assumptions, these are the results, and what is your response to it?

Now, Dr. Williams.

DR. WILLIAMS: Well, I reviewed the NDA with Dr. Van Develde (phonetic), I believe was the fellow at the time, and I don't recall the details. I haven't reviewed the NDA recently, but clearly we were comfortable with the numbers that you've seen presented, that they represented a reasonable surrogate.

There were, you know -- I don't even recall the other analyses, but we were comfortable with these, presented them to committee as such. So, you know, I don't think dwelling on other potential analyses is really helpful to this process.

DR. PAZDUR: There's another issue that

I'd like to deal with we generally don't discuss at ODAC, and that is the manufacturing of the drug. You know, we approved this drug on accelerated approval, and we have a 17 month delay here for manufacturing problems, and I just wondered if we could get some more information on this.

Obviously before the NDA is approved, sites were examined and looked at by our manufacturing and chemistry people, and I believe that this was based on your pilot data, and the problem was discovered when there was an increase in manufacturing to what is known as a step-up procedure for manufacturing the drugs for more general use.

And could you comment on that further? And again, one of the purposes that we're having this meeting is to discuss potential problems that we could use for a other drugs in the future or to remedy, and I was just wondering as a lessons learned type of situation, what do you think the FDA and yourself can learn from this?

DR. HOWELL: The problem arose -- it

happened to be synchronous with the step-up in manufacturing, but the problem arose because of a change in what the supplier was doing. So this product is made up of phospholipids and cholesterol, and the raw material goes through a variety of quality assurance steps before it's put into the manufacturing process.

When you're dealing with lipids and lipid composition, there are a very, very large number of very subtle chemical complexities to this, and once the problem was discovered, that is, that there was accelerated release of free cytarabine, it took a long time and a very extensive chemical analysis to determine what the problem was.

Having then determined that, one can set up an assay to quality assure for that particular chemical variable, but there are so many chemical variables among lipids that one could not reasonably set up an infinite number of quality assurance steps.

You learn through your mistakes. You saw that, and you put in the appropriate steps. We

were unaware that that was a variable that was important to the stability of the product at the time the NDA was submitted, and we only discovered it through this investigatory process.

DR. PAZDUR: But the phospholipid change was being done for the manufacturing step-up procedures, right? It was not going to be entertained for a study medication.

DR. HOWELL: I can't comment on that. Perhaps Dr. Schooley, Senior Vice President for SkyePharma could comment.

DR. SCHOOLEY: Could you restate the question, please?

DR. PAZDUR: I'm interested in understanding the 17 month delay, and I understand obviously it's because of the change in the phospholipid content of the liposome. I'm looking for a kind of lessons learned.

When we look at the chemistry and manufacturing of the drug, obviously we visited your plans, looked at the manufacturing process. Why wasn't this discovered at that time? That's what

I'm looking at.

The drug obviously was approved to go on to marketing. Was it because we approved it on the basis of your pilot manufacturing rather than the actual process that was going to be used in manufacturing?

DR. SCHOOLEY: Actually we had scaled up manufacturing. The product was marketed, commercial distribution starting soon after approval. So it's not due to the scale-up process, this problem, or any change that we made to any of the lipids.

I think the thing that we learned from the process was that we needed more vigilance in our quality assurance of incoming raw material, which we've recast all of our contracts with our raw materials suppliers to assure that we have a higher level of quality raw materials coming in.

DR. HIRSCHFIELD: I'd like to address Dr. George's comment about the rationale.

I'd like to point out how difficult it is to do an assessment using that endpoint and not to have any aspersions against any particular

parties, but if you follow the protocol you can't get the answer. So we had to do other scenarios, and therefore, having had that experience, we had to choose a different approach in looking at this disease.

CHAIRPERSON PRZEPIORKA: Dr. Lippman, do you have a comment before we change sponsors?

DR. LIPPMAN: Yeah, just really following up on that, this same issue I was going to raise which Dr. George said. Since there are some concerns and you learned a lot about the different scenarios using response rate and now presumably we can build on that experience, could you just go ahead and do another study using response rates, again, knowing what we learned before, which might be a harder endpoint and get around this debate we're having about what a couple weeks difference in time to detection of progression could have on the statistical interpretation of the study?

DR. HIRSCHFIELD: Well, I think no one felt certainly from our previous discussions that the response rate per se, particularly in

carcinominous meningitis was an indication of patient benefit, but that true patient benefit would become, as Dr. Martinez pointed out, from some aspect of watching the neurologic progression. That is, the laboratory changes would not necessarily be informative about the patient, given that tumors where clusters could shed. You might have a lot of cells at one visit and none at the other, and yet the patient could be still progressing.

CHAIRPERSON PRZEPIORKA: Although that is assuming that your criteria for response exclude clinical criteria, which I don't think we would. I think if you want to see a complete response, you have to say a patient feels better or has stable disease for X amount of time.

DR. HIRSCHFIELD: Correct, but as Dr. Howell and our consultants have pointed out, these lesions may not improve in some way, and we discussed that as a potential scenario, that they would come into the trial with a problem, and that taking the therapy would fix that problem.

But that didn't seem to be as plausible

as asking the question was the problem going to stabilize or was it going to get worse.

CHAIRPERSON PRZEPIORKA: Dr. George? Dr. Williams.

DR. WILLIAMS: Well, I think the difficulty with this is that, I mean, the whole field is based on cytologic response, but there's very little documentation of what that means.

I think everybody agrees that that is a very encouraging finding to see the tumor cells go away, and so I think clearly it will be part of the data that you collect in any study, and it will be very, very interesting to have.

What we are trying to do that nobody, I think, has ever done, is actually show that there is documented clinical benefit, but I think at the end of the day when the study is through, we will have not only the primary endpoint. We will have the other data to consider and a lot more data about the previous endpoints.

CHAIRPERSON PRZEPIORKA: Ms. Mayer.

MS. MAYER: Before we move on, I just

want to commend the sponsor for listing this trial on the clinicaltrials.gov database so that it's publicly accessible.

I think one source of trial enrollment we haven't openly acknowledged is patients and family members who seek out clinical trials themselves, and I think it should be noted by no means does every trial that is open to enrollment that we've been discussing.

The majority of them are not listed. I looked them up last night, in fact, and was a little shocked by that in view of the difficulties with trial accrual that we've been discussing.

CHAIRPERSON PRZEPIORKA: Mr. Ohye.

MR. OHYE: I'd like to make one small comment in reference to the discussion about doing additional neurological testing. I'd like to remind everyone that this is a transnational study, and any time you introduce a new instrument for testing, it has to be updated, and this can take a lot of time. There are a lot of operational issues connected with this.

And based on what I've heard from Dr. Carpenter and others, I would urge that the sponsor be allowed to go forward with this study.

CHAIRPERSON PRZEPIORKA: Dr. Fleming.

DR. FLEMING: I wanted to return to some of those earlier calculations that we were talking about, but before, just to clarify for my purposes, the expected approximate time to the primary endpoint in the control arm am I understanding might be on the order of 38 days? Is that what we're projecting?

I'm a little perplexed then with the enrollment taking the number of months that it's taking, that we would have to enroll 110 people to see 75 events. If the median time to events is somewhere between 30 or 40 to 60 days, then if we enroll --

DR. HOWELL: Can I make a correction of fact?

DR. FLEMING: Yes.

DR. HOWELL: It's not 100 patients, Tom, for them. It's 75 events, 80 patients in the solid

tumor arm.

In other words, remember that this trial is powered on the solid tumor subpopulation.

DR. FLEMING: Okay.

DR. HOWELL: We're looking for a 50 percent improvement in time to neurological progression in that subpopulation, estimated 75 events necessary.

DR. FLEMING: Right.

DR. HOWELL: So the accrual will continue.

DR. FLEMING: Because you're doing two analyses, one in the solid tumor and one in the pooled, and you want to have --

DR. HOWELL: Right, until there are approximately 80 solid tumor patients, five more than the events that we need.

DR. FLEMING: So at that point you want 75 events in the solid tumor group.

DR. HOWELL: Right, and at that point we expect to have 110, 120 total patients, solid tumor plus lymphoma accrued.

DR. FLEMING: Okay. Let me then move to the two issues. One is you had referred to this being powered to a 50 percent improvement in time to neurologic progression. It is, in fact, as I had thought I read, it's powered to a 50 percent reduction in the rate of progression.

That translates into a doubling. So you're actually powered to a 100 percent improvement in time to neurologic progression.

The other point that I think I heard you say was when we talk about whether this should be a noninferiority trial, I think the comment you had made is, well, that would be an enormous sample size.

And I think there's a misunderstanding here as well. If you are, in fact, powered, as you are, to a doubling, if, in fact, you legitimately could look at this as a noninferiority trial, you could actually have a smaller sample size because if you're presuming you have a doubling to rule out that you're 20 percent worse takes a smaller sample size than to rule out that you're equal.

So, for example, to be specific, it takes the exact same sample size to rule out 25 percent worse if I'm 50 percent better, and you had said, I think, your understanding was you're powered to a 50 percent improvement.

Well, in fact, you are powered to a 50 percent improvement if you only have to rule out you're 25 percent worse, and so what becomes critical here is to decide now what is the clinically relevant null hypothesis or what I have to rule out. It is currently a superiority trial, and that means when this study is done, if there's no difference or even just a very trivial positive difference, then you certainly haven't ruled out no difference. You have data suggesting no difference.

That is a negative study if, in fact, we are holding ourselves to the criterion of needing to show you're better in this endpoint to time to neurologic progression.

On the other hand, if it is judged that in this setting it's adequate to be the same or better and you simply want to rule out you're

meaningfully worse, then that clearly should be established today, but then you get into a lot of complexities because you need to define a non-inferiority margin, which in fact requires us to know very clearly how the control regimens influence this clinical endpoint.

But the thing that I want to make sure is, in fact, clearly laid out today is if this study, in fact, in the end shows very little difference, slightly better to the same, are we viewing this to be a negative result or are we viewing this to be an acceptable result because we have less frequent administration?

CHAIRPERSON PRZEPIORKA: If I can summarize then, we still have some questions about what will happen if this turns out to be a negative study, and perhaps a relook at the statistical planning will actually obviate that problem by making it a non-inferiority study.

DR. WILLIAMS: I don't think we ought to pursue that any further because we have no idea what the control arm does. So non-inferiority is not an

option.

If we were to try to rescue this from a not positive study later, I think it would be by looking at the response rate, the psychologic response rate, the anecdotal evidence. You know, I think that's the only way you would rescue it with this trial, but not by a non-inferiority assessment. We just don't know that the control works in this endpoint.

CHAIRPERSON PRZEPIORKA: Dr. Lippman.

DR. FLEMING: Are we leaving the point? I just wondered do you have a comment on this point.

DR. LIPPMAN: Well, my comment is just following up on this. Again, it would be, I think, very unfortunate to lose this drug if it turns out to be non-inferior to the standard treatment because it's given so infrequently relative to the treatment. It has a tremendous impact, I think, on patient quality of life and so on, and that's why it would be unfortunate if somehow this couldn't be done as a non-inferiority study.

Because the fact that it's not better,

you know, it has other advantages in terms of the frequency administration.

CHAIRPERSON PRZEPIORKA: But I think what I'm hearing is the division is not going to accept that at this point in time, and so perhaps it may require additional conversations between the consultants, the sponsor and the division

DR. WILLIAMS: What it would require would be somebody to come with the evidence that this drug works and produces an effect on this endpoint. Now, that's basically the bottom line for any non-inferiority assessment from a regulatory standpoint.

DR. FLEMING: But I think what you're saying, Grant, that is critical is to conclude that we have an intervention that is useful, let's say, because it is more favorable in its convenience of administration, we have to know that it's providing meaningful benefit, and if it's the same as the control arm and the control arm doesn't have documented levels of benefit on this endpoint, I only know I'm the same as something that may or may

not be effective.

But this issue right now, before these data are unblinded, this issue needs to be resolved, and what concerns me is the issue of not doing this as a non-inferiority trial because it's going to cause an enormous sample size is totally a misunderstood concept.

Non-inferiority trials are only large if you are assuming no difference and trying to rule out a small inferiority, but you're assuming a big difference. And if you're assuming a big difference, you can more easily rule out inferiority than you can rule out equality.

Now is the time for us to understand what our goals are for this trial, and if we believe that it's adequate to be the same, then the study isn't properly formulated. If, on the other hand, because we don't know what the control arm provides to establish benefit we have to show superiority, then it's properly formulated.

But then in the end if we're the same, we can't fall back and say, "Ah, we'll like this

anyway because it's more easily administered."

CHAIRPERSON PRZEPIORKA: Well, I think Dr. Williams has explicitly stated that it will not be an inferiority trial.

Dr. Blayney.

DR. BLAYNEY: Well, I mean, again, in four or five years when this data is available, we've heard that there are three or four other trials going. It may be that the endpoint of intrathecal methotrexate and the response rate for intrathecal methotrexate can be very precisely estimated because that knowledge is going to change as well.

And if you talk about rescuing a trial, that may be available data at that point. I understand the reason for trial design in advance and specifying, but it's a field where the control endpoint is fuzzy. We may have better data three years down the road or five years down the road on that to tighten that estimate up.

CHAIRPERSON PRZEPIORKA: Other questions from the FDA or the sponsor for the committee?

Dr. Temple.

DR. TEMPLE: Yeah. Nobody is unsympathetic to the idea that having something that may or may not work that you don't have to get as often might be worthwhile, but that can't pass legal muster. We have to be able to say that it works, not merely that it's more convenient.

So what I hear, Tom, is that nobody thinks we can pin down the effect size of methotrexate. Yes, maybe; maybe later, but not now.

DR. FLEMING: And if, in fact, at the time of the review of these data you could, but I would say you only could if somebody is doing a methotrexate control trial right now that's going to establish that.

So if, in fact, we are at the end where we are now, where we don't understand the effect of the control, then this study is properly designed, meaning that it has to show superiority, and in the end if we don't show superiority, it hasn't proven benefit even if it's administered less frequently.

DR. HOWELL: I would submit that it's

not possible to do a randomized trial to establish the benefit of methotrexate against a placebo in this disease. It's a trial which would never get done.

And, therefore, in the end we're still left with a quandary despite the fact that we don't have firm evidence based conclusions that methotrexate is effective. That's a regulatory issue that we're going to be left with in the end.

CHAIRPERSON PRZEPIORKA: Other comments or questions?

I have a question for the committee. We're kind of like midland here. Would you folks prefer to move on to the next drug or take a lunch?

Who wants to take lunch? You want us to move on? Okay. We'll get 30 seconds for the sponsors to change computers. Please don't leave your seat unless you're leaving the room, and we will very quickly go to the conflict of interest statement for the next drug.

(Whereupon, the foregoing matter went off the record at 11:40 a.m. and went

back on the record at 11:43 a.m.)

CHAIRPERSON PRZEPIORKA: Ms. Clifford is ready to read the 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 part of the record to preclude the appearance of conflict.

To determine if any conflicts have been made, the agency reviewed the submitted agenda for this meeting and all relevant financial interests reported by the committee participants.

The conflict of interest statute prohibits special government employees from participating in matters that could affect their personal and imputed interests. However, the agency may grant a waiver if the need for the individual service outweighs the conflict created by the financial interest.

Accordingly, waivers have been granted to the following individuals that permit them to participate fully:

Dr. Blayney for owning stock in one of the sponsors of Celebrex worth between 25,001 to $50,000;

Dr. Kelsen for owning stock in one of the sponsors of Celebrex worth from 5,001 to $25,000;

Dr. Fleming for serving on two data monitoring committees for one of the sponsors of Celebrex for which he receives less than $10,000 a year. The activities of the committees are unrelated to the product at issue.

A copy of these statements may be obtained by submitting a written request to the agency's Freedom of Information Office.

In addition, Mr. Ohye is the acting industry representative. Mr. Ohye would like to disclose that he owns stocks in one of the sponsors of Celebrex.

In the event that the discussion involves any other products or firms not already on the agency for which an FDA participant has a financial interest, that participant should exclude

him or herself from such involvement, and the exclusion will be noted for the record.

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

CHAIRPERSON PRZEPIORKA: Could the new members from the group from the FDA please introduce themselves?

DR. AVIGAN: I'm Mark Avigan. I'm the Deputy Director of the Drug Risk Evaluation Division in CDER.

DR. JUSTICE: Robert Justice, Director of the Division of Gastrointestinal and Coagulation Drug Products.

DR. GALLO-TORRES: Hugo Gallo-Torres. I'm a gastroenterologist and a medical team leader in the FDA division.

