DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

# ONCOLOGIC DRUGS ADVISORY COMMITTEE

## 60TH MEETING

Tuesday, January 12, 1999

8:30 a.m.

Holiday Inn Gaithersburg
2 Montgomery Village Avenue
Whetstone Room
Gaithersburg, Maryland

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Karen M. Templeton-Somers, Ph.D., Executive Secretary