DR. NAIR: Naroyan Nair, Medical Officer, Division of GI and Coagulation Drug Products.

CHAIRPERSON PRZEPIORKA: Thank you.

Our sponsor for this session is Dr. David Vlock from Pharmacia to discuss Celebrex, the indication being reduction in the number of adenomatous colorectal polyps in familial adenomatous polyposis patients.

DR. VLOCK: Okay. Thank you, and good morning.

Advisory Committee members, representatives of the FDA, as mentioned, my name is Daniel Vlock, and I'm Senior Director of Clinical Research of Pharmacia.

Today we are here to provide an update on the status of our Subpart H post approval commitments for Celebrex in the treatment of familiar adenomatous polyposis, or FAP.

Besides myself, the following individuals will be able to answer any questions for the committee. they are Dr. Langdon Miller and Kenneth Verburg, both in clinical research at Pharmacia; Dr. P.K. Narang, Regulatory Affairs at Pharmacia; Dr. Kerry Barker, in biostatistics at

Pharmacia; and Drs. Bernard Levin and Patrick Lynch of M.D. Anderson Cancer Center in Houston.

To being, Pharmacia is fully dedicated to completing its post approval commitments. As you heard yesterday from the FDA, Pharmacia has completed Subpart H requirements for Zinecard and Camptosar.

We are similarly dedicated to insuring completion of our commitments for celecoxib in FAP, and our post approval program is underway.

Our agenda is shown on this slide. We will present an overview of FAP, its disease course and management. We will then briefly present the results of the pivotal trial that was the basis for approval.

Following that, we will review the indication that was granted and the subsequent Subpart H commitments.

We will then present a brief chronology of events highlighting the progress we have made towards fulfilling those commitments.

FAP is a rare, life threatening disease

resulting from an autosomal dominant alteration in the adenomatous polyposis coli gene or the APC gene. There are approximately 300 new patients diagnosed in the United States each year. Overall, FAP accounts for one percent of all colorectal cancers in the U.S.

The two photos shown here illustrate the gross morphology of FAP. On the left is a surgical resection demonstration numerous adenomatous adenomas that carpet the colon or rectum. On the right is a colonoscopic view of the same thing.

Adenomas begin to develop in early adolescence. These patients can develop between 100 and 5,000 colorectal adenomas.

The cancer risk in these patients increases with the number of adenomas and if left untreated, these individuals have a 100 percent colorectal cancer risk with a medium life expectancy of 42 years.

The current management of FAP requires lifelong endoscopic surveillance, a prophylactic colectomy with ileorectal anastomosis, which usually

occurs around the age of 18 to 20.

This may be the first of multiple surgical procedures, including removal of the remaining rectum and also a duodenal resection.

Because of the limitations of routine surveillance and the risk of surgery, there was an interest in developing a medical treatment as an adjunctive therapy for FAP.

Clinical evidence supporting the FDA approval of celecoxib in the therapy of FAP was derived from a randomized, double blind, placebo controlled study conducted at M.D. Anderson Cancer Center and St. Mark's Hospital. This study was sponsored by the NCI with funding and support from Pharmacia.

Patients were randomized to placebo for one of two different doses of celecoxib. The primary efficacy outcome for the study was the percent change from baseline in colorectal polyp number as determined after six months of treatment.

The scope and conduct of this trial emphasizes the rarity of this condition. This was

the largest prospective randomized trial performed in FAP. Despite a large referral base from the U.S. and U.K., it took two years to complete enrolling 83 patients.

A shown in this figure, celecoxib, 400 milligrams b.i.d., for six months reduced the mean number of colorectal polyps by 28 percent from baseline. This was highly statistically significant compared to patients receiving placebo.

Although there was a positive trend in the 100 milligram b.i.d. dose, it did not reach statistical significance.

In addition, the 400 milligram b.i.d. dose of celecoxib was well tolerated.

On December 23rd, 1999, the FDA granted accelerated approval for celecoxib, and I quote, "to reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis as an adjunct to usual care."

As noted in the complete indication shown here, there remained outstanding questions with respect to clinical benefit, persistence of

effect following drug discontinuation, and long-term efficacy and safety.

Prior to approval, discussions between Pharmacia and the FDA took place to determine the design of the confirmatory trials. Pharmacia and the FDA agreed to the following Subpart H post approval commitments.

The first of these, an FAP phenotype suppression study, was designed to verify clinical benefit. This is a placebo controlled trial in patients who are genotypically positive, that is, they have the APC mutation, but are phenotypically negative, that is, they have not yet developed adenomas.

And the second was a FAP registry with an objective to determine both efficacy and safety parameters associated with short and long-term exposure to the drug.

Let me now discuss our efforts with the phenotype suppression study. As originally envisioned, the phenotype suppression study was a Phase 3 study of celecoxib in genotype positive,

phenotype negative children. Patients were to be randomized to either placebo or celecoxib, 400 milligrams b.i.d., in a one-to-two ratio.

A total of 231 patients were to be recruited and treated for five years. The primary endpoint was the time to the appearance of the first adenoma.

Plans for this Phase 3 study are still in place. However, as seen in the next slides, a preliminary Phase 1 trial became necessary.

The following is a brief chronology of events involving the program. The FDA concurred with the study concept in December 1999. As with the pivotal trial, which was a successful partnership with the NCI, a similar collaboration was established here.

The NCI issued a request for proposals to perform a Phase 3 study. The NCI would sponsor the trial, and Pharmacia would provide study drug and additional monetary support.

Seven months later, after the accelerated approval for celecoxib in FAP, the RFP

was awarded. M.D. Anderson was designated the lead institution of a collaboration involving seven other academic centers with an expertise in FAP, and they are listed here.

Subsequently, a number of discussions with the NCI and participating institutions took place. There were concerns about the conduct of a study in a pediatric population. One of the primary issues was the limited information regarding the use of celecoxib in children.

It was concluded that a pilot dose ranging study was needed. As a consequence a Phase 1 protocol was developed. A proposal that included both a Phase 1 and Phase 3 study was submitted to the FDA in January of 2001. In April the FDA reviewed the proposal and agreed to this approach.

However, three revisions of the protocol were required to address the complex issues inherent in performing clinical research in this pediatric population. That involved invasive procedures, use of a placebo group, and the inclusion of psychosocial testing.

Because of these discussions and the necessary revisions, it took a year for the protocol to be finalized.

So this is a summary of the Phase 1 design. Participating sites include M.D. Anderson, Texas Children's Hospital, and the Cleveland Clinic.

Three successive cohorts of children between the ages of ten to 14, four on active therapy, two on placebo, will be enrolled to receive treatment with celecoxib at two, four, or eight milligrams per kilogram PO b.i.d. for three months for each cohort, at a dose range of 100 to 400 milligrams b.i.d.

The primary endpoint of the trial is the identification of a safe dose in children for the subsequent Phase 3 trial.

Let me return to the time line. A final protocol was approved by M.D. Anderson IRB in February of 2002. Shortly there afterwards it was submitted to the FDA and soon after that a site initiation meeting was held.

At around that time, it was found that

developmental delays and investigational formulation favored by the clinicians had been encountered. Rather than delay the program any further, it was elected to amend the protocol to permit the use of the commercially available capsules.

In December 2002, the first patient was enrolled. To date six patients have been entered in the first cohort. Based on current time lines, it is anticipated that the Phase 3 trial will begin the first quarter of 2004, with the last patient in at 2006. Final analysis is planned for 2011.

Let me now turn to the FAP registry. This is a summary of the trial design. It was conceived as an observational registry studying patients receiving celecoxib compared to historical controls. The primary endpoints were the time to FAP related events and adverse events.

The chronology of the events in the registry is as follows. Following FDA agreement with the concept, the sponsor consulted with a number of experts in the field. These experts raised concerns that the data might have relatively

limited value. Since celecoxib had just been approved for use in FAP, the types of patients who had received the drug in actual clinical practice had not been characterized.

It was also noted that changes and improvements in therapeutic approaches over time where the complexity of surgical decisions might compound comparison with historical controls, and the time to an FAP event may be quite long in many patients, making adequate duration of follow-up impractical.

Prior to discussing these concerns with the FDA, it was felt that a well developed alternative to the registry should be offered. Preclinical studies had shown synergy between celecoxib and difluoromethylomithine, or DFMO. Because of the clinical interest in developing combination therapy in this disease, discussions were begun with ILEX Pharmaceuticals and the NCI.

At a meeting in May 2000, a controlled clinical trial evaluating the use of celecoxib with or without DFMO in FAP patients was decided upon.

Over the next several months, a protocol and collaborative agreement were developed with the NCI-Ilex Pharmaceuticals.

A protocol was submitted to the FDA in December of 2000.

In April 2001, a meeting was held with the FDA. The alternative study was not accepted by the FDA. The FDA felt that the proposed DFMO study did not address Subpart H commitments as it did not provide direct data on the clinical benefit of celecoxib or address long-term safety.

The FDA stated it still considered the registry worthwhile. The agency acknowledged that new therapies and differences in clinical practice may confound analysis, but it still considered this approach preferable.

As a consequence, efforts were refocused on the FAP registry.

One month later, Pharmacia began planning for a registry. Under the sponsorship of M.D. Anderson, a partnership with a collaborative group of the Americas on colorectal cancer, or CGA,

was pursued.

The CGA is a recently formed consortium of 17 registries and clinics in the U.S., Canada and South America. To gain acceptance by the CGA, it was necessary to wait for formal presentation of the concept at the CGA annual meeting in October 2001.

The proposal for a provider driven, multi-institutional registry was presented in concept by M.D. Anderson to the CGA. Following that meeting, M.D. Anderson was contracted to design and develop a Web based registry.

In April 2002, a full protocol was sent to the CGA membership for review. However, upon further review, response to this protocol by the CGA was not positive. It was felt that data entry would be too labor intensive for health care providers, thereby limiting collection of data.

Given this concern, M.D. Anderson worked with Pharmacia to develop a registry that would allow data to be entered on a Web site directly by patients. It was felt that the FAP population was motivated, was very aware of their condition, and

could provide accurate information on their condition and treatment.

The revised Web-based patient entry registry was presented to various collaborators and genetics counselors who expressed a willingness to participate in the protocol and would encourage their patients to register.

In October, the concept of patient based registry was presented at the CGA annual meeting. The overall feedback prompted Pharmacia and M.D. Anderson to fully develop a Web based patient registry. Protocol for the registry was submitted to the M.D. Anderson IRB in December 2002.

The M.D. Anderson IRB reviewed the protocol in January of 2003. It did not recommend approval. The IRB cited lack of source data verification and patient confidentiality as reasons for disapproval.

Pharmacia has recently revised the registry in conjunction with major existing FAP registries. A protocol summary has recently been submitted to the FDA.

The following is a summary of the current registry design. Sites under consideration are those with well established FAP registries. It is conceived as an observational registry assessing patients receiving celecoxib compared to historical controls.

Objectives of the registry are to describe characteristics of the population of the patients with FAP who receive celecoxib in clinical practice, describe current patterns of celecoxib abuse, evaluate the long-term safety of celecoxib, assess the extent to which use of celecoxib may alter management, and determine the impact on the incidence of FAP related events.

In conclusion, Pharmacia is fully dedicated to completing its post approval commitments. Of the three Pharmacia drugs approved under Subpart H, the commitments to Zinacard and Camptosar have been fulfilled.

In FAP we have encountered a number of challenges due to the rarity of the disease, special considerations related to the conduct of studies in

children, and specialized site coordination and study design complexities in implementing the FAP registry.

To summarize, the phenotypes suppression program that will verify clinical benefit has begun. There is continuing progress in implementing a registry utilizing well established FAP registries.

Thank you very much. My colleagues and I will be pleased to answer any questions you might have.

CHAIRPERSON PRZEPIORKA: Does anyone from the FDA have a comment? Dr. Nair.

DR. NAIR: Yeah, I have some brief comments and questions, and Dr. Gallo-Torres and Dr. Avigan also have some brief comments.

One question I wanted to address to the sponsor is in terms of your Phase 3 phenotype suppression trial, could you discuss what your secondary efficacy endpoints would be to describe clinical benefit?

DR. VLOCK: Dr. Lynch is the lead on that.

Could you possibly go into that? Oh, I'm sorry. You can't hear. Dr. Lynch, would you care to address that?

Dr. Lynch is the lead PI on that study.

DR. LYNCH: Yes. One very important secondary efficacy endpoint is the status of aberrant crypt foci. Gastroenterologists feel that aberrant crypt foci are micro-micro adenomas that precede adenomas, but there's no knowledge whatsoever about the time course from the development of early micro adenomas to microscopically evident adenomas.

And in the course of this study we'll have really a unique opportunity to characterize the mucosa insofar as the presence of aberrant crypt foci in these individuals prior to the onset of clinically evident adenomas. And we may very well be able to demonstrate the ability to modulate the numbers of aberrant crypt foci that are present even before the presence of adenomas, which is the primary endpoint.

DR. AVIGAN: Just as a follow-up to that

and sort of a background to that question, the concern with regard to this Subpart H idea, of course, is to link the original observation about polyp suppression, which was the basis of the Subpart H approval, with a clinical endpoint.

And as I recall with the adolescent population, one of the rationalizations for real clinical benefit would be the potential for delay of surgery, and that from the pediatric perspective might be something that you can get your hands around.

Is that a separate measure that you're planing to do and, in fact, how will you do that?

DR. LYNCH: Yes. That is an endpoint of the study. In individuals who do respond, who have a delay in the development of adenomas, they will be followed until the time of a surgical event, such as a colectomy, and there is a provision which is still being formulated for the full Phase 3 component of this, which is still only in draft form at this point, basically for taking individuals who are found to be on the placebo arm at the time of first

adenoma, and essentially crossing them over to active drug for further interval of treatment.

DR. AVIGAN: And just the final follow-up to that question, will the surgeons be blinded to the drug the patients are on?

DR. LYNCH: Yes.

CHAIRPERSON PRZEPIORKA: Dr. Kelsen.

DR. KELSEN: Could you describe the status of your trials in SAP, the two completed trials, and comment as to whether you have trials in HNPCC and briefly review the rationale for using COX-2 inhibitors in polyps in adults?

DR. VLOCK: Okay. For SAP, I think that was Slide No. 14. There we go. Back one.

This is an overview of the two pivotal trials that we are performing, Study 018 and Study 005. These have enrolled and randomized 35/100-plus patients to receive either placebo or celecoxib at the doses that you see here, and the endpoint is a reduction in the number of adenomatous polyps at year three.

Yes?

DR. KELSEN: Could you comment on any studies you may have performed or are being performed in HNPCC?

DR. VLOCK: I think, Pat, you can respond to that.

DR. LYNCH: Yes, let me address that.

A trial very similar in design to the original FAP trial actually has been completed in HNPCC. Because of the extraordinary infrequency of adenomas in this population and the short interval of observation of one year, this was strictly a biomarker endpoint trial, modulation of mucosal biomarkers. The analysis of that biomarker data is nearing completion.

DR. KELSEN: And could you just review for the committee the rationale which we all know, but just to go over it again, of using adult polyps and using COX-2 inhibitors and similarly linking that to FAP?

You're doing it for the same reason.

DR. LYNCH: I'm sorry. I'm not sure I'm understanding the question.

DR. KELSEN: All right. The reason that you studied celecoxib in FAP patients is because you're down regulating COX-2. The reason you're studying in HNPCC and you're studying it in SAP is for the same rationale, correct?

DR. LYNCH: Yes. The thinking being that FAP is actually an excellent model because of the relative homogeneity of the population as far as their genetic risk is concerned, the ability to quantify adenomas and eventually be able to extrapolate that extreme to the SAP population, which is in the process of being done.

DR. KELSEN: All right. I guess my point will be later on that you can look at it in the reverse fashion as well. FAP is extremely rare. It's hard to accrue patients in trial. SAP and HNPCC are far more common, and you may be able to reach in your post marketing studies to this same aim through a different pathway.

CHAIRPERSON PRZEPIORKA: Dr. Martino.

DR. MARTINO: I need a better understanding of the long-term known toxicities of

using this dose, and I'm particularly thinking of the patients that are going to go into the phenotype suppression population, which are adolescents.

And I realize that the endpoint is time to their first polyp, so to speak, but potentially if this works, you then are going to be having adolescents on this for much of their life, I would think.

What do we know about long-term toxicity in adults versus a younger population?

DR. VLOCK: I think that's an excellent question. I think that there are a few ways to address that.

Lynn, if you could pull up I believe it is Slide 27.

I think that -- no, back one. I'm sorry. I apologize -- I think that this is what we know right now in a lot of this, that in the FAP study, the pivotal study, that was a limited study of six months, and I think that was appropriate because we did not know what the efficacy was going to be, and it was not felt that we could continue

patients that way.

In that setting the dose of celecoxib in those was well tolerated.

In terms of trying to prolong this right now, what is preceding that now is information that we now have in another population, which is the SAP population, and as we mentioned previously with the randomized trials, over 3,000 patients have been randomized, and of that group approximately 600 of those individuals are receiving the same dose as in FAP, which is the 400 milligrams of b.i.d. dose.

That dose, that treatment goes on for three years in that population, potentially even longer. We don't have privy to hook to the unblinded information right now, as would be obvious.

However, that data is being shared every six months with two independent DSMBs that review the data fairly intensively, and to date there have been no concerns of any safety concerns that have been raised in those groups, and the studies are continuing.

So as it gets back to the population with children, that data is essentially moving forward and proceeding in advance of these longer term effects in children.

CHAIRPERSON PRZEPIORKA: Dr. Lippman.

DR. LIPPMAN: I wonder if you could clarify the proposed design of celecoxib and DFMO. Was that a two-by-two factorial design? Do you know?

DR. VLOCK: No, it was just a straight randomization between the two arms.

DR. LIPPMAN: And the two arms were?

DR. VLOCK: It was celecoxib and celecoxib plus DFMO.

DR. LIPPMAN: So then my question to the agency is why was that turned down. I mean, that seems to be in many ways better than a registry compared to historical controls.

DR. AVIGAN: I just want to clarify a couple of points. The two are certainly not mutually exclusive. The discussion that we held about this particular study had to do with its

context, that is, as the fulfillment of the Subpart H rather than as a freestanding study to improve the field and move it forward.

Let me also clarify another point about the labeling, how the drug has been approved. It's stipulated in the labeling if you look at it that the celecoxib therapy for familial adenomatous polyposis is adjunctive to standard of care, which essentially is regular screening and, in fact, prophylactic proctocolectomy.

The labeling stipulates that that should not be changed in any way, and one of the concerns on the safety side that we have about this agent is that when it's being put out there, albeit the patient population is small, that clinicians or patients may misunderstand its niche in context to other modalities and therapies.

So one of the measures we wanted to have in an observational sense is to find out whether there were bad outcomes because of misunderstanding of how the drug would be used, that is, inappropriate delay of surgery, inappropriate loss

of surveillance or lack of surveillance at appropriate times.

So that was part of the rationalization to go ahead and do an observational study.

DR. FLEMING: Could I add to the answer maybe to this, too?

CHAIRPERSON PRZEPIORKA: I believe Dr. Lippman still has the floor.

DR. LIPPMAN: But, I mean, misinterpreting the label won't be the first case if it happens here. I mean, that's always an issue, and I agree with that, but comparing a registry to historical control seems to me to have a number of issues.

And doing a prospective study to get a better handle on celecoxib response rate seems to me a very sort of valid interpretation of what you'd want to do in a Phase 4 commitment.

CHAIRPERSON PRZEPIORKA: Dr. Taylor.

DR. TAYLOR: My concern was also the toxicity, You've chosen five years to treat these children, and we don't have data on giving the drug

for even three years.

Any comments on why you picked five years?

DR. VLOCK: Pat, would you care to comment on that?

DR. LYNCH: Part of the reason for the long duration of the study is that the design requires that they be free of adenomas at study entry. Individuals develop adenomas over a very long time interval. So many of the subjects, regardless of which arm of the trial they're on, will have no adenomas at year one, no adenomas at year two, no adenomas at year three.

And so we've had to build into it a window in which they may develop adenomas, and with time to development of adenoma as the endpoint, we have to be able to take into account the fact that even on the placebo arm no adenomas may occur for several years.

CHAIRPERSON PRZEPIORKA: A point of clarification in the protocol. If the standard of care is colectomy between the ages of 18 and 20, if

the patient hasn't developed any adenomas by that point in time, what is the plan?

DR. VLOCK: Well, that's the average time when these adolescents begin to develop a colectomy. The decision to perform a colectomy -- and, again, I would defer to the clinicians here -- is based on what is seen in endoscopic surveillance, and I guess Pat can expand on that.

DR. LYNCH: Well, obviously the Holy Grail here would be -- and that's our ultimate goal, is to develop a medical treatment for this surgical disease -- if even in a subset of subjects we can so significantly impact the development of adenomas, we would be prepared from a clinical standpoint to treat a subject indefinitely so long as they have not yet developed adenomas. I mean that would be the ultimate outcome.

That's a very optimistic, rosy picture, and we don't necessarily expect that, but we will be following these individuals long term, and if they continue to not develop adenomas, they will continue to be treated.

CHAIRPERSON PRZEPIORKA: Other questions from the committee? Dr. Fleming?

DR. FLEMING: Yes. I was just going to respond to Scott's question because my immediate sense was what you were saying as well, which is if you're going to propose an alternative to a registry, a randomized trial seemingly would have some very significant advantages.

The difficulty though in interpreting this trial is where if I were at FDA I would have had problems. It's basically looking at Celebrex versus Celebrex plus DFMO, which scientifically tells me what DFMO adds to Celebrex. It doesn't specifically address what Celebrex itself is doing.

Now, it does, in fact, provide a mini registry, so to speak, because you would have follow-up of the Celebrex participants, but the actual randomization would only be addressing what DFMO adds to Celebrex.

DR. LIPPMAN: No, that's correct, but the point is that the registry is really just trying to get a handle on response rate, right, of Celebrex

versus a historical control, and so if you're going to use that historical control anyway, I'd rather have the prospective data on celebrex activity than from a registry is my point.

DR. FLEMING: If this trial were done, then the basis for judging the role of Celebrex would still have to come from an historical control. You would have the cohort that was in the trial that would receive Celebrex, and you would have to compare it to a group that didn't receive Celebrex.

DR. LIPPMAN: Right. No, I agree, but don't you think it would be better to at least have the Celebrex data done prospectively in a control trial so that at least you can say, you know, those data are comparable to the FAP initial trial. You know, limitations of historical control exist either way.

DR. FLEMING: I guess my sense of that is I would judge in general terms the randomized trial is always superior if, in fact, I'm randomizing in a manner that I'm understanding what the role is of the agent.

So if I want to understand Celebrex's role, I would randomize to some choice of BSC against BSC plus Celebrex.

Short of that, if I'm going to have to use historical information anyway, then surely the information I would get from that randomized trial would be useful in what I would look at when I'm doing an historical control assessment.

But if I do historical controls, typically then I want much bigger sample sizes than what I would just get from the randomized trial.

CHAIRPERSON PRZEPIORKA: Dr. Kelsen, it doesn't seem that there are potentially major problems with this protocol and if it should turn out to be positive, it would be great, but if you can address the questions that have been posed.

DR. KELSEN: Thank you.

Well, this is a little different than the other applications we've seen in the last several days because the purpose of this group of studies is to prevent a process that can lead to cancer rather than to treat a cancer itself.

If polyps themselves are pre-malignant, then the idea that a reduction in the number of polyps as opposed to removing them by colonoscopy will decrease the risk of cancer is a very plausible. It's a little controversial if you just reduce the number of polyps you will prevent cancer, but certainly it's a reasonable hypothesis.

It does have some things in common with the applications we heard earlier today and yesterday thought. The disease they were talking about for the indication is a rare disease. There are very few patients per year in the United States, and all of the issues regarding accrual and eligibility, et cetera, that we dealt with three or four times in the last couple of days hold for this.

Having said that, if we look at the question, has accrual to an ongoing study been satisfactory, well, it's a very rare disease. Accrual to the Phase 1/3 trial was slow to get started, but I think clear, strong efforts were made, and I'm glad that they've gotten that underway.

It is a little disappointing that the registry trial hasn't started yet, but I think sponsor has indicated strong efforts to try to get that done, and I believe at least they will make a very strong effort.

I am reassured a little bit in the sense that in a different way of trying to get to the answer of do COX-2 inhibitors decrease the number of polyps, there are adult models to use, and they have already completed or are near completion. I think they have completed the two large SAP trials, which will give us information in large numbers of adults. We will have toxicity data at least for a fairly long period of time in some of those studies.

And I understand there's at least one HNPCC trial that's been done. We should have some information from that. Perhaps sponsor would consider another HNPCC trial where people can get malignancies from a number of different organs so that there's more of a link to FAP with that to try to answer a question in a much more common population.

Is there strategies they can pursue for FAP other than they've done? I think they're working hard to link up with the appropriate registries to try to address it through the registry issue. It sounds like you're going abroad, as well as in the United States. I think you're doing what you can do.

And they have certainly at least gotten their Phase 1 underway. So I think we'll eventually get to the Phase 3. So I answered that.

I don't see any change in medical -- well, for aspirin maybe -- but I don't see any other change in medical practice except for other ways of medically trying to manage this, which would impact on accrual. So I don't think that's an issue.

I think sponsor has made a strong effort to achieve their post four marketing comments.

CHAIRPERSON PRZEPIORKA: Before you actually leave that point about aspirin, should something show up in the next five years regarding aspirin in this role, where would that leave us when we start to look at the data later on down the line

saying, oh, well, looking at placebo rather than aspirin?

DR. KELSEN: I think that's an excellent question. I think the editorial in the New England Journal raised some important caveats about what we should do with that.

Has aspirin become the standard of care? My impression from reading -- and I'll be interested in hearing comments from sponsor and from FDA -- was that we're not yet at the point that aspirin is the standard of care, but that is certainly an important issue.

Does FDA have comments?

DR. AVIGAN: Just on the aspirin question, we have in the geriatric population for the sporadic polyp prevention, that in a sense is a fish of a slightly different color, where we know that there are substantial numbers of people on aspirin for cardiovascular prophylaxis.

So we in that context want to know what these interactions or redundancies are. That's a separate question than the hereditary disease and

the sort of repertoire of drugs patients are on.

Dr. Gallo-Torres has a comment, but I just want to also make a point about the biological behavior of these adenomas in the hereditary disease.

There is published information that NSAID treatment of patients with FAP occasionally is associated with polyp suppression as a phenotype, but with in certain cases progression to malignancy, the development of malignant CDR. There's such in the literature.

In addition, there are animal models which show that one can generate suppression of polyp appearance, but histopathologically there is still the presence of dysplasia.

So we have taken a rather cautious view of sort of the endpoint measures and have felt compelled to, as best we can, get a sense of what is happening to patients with regards to cancer prevention long term with this disease.

CHAIRPERSON PRZEPIORKA: So what I hear you saying is that potentially you may end up

suppressing the clinical indicator of impending malignancy without actually reducing the risk of malignancy.

DR. AVIGAN: Right. It's a discussion point, but it is certainly a concern.

CHAIRPERSON PRZEPIORKA: Dr. Gallo-Torres.

DR. GALLO-=TORRES: Thank you.

I want to make two comments on the registry because I heard three times already that what appears to be the most important part of the registry is, of course, when it is compared to the historical control, which is true, but that is not the only component of the registry.

A registry is a tool that, as many tools are, has both opportunities and constraints. There are many constraints. A registry will never be, of course, able to replace an RCT, randomized clinical trial. We all know that.

But it seems to me because, of course, there's no randomization, there's no blindings, and we know these are very helpful tools to, you know,

minimize bias, but it seems to me I would also like to say that the newest protocol for the registry for the proposal that is submitted reached our desk just two days ago. So we have not had an opportunity to look into the news modified protocol.

But I wanted to make a couple of comments about the registry. The registry is a tool, as I said, that could be very useful. It's being utilized at the moment at the FDA on several drugs, for example, thalidomide, other drugs which are under restricted distribution programs, and there are registries where they're mandatory, others that are not mandatory. There are registries who are under Subpart H. There are other ones which are not under Subpart H. It's not so simple a situation.

And looking forward to the protocol that his proposal has written, we are going to look for more or less the following components of the registry in general terms, not specifically because it's not time for that.

One would need to specify clearly what

the objectives are, and in this case, of course, the objectives have to be linked to what a disposal letter said when the law was approved.

We need to anticipate the frequency of drug exposure. We need to use, you know, a comparator loop which is relevant.

The sample size to achieve the objective has to be prespecified in the protocol.

In the registry we need to be very clear about the eligibility for enrollment with the patients, the source of information. What is the source of information going to be? The physician, the patient, a parent, and so on?

What information specifically is going to be collected? It's very important to collect data on colonoscopy. What are the data we're going to collect?

What is the information about excluded patients? What did we exclude patients?

What are the methods to assess efficacy and the risk? I'm including an analytical prong. So this should be included, whatever is applicable.

It is also important to mention that it is very good to have an independent monitoring committee examining the data along the way.

Also IRB approval, informed consent.

And finally, what criteria are we going to use to terminate the registry?

So these are the main initial components. There are many other components to the registry.

What I'm trying to say is that maybe, again, the registry may not be able to replace the randomized clinical trial, but it might be able to give us very important information about the efficacy and the safety of the drug.

That's all I had to say about it.

CHAIRPERSON PRZEPIORKA: Thank you.

Dr. Lippman.

DR. LIPPMAN: You know, the discussion that David raised and, you know, I guess Mark commented about what's going on in HNPCC, and then the phenotype suppression study and the SAP studies illustrate what we've learned on most of these

accelerated approvals over the past few days, is that the Subpart H, the Phase 4 commitment, really is done to learn more about the drug in different settings.

You know, what happens in SAP or HNPCC does not negate what happened in FAP. So you learn more about it, and I think that's a good thing, but I mean, we have to rethink what the purpose of the Subpart H because, again, as David mentioned, the actual data on the direct endpoint would not pass this committee as an initial registry. I mean you just have limitations when you're in that setting.

So really the best studies, the most rigorous studies are learning more about the agent in different contexts, earlier disease, nonhereditary, and so on.

CHAIRPERSON PRZEPIORKA: Dr. Pelusi.

DR. PELUSI: Again, we hear more about registries over the last couple of days where that keeps becoming a very common thing, and I think especially when we're looking at the pediatric population and long-term survivors.

Again, we may not know exactly what we're collecting today, but does it at least provide us information in the future that may show some trends or something to go back for and also an easy way to be able to find those patients long term.

And I think, again, really looking very closely at what needs to go in registries and how they can be developed in different populations, and it also speaks strongly -- I think the sponsor did talk to the fact that many of these rare diseases have very active patient groups that are very responsive to participating, and we don't need to forget that at all.

CHAIRPERSON PRZEPIORKA: Yeah, I want to just add to that that through the course of the presentation what struck me the most was the time line and the delays, and none of which were essentially due to the FDA itself.

And I was especially struck by the fact that this is a drug which we hope would be useful in many different indications, and yet development of the pediatric formulation started after accelerated

approval as opposed to much earlier in drug development, as though it were an afterthought and not actually a part of the drug development schema.

So I'm very concerned that in the future if we have drugs go through accelerated approval, I would hope that the sponsors would have pediatric formulation thought about and even pediatric studies started much earlier, especially if they're going to be part of the Phase 4 commitment.

The other thing that I was concerned about was the back-and-forth with the registry. As Jody pointed out, there are already established registries out there, already leaders in this very small field, and if anyone is going to try to overcome the politics in such a small field, one needs to go to big guns, leaders in the field very specifically who have pretty much political control, and that is very difficult. That's extremely difficult especially with an international environment.

And I have to applaud you for doing this in this kind of a group, and I wish you well.

DR. VLOCK: Thank you.

DR. GALLO-=TORRES: Just a brief comment regarding the registry. We have, the FDA has no guidance other than a registry for pregnancies. There are several, you know, being under work.

I do have maybe one question or two toward the sponsor. You are going to utilize registries for other than -- I'm sorry -- you're going to utilize registries other than the United States?

DR. VLOCK: Yes, that's what we're --

DR. GALLO-=TORRES: Would you explain a little bit about what kind of registries are those, what sorts, what countries, and so on, if possible?

DR. VLOCK: Yes. We are in conversations with a few of the registries in Europe at the same time, as well, too. Certainly that was how the pivotal trial was done, as well, too, which was a collaboration between U.S. and U.K. sites.

And so we're going back to those sources, those large, well established registries, and are having active discussions with them as we

speak to utilize their resources both in the U.S. and in Europe.

DR. AVIGAN: I also want to just follow up on the concept of the registry and the issue of getting the detailed information from the registry which will be useful in assessing clinical issues, safety and benefit issues.

There are going to be some details, and some of these details are related to the time line of clinical events in patients who have been exposed to the celecoxib, you know, in terms of what then happened to them.

Do they go for the colonoscopies? Were there lesions found? Did they have surgery? Did they end up breaking through and have kind of that sort of information? Will you be able to garner that on a patient-by-patient basis, you know, from the registry?

And then there are other details, as well, about the registry. The genotype in this disease is somewhat linked to the phenotype. The site of the mutation, the gene actually has a n

impact on how, you know, how many polyps you get and what the exact phenotype is.

So different kindreds can have slightly different complexions without treatment even. So that also has to be taken into account as you build the kind of case of comparison.

And, again, I would be interested in knowing how you're going to link your registry data with the exposure to the drug, the details of that, and then the clinical outcome issue.

DR. VLOCK: Well, again, I think it will be very interesting discussing, you know, in detail the summary that we've submitted of that way. I think the plan on this is that a lot of the information that you're asking for already is in existing registries, and some of them are, you know, almost a century old. The one in the U.K. goes back to, I think, 1914, something like -- it goes back a long way.

So there is data following therapies for a long period of time, and these registries also routinely capture genotypic information on these

patients.

So the challenge for us is to link the drug back in to take advantage of that database and then move forward both, I think, retrospectively because now Celebrex has been around for three years in the U.S., and then prospectively to follow that and link it into what are some very well established and strong databases.

CHAIRPERSON PRZEPIORKA: Dr. Fleming.

DR. FLEMING: Well, I think maybe I'm just reinforcing what a few people have been saying. As I look at this total picture here, what we know is a result from the 001 trial, that there's a 28 percent reduction in the cancer polyps, and yet what's sobering is the realization of what you've indicated, that untreated 100 percent of these patients will progress to colorectal cancer, and it makes me think that if you have documented short-term reductions on the order of 25 percent and 75 percent remain and who knows about longer term.

And if 100 percent untreated will progress, it makes me think that probably we're more

impacting the timing of the occurrence of the colorectal cancer and the level of intervention that could be reduced, surgical intervention that could be reduced, as opposed to whether ultimately we are influencing the occurrence of the colorectal cancer, although that's unknown.

Hence, I would certainly agree with FDA's assessment that much more needs to be understood about clinical benefit, and I think the randomized trial provides a very interesting piece, which is to get at whether or not time to first adenomatous polyp can be delayed, and yet clearly so much more needs to be understood, and that's where this registry is so critical.

I'd love to get it from a randomized trial, but the registry is going to be critical in providing an enhanced sense of long-term use, what the safety is, what the impact is on endoscopic surveillance because that may be, that may be the most fundamental nature of benefit, and then ultimately FAP related events.

So it seems to me when I look at this

global strategy that the registry is a very critical part of getting a clear understanding of benefit and risk, and what it means then is the challenges that the sponsor has laid out to being able to formulate the properly comparable control group, taking into account characteristics and confounding with changes and other support care, et cetera; it's going to be critical that every possible effort be made to achieve this development of a comparable control so that we can get much better clues about the fuller aspect of benefit and risk.

CHAIRPERSON PRZEPIORKA: Dr. Taylor.

DR. TAYLOR: I think a rather concern I would have is with this drug being on the market not just for this indication and this population being very well aware of your data so far, showing it presents. How do we know that they aren't going to be taking over-the-counter drug and confounding the results?

DR. VLOCK: Well, we certainly do try to monitor that, and in the prospective studies that we put together, that is one of the things that we

attempt to control for.

Certainly in registries where we are just observing these events, we cannot control what patients are going to do that way, but we can certainly attempt to collect that data, as well.

CHAIRPERSON PRZEPIORKA: Dr. Lippman.

DR. LIPPMAN: Tom, getting back at your point again of preventing cancer and 100 percent get cancer by 40, you know, as Dr. Lynch mentioned, I mean, it would be great if we could prevent cancer and hopefully we can, but in this population, as I think was presented in the overview, they get colectomies as teens, young teenagers, and so the psychological impact of delaying that procedure to finish school without a colectomy is very important.

And I think we obviously should try to get this from the registry, but I think, Mark, you pointed this out, but that to me is extremely important.

This concept of delay, even if it doesn't completely prevent the need for a colectomy.

CHAIRPERSON PRZEPIORKA: Other questions

for the committee from the FDA or the sponsor?

DR. AVIGAN: Just again on the registry because I think it is so important, I'm just chiming in. We have had experience with administrative database linkages from certain, you know, hooks to medical records in other kinds of study design.

But I'm curious here. You know, when it comes to details about patient events, do these registries allow you or give you medical record information? Do they link to medical record information or do you get just very general sort of kind of a check column, just a couple of things plus or minus?

DR. VLOCK: I think the answer is yes and no to that. These registries, and I'd ask Dr. Lynch to chime in at some point as well, too, were designed for the surgical impact on the disease and were not historically because there was not a medical therapy out looking at those interventions.

I think one of the challenges that we're going to have to face is how to go back to these registries, those patients, and begin to capture

both, you know, prospectively, but even more importantly retrospectively the drugs that they were taking and verify it so that we could add to those questions.

But you're absolutely right, Mark. That's going to be a challenge in terms of doing this, and we're well aware of that.

CHAIRPERSON PRZEPIORKA: Any other questions?

(No response.)

CHAIRPERSON PRZEPIORKA: Hearing none, we'll call this meeting closed and resume our deliberations here at 20 minutes after one o'clock.

(Whereupon, at 12:39 p.m., the meeting was recessed for lunch, to reconvene at 1:20 p.m., the same day.)

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

(1:27 p.m.)

CHAIRPERSON PRZEPIORKA: Okay. Welcome to the afternoon session.

We'll start out by reading of the conflict of interest statement for this particular session.

MS. CLIFFORD: The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude the appearance of conflict.

To determine if any conflict exists, the agency has reviewed the submitted agenda for this meeting and all relevant financial interests reported by the committee participants.

Sarah Taylor, Dr. Sarah Taylor is recused from this portion of the meeting regarding Temodar.

A copy of this waiver statement may be obtained by submitting a written request to the agency's Freedom of Information Office.

We would also like to note that George Ohye is the acting industry representative. Mr. Ohye would like to disclose that he does own stock in the sponsor.

(Laughter.)

MS. CLIFFORD: In the event the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, that participant should exclude himself or herself from such involvement, and the exclusion will be noted for the record.

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

CHAIRPERSON PRZEPIORKA: At this time I understand that we have two people who have registered for the open public hearing late. I'd like to start with Leah Simone.

MS. SIMONE: Hello. Thank you.

Sorry. I'll stand back a little bit.

My name is Leah Simone. I'm a doctoral student at the University of Maryland in the Department of Communication.

One of my professors and I are collaborating with the FDA on a research project that is looking at the perceptions of how the FDA manages conflicts of interest of its advisory committee members.

To that end, I'd like to encourage members of the audience today, if you didn't do so yesterday, to pick up one of the surveys that are stacked up out on the table here right outside the room and just take the 15 minutes to go ahead and complete the survey.

There's a postage paid envelope inside enclosed. You can just put the survey in the envelope and drop it in the mail back to us.

Thank you.

CHAIRPERSON PRZEPIORKA: And just to follow up on those comments, I just want to point out that Mr. Ohye is not a voting member of this committee, but is here as a very welcome consultant,

and he gives us great insight into some of the things that we who sit on this committee are not very well aware of.

So in case there's any questions, I just wanted to make that very clear.

The second person for the open public hearing is Nancy Roach.

MS. ROACH: Hi. That's dangerous.

My name is Nancy Roach. I'm with the Marty Helson Cancer Foundation. We do advocacy in the regulatory arena.

We have no policy against taking money from anyone, but I have no conflicts with anything in this meeting.

(Laughter.)

MS. ROACH: And I feel like we're kind of in the home stretch of a marathon here. So I will be very brief.

The complexity of accelerated approval has been very well illustrated, some might say mind numbingly so, in the last couple of days, and I think we all get the point. And it has been

valuable. I think it shows the need to balance between predictability and flexibility, between certainty and urgency. And that's a tightrope that's very tough to walk in a regulatory environment.

This has also shown the value that you all bring to the table, to bring together experts to pass some judgments and make recommendations on these issues.

I think this has also very clearly demonstrated the value to doing this in a public arena and not just from the perspective of the people in this room, but also for the public because, you know, we get our information from press releases and from popular media, and without the counterbalance of the facts of what's really going on, sometimes our views are somewhat distorted and somewhat prematurely or unnecessarily hopeful.

So I think the public nature of this discussion is critical. I really appreciate everyone on the sponsor's side, the FDA side, and the committee's side for doing this in a

public venue because I know it's hard.

And I urge you to continue the public nature of this discussion.

That's it.

CHAIRPERSON PRZEPIORKA: Thank you very much. Much appreciated.

Any other individuals who want to make a comment? Yes, please identify yourself and your conflict.

DR. L'ITALIEN: Yes. My name is Dr. James L'Italien. I'm with Ligand Pharmaceuticals.

I just wanted to make a correction to the statement this morning that was made that only one company had listed their trials on clinicaltrials.gov. All of our studies are listed there.

So the Phase 4 commitment that we had is also listed on clinicaltrials.gov.

CHAIRPERSON PRZEPIORKA: Thank you.

And we will proceed to the next item of the agenda, but, colleagues from the FDA new to the table, please introduce themselves.

Could you please in to the microphone, please?

DR. COHEN: I'm Martin Cohen, and I'm a Medical Officer.

CHAIRPERSON PRZEPIORKA: Thank you.

The final presentation will be by Dr. Craig Tendler, speaking about NDA 21-029, Temodar, indicated for treatment of refractory anaplastic astrocytoma.

DR. TENDLER: Good afternoon, ODAC, FDA members. My name is Craig Tendler, and I'm here with my Schering colleagues representing the temozolomide clinical development team.

We're also joined today by three colleagues from the Radiation Therapy Oncology Group, or RTOG, with whom we're doing our post approval commitment study. They are Dr. Susan Chang, the PI for this study and Associate Professor of Neurooncology at UCSF; Dr. Chuck Scott, who's Director of Statistics at RTOG; and Brenda Young, who is head of Regulatory Affairs at RTOG.

We're here today to discuss the

accelerated approval of temozolomide for patients with refractory anaplastic astrocytoma, as well as the status of our post approval commitment study.

Specifically, we'll review the Phase 2 study 94-123, which is the basis of the accelerated approval, as well as the key study parameters and the milestones of the post approval commitment study RTOG 98-13.

In addition, we'll discuss some ongoing challenges associated with the conduct of the post approval commitment study and the initiatives that we are taking to expedite completion of the post approval commitment study.

I will conclude with a summary of our temozolomide development program in primary brain cancer.

The original NDA package was intended to support a full approval for temozolomide in recurrent glioma and consisted of three trials: a randomized Phase 2 study, as well as a single arm Phase 2 study in recurrent glioblastoma multiforme, and a single arm Phase 2 study in recurrent

anaplastic astrocytoma.

The recurrent GBM package was not considered adequate for approval, but the agency agreed to consider the study and recurrent AA as a basis for accelerated approval.

Temozolomide was granted accelerated approval in August '99 as shown on this slide for adult patients with refractory anaplastic astrocytoma, that is, for patients who at first relapse have experienced disease progression on a regimen containing both nitrosourea and procarbazine.

The basis for the accelerated approval of temozolomide for refractory anaplastic astrocytoma was a large, single arm study conducted in 162 adult patients at first relapse. The study was conducted in 32 centers worldwide and took about three years to complete.

This represents the largest study ever completed in relapsed anaplastic astrocytoma, and with an intensive effort in this recurrent patient population with a shorter time to disease

progression than in newly diagnosed patients, this study still took about three years to complete.

And I think that just gives some pause and gives you some idea of the challenges when conducting studies in this patient population.

The primary endpoint of the study was progression free survival at six months as assessed by gadolinium-enhanced MRI, and there was independent central review of objective tumor assessments.

Secondary endpoints included objective response rate and overall survival. The study was designed to rule out a lower boundary of the 95 percent confidence interval for the six month progression free survival rate for temozolomide of ten percent, assuming the actual six month progression free survival rate for temozolomide in this setting would be 20 percent.

The lower boundary of ten percent was considered minimal evidence of anti-tumor activity.

Summarized on this slide are the overall efficacy results of the study as reviewed and

confirmed by FDA. For the intent to treat population, the progression free survival rate at six months was 51 percent, with a lower boundary of 43 percent, which is well above the prespecified objective of ten percent that was stated in the protocol.

The median survival was 13.6 months, and the overall response rate was 33 percent, which as I mentioned previously was independently confirmed by central review as well as by FDA.

In this single arm study, the FDA felt that tumor progression was not a reliable enough endpoint on which to base approval. However, FDA reviewers identified a subpopulation of chemotherapy refractory patients, namely, those who had progressed on nitrosourea and procarbazine containing regimens for whom there is no available therapy and which there was compelling evidence of the anti-tumor activity.

On this slide, you see the 54 patients that were identified to meet that criteria of having been refractory to procarbazine plus nitrosourea.

In this heavily pretreated population, the objective response rate was 22 percent with a nine percent complete response rate. The median duration of response was 50 weeks, and for those achieving a complete response, the median duration of response ranged from at least one year to some patients having a response duration of up to two years. The median survival for the entire refractory population was 16 months, almost 16 months.

Recognizing the limitations of historical comparisons, this is nevertheless better than similar studies reported in the literature.

The safety database which supported the accelerated approval for temozolomide consisted of 1,017 temozolomide treated patients, of which 400 were relapsed glioma patients from three clinical trials. Temozolomide was administered with few dose modifications. Most of the adverse events reported were of mild to moderate severity.

Study treatment discontinuation due to adverse events was infrequent, and Grade 3 or 4 myeolosuppression was also quite infrequent and

noncumulative.

This is all very much consistent with the overall safety profile of temozolomide since approval. That is, temozolomide is a safe oral chemotherapy agent with a convenient dosing schedule with which the vast majority of treated patients do not experience bothersome side effects.

ODAC agreed that the subpopulation of relapsed anaplastic astrocytoma patients who were enrolled in this study after failing procarbazine and nitrosourea would not be expected to respond to other therapies. In essence, they agreed that this constituted the setting of unmet medical need.

ODAC also agreed that objective response in this patient population could be an adequate surrogate for clinical benefit, as long as it was well defined and of sufficient magnitude to overcome background noise.

With agreement that the criteria for accelerated approval had been met, the committee was then asked if the submitted Phase 2 study demonstrated that temozolomide is effective for the

treatment of relapsed anaplastic astrocytoma patients who had failed prior nitrosourea and procarbazine.

They answered unanimously yes and also agreed that the safety of temozolomide was acceptable for this indication.

Now I'd like to turn to our post approval commitment. Independent of considerations for post approval, beginning in 1998, we had initiated discussions with RTOG for developing a protocol concept for a Phase 3 study of radiotherapy plus temozolomide in newly diagnosed anaplastic astrocytoma patients.

The proposed design of the study as agreed to by Schering and FDA was a three arm randomized trial comparing radiotherapy plus temozolomide, radiotherapy plus BCNU, and radiation plus the combination of BCNU-temozolomide in first line anaplastic astrocytoma patients with a primary endpoint of overall survival.

At the time, there was a strong scientific rationale for evaluating the

temozolomide-BCNU combination based on the fact that temozolomide has been shown to lower levels of alkylguanine alkyltransferase, potentially sensitizing the cells to BCNU.

When it was clear that Schering would be conducting this as a post approval commitment study, we recognized the need to collaborate with RTOG to provide the broadest access to study participation rather than setting up our own competing trial in this rare indication.

The FDA agreed that the proposed design of the RTOG Phase 3 trial would provide evidence of clinical benefit for temozolomide, and as such, represented an adequate confirmatory study consistent with the post approval commitment guidelines.

However, the agency requested that the Phase 3 portion of the three arm study be preceded by additional safety assessment of the temozolomide-BCNU combination in the proposed study population.

The target completion date was June 2001 for that commitment, and the safety data were

submitted in July 2001.

While not directly related to the post approval commitment, we also conducted Phase 1 and Phase 2 studies of temozolomide in children with recurrent brain tumor in collaboration with the Children's Oncology Group and the U.K. Children's Cancer Study Group.

The clinical study reports were submitted in September 2002.

Finally, Schering and FDA agreed to the submission of a final study report from the ongoing Phase 3 portion of the post approval commitment Study 98-13 and first line anaplastic astrocytoma with a deadline of June 2007.

Now I'd like to take you through the actual timing of some of the key post approval commitment study events from submission of the first protocol to FDA in June '99 to the current date.

The draft protocol, as I mentioned before, was first submitted to FDA in June '99. Accelerated approval had been granted in August '99, and a revised protocol incorporating FDA comments

was resubmitted to the agency in October of '99.

In December '99, FDA indicated, again, as I mentioned, that additional safety data would be needed on the combination, and that would have to be provided before the Phase 3 portion of the study could be initiated.

Final agreement on the design of the Phase 1 safety assessment was reached in February 2000, and the RTOG filed the IND for the study in April 2000.

The Phase 1 safety assessment of the temozolomide-BCNU combination commenced in June 2000. Completion of enrollment occurred nine months later with the submission of the safety data to FDA in July 2001.

After the initial assessment of safety of the temozolomide-BCNU was completed and deemed unacceptable due to the dose limiting myelosuppression and pulmonary toxicity, there was still a great deal of scientific interest of exploring and defining a combination of temozolomide-BCNU that would be tolerable and could

potentially offer benefit to patients.

And thus a second cohort utilizing a less intensive BCNU regimen was evaluated by the RTOG beginning in 2001.

The completion of that second safety enrollment occurred in January 2002, but unfortunately toxicity again was unacceptable, and the combination arm of the Phase 3 study was dropped in June 2002.

We've now recently initiated the Phase 3 portion of the trial beginning this year. With the additional safety assessments completed, the Phase 3 portion of the program, which is now focused on comparing radiotherapy plus temozolomide versus radiotherapy plus BCNU, has recently been initiated. There are now 11 patients enrolled in the Phase 3 portion, and when all sites are open, the anticipated enrollment will be 24 patients per month for a total of 4654 patients.

Despite the aggressive enrollment rate, study completion time lines are primarily driven by a long duration of follow-up, which is needed for

events given the anticipated median survival of 36 months in the control arm and the protocol specified objective of improving survival by 50 percent in the temozolomide group.

Accordingly, we've turned to the intragroup structure where participation in the Phase 3 portion of the post approval commitment study is available to a wide group of radiation and medical oncologists across the United States with the study ultimately to be open in more than 300 sites.

The Phase 3 portion, the protocol calls for a number of interim analyses to be conducted when 63, 126, 188, and finally 251 events have occurred. Summarized on this slide are the projected years when these protocol specified interim analyses will occur, as well as the survival hazard ratio which would be needed in each of these interim analyses to cross the boundary.

As you can see, while the final analysis, based on 251 events is projected for 2007, there are at least two chances before that date of

achieving the target hazard ratio prior to that commitment date.

So what do we see as the ongoing logistical challenges ahead of us for completing this important Phase 3 trial in newly diagnosed patients with anaplastic astrocytoma in a timely manner?

First, as other sponsors have said today and yesterday, we're dealing with a disease with a low and declining incidence. In fact, only 3,000 patients, approximately 3,000 new cases of anaplastic astrocytoma in the United States are diagnosed each year.

Secondly, the median survival of our targeted study population is in the range of three to four years, thus requiring a rather long duration of follow-up for the specified number of events, in this case deaths, to occur.

How are we dealing with those challenges? Well, in collaboration with RTOG, we're taking a number of initiatives to expedite completion of the project. We have specifically

focused on enhancing awareness of the study among both the investigators, as well as the patients.

Specifically, we have scheduled investigator meetings, the first of which is planned for ASCO, and a developing communication plan to target neurosurgeons for timely referral into the study.

In addition, we're conducting monthly teleconferences with the lead investigators from each of the participating cooperative groups.

For patients, an Internet listing is being planned, and patient brochures are also in development and will be available for distribution by the end of this month.

Importantly, the main brain tumor advocacy groups have been contacted and are highlighting the importance of patient participation in this study.

Also, project management support has been given to RTOG for dedicated staff to facilitate the conduct of this study, as well as additional support for the individual sites for enhanced data

management support.

Finally, international sites are being considered outside of North America for participation within the RTOG study. While it has taken somewhat longer than anticipated to complete the initial safety portion of the Phase 3 post approval commitment study and with the challenges of conducting a large randomized trial in a patient population that is dwindling, relatively rare, with a long survival follow-up notwithstanding, we believe that the timely completion of this study, this high priority temozolomide study in newly diagnosed AA, is still very much achievable.

I'd like to conclude by sharing with you another ongoing, large, randomized trial that we are supporting in collaboration with the EORTC and the NCIC for newly diagnosed GBM patients.

Here the trial is comparing temozolomide plus radiotherapy versus radiation alone in newly diagnosed GBM. Enrollment of 573 patients was completed about a year ago, with a final analysis scheduled for later this year. The primary endpoint

is overall survival.

Similar to a post approval commitment study with RTOG, this study may also be adequately designed to confirm the clinical benefit first seen in the Phase 2 study in refractory anaplastic astrocytoma, and we have initiated discussions with FDA in terms of whether this study could be used to satisfy the post approval commitment.

Finally, beyond the Phase 3 trials in newly diagnosed anaplastic astrocytoma and newly diagnosed glioblastoma multiforme, we are conducting a Phase 2 study with RTOG in anaplastic oligodendroglioma, and are planning to initiate a large, randomized trial in low grade glioma later this year.

In summary, we continue to pursue a broad clinical development program of temozolomide in primary brain cancers to explore the potential benefit of temozolomide in these related indications.

Thank you very much.

CHAIRPERSON PRZEPIORKA: Dr. Cohen, do

you have a comment?

DR. COHEN: Well --

CHAIRPERSON PRZEPIORKA: Could you speak into the microphone, please?

DR. COHEN: Yeah. Well, I think that De. Tendler has given a balanced and rather comprehensive overview of the temozolomide development program and interaction with FDA. There are a couple of issues though that we could talk about.

One was the amount of time that we spent in doing the Phase 1 evaluation and the combination of temozolomide and BCNU. I think in our conversations with the sponsor, we had suggested that this might be done in all brain tumor patients, that glioblastoma multiforme patients could have participated in that, and that would probably have increased the rapidity with which the study finally was initiated.

And the other question I would have is when were all of these initiatives to increase accrual started. Were they started relatively

recently or have they been ongoing for several years?

DR. TENDLER: I'll take the second question first. In terms of the initiatives, most of these were started when the Phase 3 portion was initiated this year. In terms of the Phase 1 portion, typically these are not done as multi-center studies, and these initiatives would not really be worthwhile.

But I'd like to ask Dr. Susan Chang to address your question about the conduct of the Phase 1 study, restricting it to newly diagnosed anaplastic astrocytoma patients instead of opening it up to a more wide brain tumor patient population.

DR. CHANG: Thank you.

For purposes of disclosure, I do have clinical research support from Schering. I just wanted to disclose that.

We felt, I think, that for this population of patient, looking at the combination of BCNU and temozolomide specifically in anaplastic astrocytoma with radiation therapy would be very

important.

There were Phase 1 studies done in recurrent glioblastoma patients, but again confining it with the radiation therapy in this relatively younger cohort of patients versus the older patients with glioblastoma, which is where the population of patients tend to be.

We thought that would be more reflective of the patterns that we would be able to see subsequently if we were trying to initiate a randomized Phase 3 trial with large numbers of patients.

CHAIRPERSON PRZEPIORKA: Questions from the committee?

I do have one question. Whose idea was it to actually use the double combination of temozolomide and BCNU? Did that come from the company or from RTOG?

DR. TENDLER: Susan, do you want to?

DR. CHANG: This was as a result of investigations through one of the North American brain tumor consortium groups, one of the brain

tumor consortiums funded by the NCI. So we have actually done, as I have mentioned, a Phase 1 study of the of the combination.

BCNU and nitrosourea have been the only drug that's been approved for patients with malignant glioma, and the difficulties with this agent is the level of drug resistance in this population of patients.

And the hope was that with a combination of temozolomide, which on its own has shown activity in malignant glioma, that the combination could be synergistic and perhaps be more efficacious for the patient population.

So that was something that was scientifically driven, I think, through the CTAP and NCI, as well as the RTOG. It was a combination.

CHAIRPERSON PRZEPIORKA: I like the idea. I like the scientific idea, but I have to point out that that may have made a major stumbling block in drug development since it did not address the question or add to the question of whether or not this drug was effective in this setting, but

certainly set the development plan back some time.

Dr. Cheson.

DR. TENDLER: It was always going to be included. If the combination was defined to be tolerable, it would have been included as a third arm in the randomized study. So we were still going to have the comparison of radiotherapy plus temozolomide versus radiotherapy plus BCNU, which at the time and still is considered the standard of care for these patients.

CHAIRPERSON PRZEPIORKA: Dr. Cheson.

DR. CHESON: A simple question. Are you doing a quality of life analyses in your randomized studies?

DR. TENDLER: We had a formal quality of life integrated into the protocol. The current RTOG trial that's not looking at formal quality of life, we are looking at the mini mental status, I believe, as well as changes in Karnofsky performance status, but not formal quality of life studies.

CHAIRPERSON PRZEPIORKA: Dr. Kelsen.

DR. KELSEN: The original design was to

include the combination of BCNU and temozolomide plus radiation, and then a question was raised as to the desire to get Phase 1 data before the study started. Do I have the time line correct?

DR. TENDLER: Yes. There had been a previous Phase 1 study looking at temozolomide-BCNU combination back with CTAP. I think it was beginning in '94-'95, but that was not with radiotherapy, and the feeling was that that would not be sufficiently predictive of the safety profile in this patient population.

So the request was made specifically, and actually was by RTOG and FDA to go ahead and do a Phase 1 component before adding this third arm of the combination into the pivotal trial.

DR. KELSEN: I was actually getting as to where the request to do that study came from, and you've answered that question.

In retrospect, it certainly is very, very prudent to do that.

CHAIRPERSON PRZEPIORKA: Dr. Martino.

DR. MARTINO: Actually just to follow up

to that question, what was the actual toxicity that made the combination impossible?

DR. TENDLER: In the first cohort, it was mainly infections, and I believe 50 percent of the patients needed dose reductions by the second cycle, and the second one was, again, myelosuppression and pulmonary toxicity.

CHAIRPERSON PRZEPIORKA: Dr. George.

DR. GEORGE: I have a question about the pool on the study. Is there a history on which this projected enrollment is based or is this based on people's estimate?

DR. TENDLER: Actually I'm going to let Dr. Chuck Scott from the Operations Group address that question.

DR. SCOTT: The RTOG had conducted a predecessor trial in our group alone where we accrued 12 patients a month, and our feeling was that by expanding this to the inner group process and with the initiatives that have been put in place to enhance accrual, that we should be able to by June get up to 24 patients a month.

CHAIRPERSON PRZEPIORKA: Dr. Blayney?

DR. BLAYNEY: Yes. May question to the FDA talks about -- I wasn't, I don't think, a member of the ODAC Committee at the time. It looks to me like this was a post hoc analysis of a subset that looked like there might be some benefit.

Does the sponsor's commit -- and in the spirit of the Subpart H regulations, does the sponsor's commitment to look at the GBM, which was the glioblastoma multiforme group which was originally what they studied, would that satisfy their post marketing Phase 4 commitment?

DR. COHEN: Well, as DR. Tendler represented the study results, the trials in GBM were negative. The data from the anaplastic astrocytoma patients who were refractory to BCNU and procarbazine did show five long duration complete responses, a minimum duration of one year for those responses.

And on the basis of that long duration complete response data, ODAC voted unanimously to approve treatment for anaplastic astrocytoma, but

not for GBM.

So that the sponsor's subsequent development plan for anaplastic astrocytoma seems reasonable.

DR. TENDLER: Can I just clarify that though? The survival endpoint was not met, but the primary endpoint, which was progression free survival at six months, there was a statistical significant improvement.

However, there was concerns about the suitability of the endpoint to support an approval for GBM based on those results and that endpoint.

DR. WILLIAMS: I think your question was if the Phase 4 study is in a somewhat different disease, is that close enough. I'm not sure that we've made a determination, but I would think it might be somewhat academic. I mean, it could lead to full approval in that indication and then have the discussion about whether or not that's enough information, and I'm not sure that we've had that discussion.

CHAIRPERSON PRZEPIORKA: Dr. Temple.

DR. TEMPLE: Well, once again, I think the theory of this always is that you think you've proved the principle. You've learned something about what responses with this drug mean, and you know, we'd probably come before the committee to find out whether you'd buy that, but I think that's the idea.

But if the response rate is very low -- I know I said this yesterday -- it's not going to be easy to move the survival curve for the whole population.

So it's often easier to do that in a less advanced form of disease.

CHAIRPERSON PRZEPIORKA: Others? Ms. Mayer.

MS. MAYER: A question for the sponsor. What will be the impact of the availability of this drug on the market on your ability to accrue for the commitment trial?

DR. TENDLER: Right now we're told from the experts that we're working with that the standard of care for newly diagnosed patients with

anaplastic astrocytoma is radiotherapy plus BCNU.

Obviously with the data, more and more data being generated with temozolomide, there is a concern that some patients may go right to temozolomide without participating in the trial and without the data coming out from this randomized Phase 3 trial.

But I think for now, after discussing this with our RTOG consultants as well as other investigators in the field, they believe that it's ethical and important to give informed consent and enroll patients on this trial, and they do not feel at least up front in enrolling these patients that that will be a major hurdle.

Obviously that remains to be seen over the next year or two.

CHAIRPERSON PRZEPIORKA: Other comments?

DR. MARTINO: Can I ask you to address the three questions?

If you chose not to, we have no one to address this. I will take it upon myself and ask if anybody else has anything, to chime in.

Has accrual to the ongoing trial been satisfactory?

And I would say, yes, it has been satisfactory in terms of accrual, though we are concerned about the need to stop and do a Phase 1 study for an arm that really does not answer the question that was asked.

However, it looks like accrual is back on track for the right study.

Have circumstances impeded the ability to conduct the trial or should alternatives be considered?

And I think the question was raised regarding the other Phase 3 trial as first line therapy being a suitable alternative should this one be negative, albeit in a different indication.

Any other comments or questions?

(No response.)

CHAIRPERSON PRZEPIORKA: Hearing none, any questions from the -- yes, Dr. Fleming.

DR. FLEMING: Just additional thoughts. Rick you had said yesterday when we were talking

about what strength of evidence might be expected and should we anticipate that we would be targeting comparable strength of evidence to establish clinical efficacy when it's achieved in an post accelerated approval setting, in a non-accelerated approval setting.

It appeared, if I caught it, that your trial I'm delighted to see is targeting survival, but it looked as though you were dealing with a one sided .05. The tradition for standard of strength of evidence, we use a two sided .05, but of course, what we all know that that means is a two and a half percent false positive error rate, which is a one sided .025.

Was that a misprint or was that --

DR. TENDLER: No, that's correct. That's per RTOG procedures. Maybe you'd like to comment on that, Chuck.

DR. SCOTT: Yeah. We've had several discussions with NCI about the design of our Phase 3 trials in brain tumors, and it has really come down to the idea that what we're trying to do is have an

interest only in the one sided hypothesis.

And so this trial was designed in concert with their sponsorship as well. So we have this study designed and it's not as a one sided trial.

DR. FLEMING: And that's really not getting at the issue because we're traditionally one sided. Basically I realize we're not going to approve an agent when we have a two sided .05 that's in the wrong direction.

My interest is in making sure -- all of our interest, i think -- are in making sure that if we conclude there's benefit, that we're reasonably confident that there is, and in essence, we're always doing a one sided .025.

So it would be in this case a situation that not only would we be relying on a single trial, but we'd be relying on a single trial with twice the false positive error rate if we weren't, in fact, looking at the traditional one sided .025 or two sided .05.

Bob, it looked like you had something

related to say.

DR. TEMPLE: Well, we've always said exactly what you said. We don't care if you think of it as one sided or two sided as long as there's one chance in 40 of making an error.

DR. FLEMING: Right.

(Laughter.)

DR. TEMPLE: But we -- and I don't know if this applies here. Other people will have a better feel than I would -- we do sometimes exercise priors and think of things in those terms, and there are even a couple of one sided .05 approvals.

Nifedipin for vasospastic angina was approved based on a one sided test, although I'm not sure I could defend it. So it's not that we would always say it absolutely has to be this way, but there would need to be a reason for dropping down from the usual standard.

DR. FLEMING: Yeah.

DR. TEMPLE: I'd say just doing it without explanation would be funny, but there could

be other information that might make you want to do that. That would be something everybody would have to talk about.

DR. FLEMING: Indeed, we talked about this not only here, but across all Advisory Committees on multiple occasions saying: what is an acceptable strength of evidence? And is survival a particularly compelling endpoint for which you might accept somewhat less strength of evidence, i.e., one really good study with a compelling result?

I think that's the terminology I've often heard, and I would understand if it's an extremely safe intervention and there are other very strong favorable factors in terms of symptoms, surely that's all true. But in general, when we're designing a trial, in the absence of knowing all of those other things, it's my understanding we're still saying strength of evidence for concluding survival benefit would be at least an .025 false positive.

And this issue of, gee, we're going in the right direction here is totally irrelevant to

this.

DR. TEMPLE: Especially when you're talking about a single trial. I mean usually we say -- again, everything is subject to discussion -- usually we say when you're relying on a single trial you ought to be more robust than usual, not less.

DR. FLEMING: Another question, but, Rick, did you want to comment on this issue before -- okay.

I'm pleased to see that there is interim monitoring here because certainly with the survival endpoint, in particular, there are ethical considerations to insure we're safeguarding patient interest beyond the important efficiency factors that we can achieve by arriving at earlier conclusions if the initial results are extreme, either extremely positive or extremely negative.

My reservation here is the suggestion that the data monitoring committee is going to be blinded or given blinded data, and as the FDA guidance document indicates, particularly with the survival endpoint, it's very important that this

monitoring occur.

It's also very important that it occur in an unblinded manner by the DSMB, who would be then using these proper monitoring guidelines.

CHAIRPERSON PRZEPIORKA: Other comments, questions from the sponsor or from FDA for the committee?

Dr. Martino.

DR. MARTINO: Question not quite related to the data that you've provided. There is use of this agent in patients with metastatic disease to brain. Can you comment on what the company is doing relative to that set of circumstances?

DR. TENDLER: Yes. We actually are just planning to launch a Phase 3 randomized trial in patients with non-small cell lung cancer and brain metastases, comparing the combination of radiotherapy, whole brain radiotherapy alone versus temozolomide plus whole brain radiotherapy. That should start in the next three months.

DR. MARTINO: The doses will be the same as you're using here or you're using a different

schedule?

DR. TENDLER: The schedule is a little different because that's given concurrently with radiotherapy for a two week portion, and then an extra week is given, and then the patients are allowed to go on to whatever standard of care is used in second line non-small cell lunch cancer.

So it's a little different than the dosing here, which is on the five day schedule.

CHAIRPERSON PRZEPIORKA: Dr. Pelusi.

DR. PELUSI: I would just like to comment that I really like seeing the fact that you're really done some intervention here to try to recruit patients from their own medians in terms of their groups, as well as developing a patient brochure and using the Internet.

I would hope, too, though that Dr. Kelsen's information about quality of life is taken into consideration because, again, that becomes a huge issue for patients, and it's their way to participate as well.

CHAIRPERSON PRZEPIORKA: Other

questions? Dr. Pazdur.

DR. PAZDUR: I just wonder if the committee has kind of an ankle untied here. I am personally very unhappy, okay, and I want to just bring this out.

We have a drug here that was approved in 1999. Okay? And we're first getting started with confirmatory trial in 2003, okay, trying to increase enrollment here. And I think it points out some real big problems.

First of all, in my initial introductions I think I made it quite clear we've got to start thinking of development plans here, okay, not just let's take a step-by-step, very narrow approach to drug development.

How could we have improved this picture here? Should they have, for example, done earlier combination trials?

Whose responsibility is it to get this Phase 3 trial done? It certainly isn't RTOG's. It's the company's responsibility, and if there is problems with the RTOG, maybe they need to step in.

It's their responsibility.

And I really want to send that message to you, Craig. I had this conversation with you over the phone, and I want to make it a public record.

It is the responsibility of the company, not RTOG. It is the responsibility to have a statistical plan that would fit FDA's standards, not what would be acceptable to the RTOG because that's what RTOG has always done, and therefore, we're going to be looking at this.

You have a drug out there, and maybe this is a good foray into, you know, our discussion. You have a drug out there. The company obviously is making a profit off this drug. There is a real drug out here. It's not a drug that -- it may be a drug. What should the commitment of the company be as far as multiple studies going on?

Tom, you asked about what is the level of proof that one would need. Well, you know, we have always insisted that sponsors should do two trials, you know. It says well conducted, well

controlled trials. The plurality gives us that option.

And one of the questions I'd like to pose to the committee as we segue into a more general discussion: should multiple trials rather than only one trial be done for many reasons?

Number one, one may fail just by chance. There may be methodological problems. You've seen many problems here with accrual. Okay?

And I fully understand sometimes where companies when they're not sure if the drug is going to get approved, where they have to be careful as far as expenditures for a given trial.

But here we have a known drug. There should be a willingness to invest in this drug and make sure the American public knows the benefit of this drug and makes Phase 4 commitments.

So although the committee has focused on many plans or many comments here, I'd just like to emphasize that I think there are a lot of lessons that can be learned from this experience, and we should not be happy with the fact that, you know,

this drug was approved in 1999, and, yes, there were problems along the way, but how could we have addressed those problems?

Because it truly is unacceptable that we're now just beginning a trial and accrual is poor, and now they're making attempts to improve this. What were other alternatives?

For example, your EORTC study? I was very unhappy to learn that that was not being done under an IND. If you planned on submitting that obviously to the FDA, we should have seen that study. It was not submitted under an IND, and I would especially want to publicly criticize you for not doing that. I think it really should have been because you have not met your Phase 4 commitments, and that could be a potential Phase 4 commitment.

Thank you.

DR. TENDLER: Can I response?

DR. PAZDUR: Yes, by all means.

DR. TENDLER: I think your comments are all fair, and we stand behind the commitment. We have not shirked this responsibility to RTOG. I

think we learned in hindsight a lesson about trying to conduct a Phase 1 study as part of a Phase 3 protocol, and the inherent difficulties in doing that; a reluctance to put newly diagnosed patients on a Phase 1 study which is totally understandable.

So, yes, I think everything you said after the first safety assessment was conducted, maybe we could have done more to push the fact there and say we cannot define a combination with BCNU and temozolomide, and let's proceed to the Phase 3.

But there was tremendous scientific interest, and I'm not, you know, saying that in a minimal kind of way. There really was a lot of interest to try to find a combination that was going to be tolerated to hopefully benefit patients with the combination.

The other aspects about starting studies when commitments are granted, just again for the chronology, for the accuracy of the chronology, we did not file originally for accelerated approval. We were seeking full approval. At that time, you know, we learned that the progression free survival

endpoint would not be in the GBM, and the randomized GBM study would not be acceptable for full approval and actually was working with FDA, which we worked to identify a patient population that was refractory that could be the basis of an accelerated approval.

But both discussions with EORTC and RTOG started before the accelerated approval was granted for the refractory anaplastic astrocytoma indication.

So you know, with what you've said we do take those comments seriously. We did, in fact, start discussions. We had every intention and continue to support Phase 3 trials in front line patient populations, and now we're doing everything possible to make sure the enrollment is completed and the study is completed as per the originally agreed upon commitment deadline, which was June 2007.

CHAIRPERSON PRZEPIORKA: Dr. Martino.

DR. MARTINO: The group in front of us right now is not the group that I mean to focus on. I mean this to be a general comment, but there's a

recurrent theme that has struck me over the past couple of days, which is that an accelerated approval has been given to a drug. That then allows the drug to be marketed.

It then allows physicians to not only use it for the indicated purpose, but for other things as they deem fair and appropriate.

Therefore, the marketplace has access to this drug. Therefore, the sponsor has dollars that come from this marketplace use, which is more and more generalized as more and more time has to pass.

Therefore, if I were a company, I'm not sure that I would have the same due diligence, as we like to call it, towards getting some of these studies done as I would if, in fact, I were going for full approval.

So the very existence of this type of an accelerated approval creates a circumstance, and even though I suspect that people mean well, but there are certain realities in their lives as well, which is that you've given them an approval, and you're sort of paying a price for the fact that you

gave an approval with a modest degree of information to support it.

And I really think that I don't know how to solve that problem, but I see that as the inherent problem to all of us.

CHAIRPERSON PRZEPIORKA: Can I ask? I've heard a number of sponsors say that they have a commitment to do XYZ study by a certain period of time, which I think is part of your written Phase 4 commitment. Would you be willing to pull the indication if they did not complete their study within the written period of time, almost as it is a contract?

DR. PAZDUR: I think we really have to discuss that. I think I'm not going to answer a yes or a no question here. That certainly is a possibility. Here again I think we've addressed this. It really depends on other information that is available. This is only one part of the life of a drug, so to speak. There are other studies that could be being done.

The whole purpose of bringing this to

this forum is to highlight this issue, but it is obviously something that we want to give more emphasis to at this time.

DR. TEMPLE: But, I mean, the rules are clear. We can take that into account and act against the drug. As Rick said, that's a complicated decision whether to do that.

CHAIRPERSON PRZEPIORKA: Mr. Ohye.

MR. OHYE: I think all sponsors are very jealous of their reputation, and I haven't seen any example of any sponsor failing to exercise due diligence in terms of their requirements because they're going to be dealing with FDA not just for this drug, but for many other drugs, and so they're going to be very diligent and carry out all of their responsibilities, you know, to the fullest.

And I can tell you I'm very concerned about this because I've been in this business now retired five years, but I've been in this business over 30 years, and I know that Dr. Temple has a long memory.

(Laughter.)

CHAIRPERSON PRZEPIORKA: Dr. Cheson.

DR. CHESON: It seems like we're seguing into the discussion. Is that okay?

CHAIRPERSON PRZEPIORKA: Yeah. If you would like to take a seat, that would be great.

DR. CHESON: Yeah. First of all, and very importantly, I would like to thank Dr. Pazdur and his colleagues for having this meeting because I think everybody has learned a lot. It has brought an extraordinary number of important issues into public forum, and it has been a very thoughtful and provocative session, and I'd like to thank my colleagues for their active participation, which I think was the best ODAC meeting that I've certainly attended.

And I'm sure that this will lead to some open and maybe not so open planning and thinking, but I'm sure in a very constructive direction.

One thing that a lot of my colleagues have learned, and I've been in this business longer than some, is what accelerated approval means, and now the definition, although we don't like the term

very much, has become real to some of them and some of us, there is a risk here of the pendulum swinging.

There will be, I think, a little more vigilance in the decision making by the members of the committee who are present today, and maybe a little more reluctance to approve certain drugs on some of the meager evidence which they're being presented.

Because we're faced with a number of potential scenarios, and I'd just elicit a few, and I'm sure you can come up with a lot more.

First there will be the slam-dunkers, those accelerated drugs which kind of zip through and have a wonder Phase 3 with no problem whatsoever.

And then there are the ones that are just never going to happen. There are those where the accelerated approval is followed by a study which is negative, and that may be in the same indication or a different indication. What do you do with that?

Then there is the problematic one where the accelerated approval is preceded by negative studies, large negative studies, which can be exceptionally problematic, not that that would ever happen, of course, right?

(Laughter.)

DR. CHESON: And there are others I can't read without my glasses on. You know, the confirmatory, and what happens where you have one instance here where the confirmatory trial may be negative, but in a different indication? We ran that this morning.

I think when the companies address the development and design of their confirmatory trials, which should be before, you know, we agree with the developmental concept here, it's not only due diligence, but it has to be due realism.

And we've seen a series of mistakes that could have been easily predicted. We all know that when a drug gets out there, the likelihood that a patient is going to go on a trial is greatly diminished.

And I think waiting until the problems arise and then trying to fix them is going to delay the process a lot more than anticipating the problems and trying to be proactive in preventing them or seeing other options, not just going to a group, not just going to a bunch of investigator, but realizing -- and I think it should be really hammered home after this meeting -- that this is a real problem.

And either the process has to change or the way the companies approach the process has to change, and I think a little bit of both has to happen.

And I would -- I don't want to talk here forever, but I think when you make your decisions on the scenarios that I came up with, as well as others that I'm sure my colleagues will come up with, I would hope that the committee would be involved in some of the decisions about what you can do because I know some of these will be very difficult decisions.

It's hard to yank a drug. There are a

lot of political and emotional ramifications, as you eloquently described. But I think this committee would really appreciate the opportunity to participate in some of these decisions, and it would serve as an excellent sounding board for some of the very difficult decisions you're going to have to make.

Because they're going to be very different with every drug and every scenario, but a lot of the problems come from the company not being thoughtful enough in their developmental strategies, and I would encourage the companies to learn from this meeting as we have learned from this meeting that the problems are there and think about them ahead of time instead of trying to clean up the mess and taking ten years, 12 years to get a drug through the system and run the risk of getting it yanked, which I think at some point some of these probably should be because, you know, they're not fulfilling the obligations.

And I'll be quiet. I promise. But, again, thank you for this opportunity.

CHAIRPERSON PRZEPIORKA: Just to summarize the last couple of days, what I've come to learn over the past actually couple of years is the idealized drug development plan starts with the preclinical studies, the production information, the pharmacokinetic studies, and at the time Phase 1 is completed, hopefully the pediatric studies and development of any assays for eligibility or endpoints after they get started.

Their Phase 2 studies are conducted, and once there is some idea that there may be some activity, we would hope that the sponsors would have a plan for expanded access, as well as some investigator initiated studies in the same or other diseases to look for the optimum dosing, followed by the Phase 3 studies, and wherever accelerated approval happens to fall out, either after Phase 2 or Phase 3, the confirmatory trials.

And that's the idealized setting, with the optimal being when the sponsor hits this room the Phase 3 study is underway, and we're actually looking at accelerated approval on the basis of a

surrogate, and the confirmatory trial may just be let's wait and see what survival is on that very same study.

The problems that we have seen here in getting those trials through after accelerated approval has been an issue of drug production, which had to deal with getting the company back up to speed on GMP, starting the pediatric drug development way too late, having too few patients and a very small cohort of eligibility to actually complete a Phase 3 study in a timely fashion, having two complex designs, adding arms for scientific indications rather than actually to address the question at hand.

Excessive toxicity which really led us to think twice about whether the drug should have been let out for accelerated approval in the absence of a true response that we could really take to market.

Competition with the drug on the market, leading to reduction in accrual or even other competing trials.

And the worst of all is having a design with the placebo arm which I think in the 21st

Century most of us would not find very acceptable at this point in time.

And from all of these as far as I can tell, I think you're correct, Dr. Cheson. The vast majority will require change in the mindset of industry.

The urgency burden to get this through is on the industry, not on the FDA, not on the public, not on the investigators. It's on industry.

In fact, there is only one issue here that I could actually say that FDA may have, potentially, possibly have some input in, and that was to stop the design of adding the double drug trial from the last sponsor in saying this is not relevant to the question, you know. Get on with your original plan of looking at the two arms themselves.

And having said that, I wanted to see if there are any other questions. Actually there was one other one.

We had talked earlier that if the confirmatory trials come back negative, this committee would probably support yanking the indication, but as was pointed out, sometimes there are ongoing randomized trials ahead of time either by the sponsor or by others.

Dr. Pazdur, would you ever foresee such a circumstance? And how would that information get to this committee when they were deliberating a presentation or a drug for accelerated approval?

DR. PAZDUR: Where we have known confirmatory trials at the time? Well, I think that we have to see all data before we make a decision so that we know what trials are ongoing, and that really should be brought forth to the committee.

Whether or not the FDA has officially agreed that these are confirmatory trials or not, that could be a matter of speculation or either communication or miscommunication between the company and the sponsor.

But I think anything that could bear upon a decision, especially if it's in the same

indication or a related indication absolutely needs to be presented to the committee because that would bear into any decision, and we did that obviously, and those trials were presented in the case of Iressa that was presented last ODAC.

CHAIRPERSON PRZEPIORKA: And in the instance of a drug that's brought before this committee and we know of either published or unpublished information on trials that were not part of the sponsor's own development that are negative, and the sponsor does not present this information at this meeting, would the FDA present that information or would you be relying on us to bring that information forward?

DR. PAZDUR: No, we would present that, but hopefully we would have had these discussions. Remember our discussions regarding the ODAC committee are not separate from the sponsor in the sense that we do communicate with them beforehand, share slides frequently with them, discuss what we are going to present.

So hopefully this would have been

fleshed out, exactly what is going to be presented by the sponsor and what is going to be presented by the FDA.

CHAIRPERSON PRZEPIORKA: Dr. Redman, do you have a comment?

DR. REDMAN: Yeah, I just want to make a comment to some comments that were made much earlier just to give another side of the coin of the last sponsor going to a cooperative group and trying to run a trial and then being faulted because the cooperative group wanted to add a third arm.

I mean most of us have dealt with cooperative groups. It reminds me of the fairly tale or the story of the kids having to pass the word along and by the time it gets to the end of the 30th kid, it has no relationship to what was put in at the front end.

And cooperative groups, what actually sometimes comes out at the back end is actually better than what went in, but I can't fault the sponsor that needs to do a large Phase 3 trial of going to RTOG, going to SWOG, going to ECOG and

asking for their assistance.

And a lot of times the cooperative group goes back to them and says, "Yes, but it's more scientifically interesting to us as a group to do it this way."

See, then you really can't turn around and say, "Okay. We're not going to use you."

DR. PAZDUR: Bruce, we encourage, and I personally encourage, interactions with the NCI cooperative groups, and I want to send a clear message that my comments are not meant to be anti-cooperative group. We encourage participation of sponsors with cooperative groups both on registration studies, primary registration trials, on risk reduction trials, on adjuvant trials. We have accepted their data.

I am totally supportive. I think it makes complete sense to utilize that mechanism. In pediatrics, as Greg will attest to, we have been very interested in a close interaction between sponsors and COG.

Nevertheless, that obligation to meet

the Phase 4 commitment rests with the sponsor, and he must do that with due diligence because he has that responsibility. That company has the responsibility.

And if it doesn't appear that that is going to be met in a timely fashion or in a logical fashion that would meet the regulatory requirements, there are other avenues available to him, to that sponsor, either to discuss alternative trial designs with us, to do an international study sponsored by the company.

And here, again, one of the issues that I wanted to bring forth is what is the quantity of data that we should ask. Heretofore, most of the times we've been discussing one trial that is going to be our confirmatory trial, and as you know, in other areas we have requested two trials to be done.

I'll just remind you that the AIDS patients usually have two trials that are very large at the time of an NDA submission being sent forth to them.

So I'm not arguing. I realize that

there's a complex interaction between the groups and the sponsor, and that can be somewhat difficult. They have different objectives sometimes. Sometimes the cooperative groups might want to answer an interesting scientific question.

But nevertheless, it is the obligation of the sponsor to fulfill the Phase 4 commitment, and if that isn't being met, maybe they have to take a look at different avenues.

CHAIRPERSON PRZEPIORKA: Dr. George.

DR. GEORGE: Yeah, I wasn't going to speak to that, but I have a brief comment about that since I'm the group statistician for one of the cooperative groups.

I think that this arrangement should be highly encouraged because I think it's a good way for mutual benefit. It's probably an educational process that there isn't this communication going on. There's a lot of communication going on between the groups at NCI, but not with FDA. So there could be a communication issue.

But I just wanted to list some things

that I've learned from all of this, I think, and that is that the accelerated approval is really based on weaker evidence, that is, in fact, it's based on assessment of likely effect than any real data on clinical benefit when it's given.

One sidelight of that is that the public and media, it's pretty clear, interpret it actually in exactly the opposite way. This agent not only has approval. It has accelerated approval, and that's just a terminology issue and something we can't get around, I don't think, but it is something that we have to live with, and I think it has had some effect on some of these subsequent trials.

But one thing that implies. Since we know it's going to be based on weaker evidence, I think that this just echoes what Dr. Pazdur has stated at the very first. Really we need plans in place for post marketing commitments at the time we're considering this, and so I think when we're considering these accelerated approval applications, we should be reviewing what their post commitment, what their plans are.

And, in fact, in my case, I would say that it would greatly influence whether I would vote for accelerated approval depending on what those plans were. Ideally now, these would already be ongoing, but it may not be, but still that I think is going to have to be an important part of this process.

Along those lines, when we're evaluating what those plans are, I think one thing I've noticed going through these two days is that we don't do enough of what I.G. Goode years ago called using the device of imaginary results. Have a plan and think about all of the possibilities that could happen, all of the kinds of results that might occur from those plans.

It might not occur that your agent, in fact, produces better survival or you have a three arm study and there might be some very confusing results that could come out of it.

So think about all of those things hard before you decide what to do.

Another thing is I think I've come to

the conclusion that we should never allow accelerated approval on unplanned subset analyses of applications for full approval. That should just be known ahead of time that that is not going to happen.

So in other words, if you're going for accelerated approval, go for it, but it's not a second prize to full approval.

In fact, ideally what I've found, there were a couple of cases like this; that it seemed to me that the accelerated approval is actually built into a trial that can give full approval is a really nice model because then you actually base the accelerated approval based on some early analysis. Say, just to take a simple analysis, it might be based on response rate where the endpoint of the trial is really survival. So you can potentially go for accelerated approval based on response rate, but with the same patients and not jeopardize that study presumably; continue that study, and that would be an important -- I like that design, in other words.

Enough said.

CHAIRPERSON PRZEPIORKA: Dr. Brawley.

DR. BRAWLEY: I think he has a hot, burning comment. Can we yield?

CHAIRPERSON PRZEPIORKA: Okay. Dr. Temple, he yields to you.

DR. TEMPLE: Okay. Just a few things. I've said some of these things before. There's a reason why you don't always make the trial that gets accelerated approval the same as the one that's going to get you full approval, because it's way, way harder to actually show those desirable endpoints when the response rate is very low.

So, I mean, we love trials that you can just continue because then it's all done and you're definitely going to get an answer, but that doesn't mean it's going to work out or give you the answer you want.

The other thing I heard was this sort of dislike of these three arm or add-on trials, and I'm curious about that because in the trials that they're actually doing, they're going to have to be better than the control agent, which maybe they will

be.

But a drug that's perfectly good, but that is not better than the control agent might be able to add to the control agent.

Now, in this case, they didn't have the tox. data and it didn't work out, but we commonly advise people that doing add-on studies, which by definition show differences between treatments, are a good idea, where it's implausible that you're going to actually be better than the control, but sometimes you are, or where you have to resort to an non-inferiority design, which is very, very tricky, very hard, and fraught with danger.

So obviously you have to have the tox. ready. The two have to be compatible and sensible, but I must say we commonly know -- we still like that design, certainly very common outside of oncology when there's a good standard therapy.

No, none of them have to be in the -- but even in a non-refractory setting, it's fine if your drug is better than the control agent, but you can't always count on that, and it might be valuable

if it added to the control agent, if that was a sensible thing to do.

I like it because it's an easy design to interpret. Non-inferiority designs are murder, and the combination being better than the single agent is very easy to interpret. So it has some attractiveness that way.

CHAIRPERSON PRZEPIORKA: I don't want to discourage such a design. As you have said, it's a nicer design and gives you more information right off the bat. The only problem is, as you pointed out, the information was not available.

And I don't work for a drug company, but I do know in my own research I need to move the field as fast as possible in order to improve patient outcomes, and if it's between do a two arm study now or stop for two and a half years to do a three arm study later, I'm doing the two arm study now and doing the pharmacokinetic study someplace else.

DR. TEMPLE: Right. I think everything that people have said though is that if you plan

ahead, you don't have a three year delay, and that's certainly what we would encourage.

Just one or two other things. This was the creator of the division, and like all of you, I think it was a terrific display to do.

I just want to say something that might not be appreciated. We still -- I'm saying it for me anyway, and I think it's for everybody else -- still believe in the idea of accelerated approval. We just want to see it work properly. But the idea that you could have some information of a less definitive kind, still good evidence, but of a less certain relationship to outcome as a basis for approval in diseases that have no treatment still seems very sound, and nobody is challenging that by showing how it has all gone.

I just want to be sure everybody understands that. We want to see it work well, and I guess I have to say it isn't only the companies that have screwed up from time to time. We have been insufficiently dogmatic about insisting that these things be planned out well ahead of time. So

this is a mutual effort to do better. I just want to emphasize that.

CHAIRPERSON PRZEPIORKA: Dr. Brawley.

DR. BRAWLEY: You may not have been here yesterday, Dr. Temple, when one of the proudest things I did was I forced Dr. Pazdur to defend accelerated approval.

(Laughter.)

DR. BRAWLEY: The need for confirmatory testing is obvious, and the need for confirmatory testing plans need to be in place at the time of submission for accelerated approval is to me very obvious. My remark is going to be very short because Dr. George and Dr. Cheson really summed up things very, very well, I think.

I, too, learned a great deal. One of the things that I focused on is that in Phase 4 confirmatory trials, there really is a conflict of interest of sort among the companies. I haven't seen any evidence that this is effective corporate behavior.

But we all need to realize that the

company can either sell the drug or promote the study that will confirm the drug for permanent approval, and sometimes we could even be in a situation where a company might lose faith in a drug and actually slow down those confirmatory trials so they can still sell drug.

I'm not saying that that has happened. I've actually seen no evidence of it happening, but in the current environment, it creates the possibility, and we've all seen corporate irresponsibility in the newspapers recently in terms of drug development, and I for one am very concerned about the patients who will not get those drugs because of that corporate irresponsibility.

Again, I'm speaking of things I read in the newspapers and not things I've seen in the companies in the last two days.

In terms of the issue of withdrawal, I think Dr. Cheson used the word "pharmacopoptosis."

(Laughter.)

DR. BRAWLEY: If there are Phase 4 trials that demonstrate that a drug does not work, I

don't think you at the FDA are going to have to worry about whether or not we move to pool it. Quite honestly, I think the medical community will do that for you if those Phase 4 trials are done adequately and published.

In terms of the name, accelerated approval, I learned a great deal about what it means and doesn't mean. A couple of us over here for the last day and a half have been writing other potential names.

I understand accelerated approval has been the law. So we can't change it to provisional approval or conditional approval or, my personal favorite, which is premature approval.

(Laughter.)

DR. BRAWLEY: We do have to -- and Ms. Napoli said it yesterday in the public hearing best -- we do have to work hard to make sure that people know that these drugs have been approved by a process, meaning that things are early. What is known about this drug is not what would be known about a drug in a normal approval situation.

I know of at least one company whose advertising actually encourages you to use this new hot drug because it went through accelerated approval. It was so good. It makes everyone thing it was so good, it was a slam dunk, and so it was approved by the FDA quickly, and we've all learned that that doesn't mean much at all.

Accelerated approval means, as Dr. George said, that the data is very tenuous.

Also, we mentioned yesterday, and I'd like to mention again, there are a number of instances where drugs in a Phase 2 setting that have never been tested in Phase 3 have, when tested in Phase 3, been found to not just be not useful, but actually have been found to be harmful, thus the importance of Phase 2 testing.

Such things as beta carotene administered daily to smokers. It was thought for a long time that that was harmless. I can even recall saying, "It's just a vitamin."

In a randomized clinical trial twice now it has in two randomized clinical trials -- beta

carotene increased the risk of lung cancer in smokers. The placebo was more effective than beta carotene.

Premarin and Provera, as we talked about yesterday, something that we used in this country for over 50 years because it was a good idea and some smart people thought it was good for women, and finally the randomized clinical trials, which were very difficult to do because everybody assumed it was okay; the randomized clinical trials ultimately showed that Premarin and Provera increased the woman's risk of breast cancer significantly. Do not treat the osteoporosis that it was thought to treat.

It does prevent colon cancer, but the preventive aspects of colon cancer for the drug are so minuscule and the harms are so high that Premarin and Provera, as most of you know -- and the Wyeth people here can tell you -- specifically, sales have fallen dramatically in the last six months.

Bone marrow transplant in breast cancer. We were all taught as young medical oncologists that more is better, and those bone marrow transplant

randomized studies, randomizing women to either high dose chemotherapy or bone marrow transplant were delayed for some time because everybody assumed bone marrow transplant was better.

Phase 2 data suggested it was better. We don't do bone marrow transplant in breast cancer anymore after the four randomized trials that were good were published, and there was one where there was some significant fraud.

Screening for neuroblastoma with Urine VMA or screening for lung cancer with chest X-ray, all widely accepted, ultimately thrown out after randomized clinical trials showed that they were both more harmful. Neuroblastoma screening with the urine test was more harmful to three and four year old kids.

So ultimately one can have net harm after Phase 2 clinical trials. It's very dangerous to get up and offer someone hope in a small molecule, not even to someone who probably doesn't even know what a small molecule is, when in actuality you're offering a little bit of hope and a

lot of risk and perhaps a lot of danger.

And I speak specifically to some of the advocates who spoke yesterday who dramatically exaggerated the potential effect of a number of drugs that are already marketed. Quite honestly, I don't know many people who get cured of their disease from some of those small molecules that are currently marketed, but we heard yesterday not only that there were 800,000 people looking for these drugs when there's only 500,000 cancer patients per year in the United States, by the way, but we also heard exaggerated benefits of the drugs.

I am really unsure -- I'll finish by saying I'm really unsure the risk concept is appreciated by physicians, as well as by patients, and one thing that the FDA can really do, I think, is work hard to make sure that people actually understand what this -- I think you're stuck with the phrase "accelerated approval." I think you have to really work very hard to make people in the medical community understand what accelerated approval really means; make people in the advocacy

community really understand what the potential of these drugs actually is.

Thank you.

CHAIRPERSON PRZEPIORKA: Thank you.

Dr. Kelsen.

DR. KELSEN: Just to follow up Dr. George's point about distinguishing in the minds of the public and perhaps physicians the difference between accelerated and full approval, would you consider placing as part of the labeling indication a brief description of what accelerated approval is or maybe --

DR. PAZDUR: We do, but I think it cannot be interpreted by most people because they don't understand it. Okay?

Under the indication it says something to the effect clinical benefit has not been demonstrated or this drug was approved by a surrogate endpoint and clinical benefit has not been demonstrated.

And I think unless you have a real thorough understanding of the process, et cetera,

that is lost on most people, and maybe we have to revisit how we do that, either through patient package inserts or better description in the label.

But it is there. There is a specific disclaimer, but here again, I think it may be lost on the vast majority of people that don't work at the FDA.

CHAIRPERSON PRZEPIORKA: Ms. Mayer.

MS. MAYER: I think the reason that Dr. Brawley's eloquent examples of harm are so instructive is that they reach us on a level that we don't often discuss here, but which is really why we're all sitting here in this room, which is that we have a profound wish and hope for treatments to be available to help patients with cancer to cure them.

This is what animates everything that we do, and it's also, I think, one of the reasons why there have been so many problems with accelerated approvals, because this is the place in the regulatory process where we can set aside our hard discriminations and firm refusals and say, "Well,

yes, maybe. Maybe this will work out. Maybe we can defer until later that difficult discrimination."

And I think until we can really tackle what Dr. George was saying earlier about the necessity for planning and thinking ahead, taking into account our own individual vulnerability to be influenced by patients who are standing up and talking about personal experience, which is anecdotal evidence, and our own wishful thinking, that until we can acknowledge that, I don't think we can move ahead in this process to make really reasoned decisions; that we need to see perhaps more clearly how deferring a decision can be of greater benefit for more people, which is what my personal believe is; that it's better to wait for the good science.

CHAIRPERSON PRZEPIORKA: Dr. Fleming.

DR. FLEMING: I'd like to thank my colleagues on the board and at the FDA for some terrific insights, and I'd like to maybe just reiterate some of these and maybe extend a few of these points.

There's no question that the accelerated approval process is well intended, with the concept of trying to get quicker access in a life threatening disease setting to agents that have promise for benefit.

There are, however, many significant concerns that listening to all of the discussion over the last two days, it's a very sobering process. I'd like to begin with what Dr. Brawley had to say, and that is in my words an effect on a biological marker certainly established biologic activity, but may not establish clinical efficacy.

And he has given an array of very relevant examples. A number of us have also written about a wide array of other examples. The literature is full of examples where effects on markers didn't accurately predict the effect on clinical endpoints, essentially in part because the disease process is complex, and there are typically many pathways through which the disease process influences clinical endpoints, only some of which may be mediated through what the marker is

capturing.

And interventions can have unintended, as well as intended, effects, and those unintended effects are typically unrecognized and unrecorded. And so it's not until we do the clinical endpoint studies that we really understand more fully what the actual tangible effect is to patients.

But other issues arise as well with the accelerated approval process that are very critical here. One that we've heard about is the slower enrollment that can come after the agent is being marketed. The Ontak example is a classic example where enrolling nine and seven and nine patients per year into trials, where the sponsor has said there's no question that with the product being available enrollment into placebo controlled studies is much more difficult.

There's a much greater chance of cross-ins, and so we do care about survival. It's much more difficult to do the types of studies that over the time period that would have to be engaged to be able to reliably detect whether the treatment truly

influences outcome, such as survival.

And there is this issue of sense of urgency, and, Rick, I'd like to reassure you that at least as one person, I didn't just keep raising the issue because I didn't know how many times you kept wanting to hear it. We repeatedly were referring to this issue yesterday in particular.

I want to be fair and say it has been a privilege to work not only on behalf of FDA on these Advisory Committees, but to work with industry sponsors in the design, conduct, analysis of clinical trials. And there is no question in working with those sponsors that they are committed to doing what is favorable for public health.

There is also, however, no question that the urgency is reinforced significantly by financial considerations. That's very obvious in terms of how the process is undertaken in a premarketing setting, and my sense, my suspicion and, I think, reinforced by broadly what we're seeing is there clearly isn't that same at least financial aspect to the sense of urgency, and I think that is something that has to

be addressed because the urgency of moving ahead to get at truth is still profound, even after the accelerated approval has occurred.

And I definitely endorse the idea that there needs to be a much more proactive planning for the concept of accelerated approval. It seems to me that at least in a number of these cases we were in a drug development process where at some point it looked like, gee, this could actually yield an accelerated approval application, without much earlier stage planning that this is where we're headed, and there are lots of things that have to be in place.

And so, Rick, you had pointed out how could we go from 1999 to 2003 before it is that we get that study in place, and I think the sponsor in this case said, well, in this particular instance the accelerated approval is something that emerged. In fact, I think the words that they used is the FDA identified this subgroup of patients in whom there looked like to be an effect.

And the consequences then are that we

are a number of years -- maybe it could have been less than a number of years -- but this didn't appear to be a situation where the accelerated approval had been planned early in the process so that we were in a position to have timely implementation of those studies that, in fact, we will depend on to get the ultimate results.

The other aspect here that to me is critical is strength of evidence, and I was reassured that the position here is that we are, in my words, targeting establishment of comparable strength of evidence. We are targeting the establishment of comparable strength of evidence.

And yet what to me has been apparent listening over the last two days is that there's a strikingly vague formulation about when and even whether accelerated approval would be withdrawn if we don't achieve that targeted level of strength of evidence.

And we had by my count three specific applications where the trials had been completed and, in my words, the results were not favorable,

and yet there is an uncertainty about where we're going.

And when I looked at these eight applications over lunch break today and just added up where we were from when the original accelerated approval was granted to when we're projecting the completion of the next trial, the average is at least ten years. And that's just getting to the end of the next trial.

And it's not clear to me once we get to the end of that next trial whether or not that's going to be a result that's going to, in fact, lead to another indefinite extension.

So my fear is, my concern is that what ultimately we have at least if we use the experience of the last two days for me is a perception that accelerated approval isn't accelerated approval. It's tantamount to approval because it's so extraordinarily hard to withdraw.

And my concern is if one truly wants accelerated approval and doesn't want to raise the bar for what it is going to take to achieve an

accelerated approval, then doesn't there have to be a clear sense in formulation as to what the expectations are and when, in fact, or what exactly is going to be required and when it's going to be required basically to provide the reassurance.

I guess my own sense about this is with the reservations that I had about accelerated approval, I always felt that at least I could be reassured that we would still get at the truth. We would ultimately get at the truth in a timely way.

And so we were, in fact, potentially providing earlier access to patients that could be beneficial if this intervention is beneficial. But if it turns out to be biologically active but not clinically effective and potentially toxic, there would be a horizon. There would be an end time frame to this.

And my reassurance was with that end time frame, that was a risk that, in fact, could be legitimate in the context of the intended benefit. But if there isn't that horizon and accelerated approval, as even George was pointing out, is based

on relatively weak evidence, then my own sense is we have to raise the bar.

And if the intention is not to raise the bar, then it can't be, as Dr. Brawley was saying, premature approval. I mean, I have always believed it's conditional approval, and it was, as Bob Temple said, a political aspect or politically incorrect to call it actually what it really is.

But the bottom line, as I see it, is if we truly want to maintain the concept of accelerated approval with the lower bar, then something much more specific must be understood about what the expectations are so that we do achieve comparable strength of evidence within an acceptable time frame.

CHAIRPERSON PRZEPIORKA: Thank you, Dr. Fleming.

Dr. Pelusi.

DR. PELUSI: Again, in the spirit of going around and basically saying what these two days have meant, I must say that after being an oncology nurse for 30 years, that puts me in the

same age category as Dr. Temple and Mr. Ohye --

(Laughter.)

DR. PELUSI: -- that big changes have been made, and to see this whole journey, and that's the way patients describe it, as a cancer journey, and to see where we are in drug development and some of the questions that are now being at the table, 30 years ago we didn't think we would be at this table.

We also didn't have the survivor's movement 30 years ago because we weren't having enough patients long term, and so when I look at what was done in terms of this accelerated approval, we all wanted drugs out there. And I think this has been said over and over again, but we need safe drugs.

And I think if really you ask patients and you ask patients' families, yes, they want options, but they want safe options. And in the emotion that gets caught up in many of the discussions, it's because many people who come to the podium, many people who are out there that express their concerns are dealing with this

situation right now.

Many times when we look at the data, we don't see those faces. We aren't the ones even though we are caring for them, we aren't the ones that are there in that time and effort. And you can't explain all of this in one or two office visits.

And I think Otis' point is very well taken in terms of education of the public as a whole, and I think, Rick, you have done this very well in terms of doing this meeting because I think all of us had wide open eyes, and I think the advocacy groups did as well.

And the question becomes where do we participate. Back in '71 there were two researchers who made the statement that survival rates, while very justifiable in their right, did not really set the course of what happens when those drugs are put into patients. What is the cost to the patient in terms of their physical functioning, in terms of their social functioning, and in terms of society as a whole?

And I think now is the time, as we begin to explore this, is that we do have a lot of survivors. We have a lot of family members who are willing to join in and help with this process and I think with good education, really begin to say what are our options and are they good choices.

Because, again, having that knowledge helps make that decision. And many times we don't hear the voices of those patients who did not do well in the trials, and I would, again, encourage as trial designs are done, is to really look at those people who are off study, whether for progression of disease or who have had deaths related to the disease. What happened in those families? Because that gives us guidance maybe in a subjective nature, but when we have to put those drugs in the community, in the homes, it becomes very important that we understand what we need to be prepared for.

So I thank you, and I applaud you for doing this meeting. And I would hope that you would look at the role of the public hearing and also of the patient and consumer rep., maybe of taking on a

different flair in order to discuss some of these issues, whether it be at different forums or pre-meetings or getting input and presenting kind of overall consensus, and then having something coming from the meetings, Rick, back to some of these advocacy groups, again, about why it's so important to understand what the data truly means, whether it be a newsletter -- as I know from the Oncology Nurses, we get an on-line zip as soon as something happens -- and maybe we need to really look at that for consumers as well.

So I just, again -- it's a evolution, and we have done some really positive things. We just need to really look at the process and build on what we've done.

Thank you.

CHAIRPERSON PRZEPIORKA: Thanks.

We're going to be losing some of our members to airlines here soon, and I don't want to cut off conversation, but I do want to acknowledge some folks who are leaving or on the way out the door. Dr. Blayney, Dr. Kelsen, Dr. Lippman, and Dr.

Pelusi, who have served this committee very well, and we will not be having a committee meeting in June. So this is their last meeting, and I, for one, thank you all. It has been a pleasure to work with you sincerely.

So as you need to tiptoe out the door, please feel free.

And Dr. Carpenter had something --

DR. PAZDUR: Donna, could I just add something?

We from the division would also like to thank these individuals because many times what people do not realize is the intense amount of effort that people play behind the scenes.

This is one public forum, but we rely heavily on members of the committee as consultants throughout the year in teleconferences to us, in doing special protocol assessments, in being at company meetings.

So I would like to also take this opportunity to thank these individuals that will be leaving the committee.

CHAIRPERSON PRZEPIORKA: Thanks.

Dr. Carpenter.

DR. CARPENTER: Just one brief comment. You had said something about how arcane the information is about accelerated approval. I think the package insert is something that's looked at widely, and some way to indicate that it is, in fact, a different kind of approval and that in some ways it's limited would probably solve some of the communication gap between the agency and the people it's trying to communicate with.

So I would just encourage your efforts in that direction.

CHAIRPERSON PRZEPIORKA: Dr. Blayney.

DR. BLAYNEY: Yes. I wanted to thank you, Rick, and your teams for putting this together. It sounds like a lot of energy, a lot of thought went into this, and I think I've learned something.

I won't reiterate the comments, but the comment that Donna made reminds me that institutional memory is short, and if you are going to bring things back to this committee, I would

encourage you to incorporate some of this definitional training into the committee orientations.

We had a very thorough ethics orientation, but I think it would be useful to introduce new members to the terms that are used, particularly accelerated approval.

And you did mention, the last thing, the stick to enforce some of the vigor that you want to infuse the post approval process. One of them was withdrawing the indication. You mentioned earlier that you had also thought about perhaps the niche or the definition of unmet medical need until -- did I understand that you said if the post marketing commitment is not made, you might continue to define an unmet medical need for that indication?

DR. PAZDUR: That's an area of discussion, and as I mentioned, one of the possibilities to encourage further development in a particular indication that has not met clinical benefit in that indication might allow other people to come into that indication if the first drug that

got accelerated approval demonstrates clinical benefit outside of that indication.

But here, again, that's under discussion.

DR. TEMPLE: Remember the whole condition for doing accelerated approval is that there can't be something that fills whatever this need is. So you might think that when one drug gets accelerated approval, okay, the need is filled.

The question is: does that, without the confirmatory evidence, fill that need?

And we're thinking about that.

DR. BLAYNEY: And you know, based on what we've heard today, the competition for, if you will, scarce patient resources in a clinical trial, my view would be no. That need is still unmet unless there were the preponderance of evidence shows that it's a --

DR. TEMPLE: We may even agree with you. Just to make people who don't like the term "accelerated approval" much, let me tell you that the other condition in which we used "accelerated

approval" is where the drug is considered so dangerous that it has to be marketed under restricted distribution.

Now, you might wonder what's accelerated about that, but that's the term anyway.

DR. BLAYNEY: Thank you.

CHAIRPERSON PRZEPIORKA: Dr. Taylor.

DR. TAYLOR: Well, I think the meeting has been a learning experience for all of us and for the community. I look at it in two different ways though. I think the first way to look at it is we're all being Monday morning quarterbacks, and it's very easy to be a Monday morning quarterback and be hard on the committee for having made decisions to accelerate something and hard on the drug companies because they haven't carried out projects.

But I don't think we can always foresee what we're going to have to do or what's going to happen or even our understandings of things. So I think we should be kind to ourselves and the committee and industry from that point of view.

I also see this as learning from history, and I think that's an extremely important thing; that we know in medicine by our QA studies and in the world that if we don't learn from history, then we don't go anywhere.

And for myself, I think I have more of a doubt about whether accelerated approval should be given at all, but the fearful thing is when you look at, as he stated, that it will be ten more years before these other trials that are confirmatory trials are done, then you wonder how long you would wait to have these new agents.

And you really have to weigh everything very strongly.

CHAIRPERSON PRZEPIORKA: Thank you.

Mr. Ohye.

MR. OHYE: First, I'd like to thank on behalf of industry or maybe, after all of the castigating I heard, on behalf of the "dark side" what a really yeoman's service that Drs. Blayney, Kelsen, Lippman and Pelusi have given the committee, and I will miss them, and I hope that if they have

an opportunity to -- I don't know what the term is -- re-up, I think their wise and unbiased counsel would be very graciously received, and godspeed, and thank you very much.

I have to respond to a few things, if you don't mind. First, there's this issue of irresponsible promotion of accelerated approval drugs.

I don't know if you're aware, but no accelerated approval drug can be approved without having all promotional platforms preapproved by FDA. That's written in the regulations.

It doesn't go on forever, but that's a very important aspect here, and I think it should be there.

I think with reference to that rare, irresponsible sales rep., we in industry want to hear about these people or he or she because they are not doing what we want them to do, not doing what we've trained them to do, and please, anyone, if you see someone trying to promote a drug outside of the labeling, we want to hear about that because

that's wrong, and we will not tolerate that.

I think I'd like to end by saying I think accelerated approval works. Good standards are in place, and without accelerated approval, we wouldn't have these drugs started by physicians, for example, like SkyePharma, and for very rare indications see the light of day. We wouldn't have Gleevec on the market. We wouldn't have the advances in HIV therapy.

And I think today we've heard about the great difficulties when you have very rare unmet needs and how difficult it is to do all of the sophisticated planning when you're trying to get this important drug made available for patients.

So I ask you all to please keep this in mind, that accelerated approval works, and there are a lot of important drugs out there that are doing a lot of good because this provision is in the law.

And I remind you that it is in the law, and what we have to do is to make sure that it works.

Thank you.

CHAIRPERSON PRZEPIORKA: Thanks very much.

Any other comments from the comment?

(No response.)

CHAIRPERSON PRZEPIORKA: I'd like to ask the FDA if they are satisfied with our discussion or if you have other questions.

DR. PAZDUR: No, but I have some closing comments.

I'd like to thank the committee for their attentiveness and their consideration, and I think through this forum they've seen what we have been seeing over the past years.

In my comments yesterday from the microphone, I think I made it real clear to everyone that the division believes in accelerated approval. This is only one aspect of accelerated approval, the completion of Phase 4 commitments, and we believe that this is an extremely important part of the accelerated approval process, but nevertheless, the life of a drug is very complicated and has many avenues to demonstrate clinical benefit, including

the practical use in the community.

But nevertheless, one cannot ignore these Phase 4 commitments.

This has been somewhat sobering for all of us, I think, because you have seen the problems that we have seen of trials not being done on time, problems with trials, delays in trials.

I'd just like to echo, you know, the comments that Tom made. If these were registration trials, would they have been done faster? I don't know the answer to that question.

I have a little voice inside of me that says, "Probably so." However, that is a bias on my part that I will label as such.

I would also like to remind the members although we are sober at this time with the accelerated approval process, I can't tell you how many times I get pelted when I go out and talk and say, "What's wrong with you? How come you haven't approved this drug? It has a six percent response rate and there's nothing else for these patients. Why isn't this drug on the market?"

What's the answer to that question? It's a very difficult question, and it's a balance between trying to get out drugs to people that need them, that don't have anything else, yet demand some standards in the drug approval process.

And, again, if we were certain that people would do these on a timely basis, it would be very easy to be very positive about letting everything that comes into our purview out as quickly as possible, but I think we do have a responsibility for this.

Also, what we see inside the FDA is basically meetings with sponsors after a drug where we approve the drug on a 12 or a 15 percent response rate, and the next week a sponsor comes in and says, "Well, will you take a response rate of ten percent? And will you approve this drug on 100 patients? How about 70 patients? How about 30 patients with four responses? This is an unmet medical need."

Where do we draw the line? And we've had this discussion internally, and ultimately we have control over the situation here, but it is a

tendency that can be observed, and as Tom says, we believe that many of the pharmaceutical companies are responsible, but here, again, there are financial pressures that come into bear not so much from even the medical community or the physicians that are working in them, but by the external world, their stockholders, et cetera, that want rapid drugs.

So I guess the reason why I'm saying this is although we've had this very sobering experience, I hope people will take it forward and not lose that this accelerated approval has two sides of the issue. Not only is it to get the drugs out as quickly as possible to patients who need them that are desperately ill, and everyone at the FDA realizes this. We're one of the few divisions in the review divisions at CDER that have an entire subspecialty staff that works with us. They're all Board certified medical oncologists or surgeons or pediatric medical oncologists.

So we fully understand the need of these people, and I think we all need to hear that we're

not working against the American public. We're working for them, and when we delay a drug it's not because we're trying to do something nefarious or work against the patient population. It's just the opposite reason, that we're trying to work for the patient population.

I'll get off my soapbox, but I'd just like to recommend or thank really the large number of people that really brought this project to fruition. Although I have a lot of ideas, ideas are not any good unless people carry them forward, and I'd really like to thank Dr. Grant Williams, who was very instrumental in this meeting; especially Dr. Ramzi Dagher, who really did most of the work in putting things together; and Diane Spillman, who is a project manager in the division, who really coordinated countless numbers of meetings not only with sponsors, but with you when we had telephone conversations with you regarding your role in this meeting.

So, again, we really appreciate your help. We want everyone to realize that we're trying

to have a balance here of getting drugs out to desperately ill people, but also having to have some standards in drug development that will serve the medical community and oncology patients in the long run.

CHAIRPERSON PRZEPIORKA: Thank you, Dr. Pazdur, and I call the meeting adjourned.

Thank you.

(Whereupon, 3:19 p.m., the meeting in the above-entitled matter was concluded.)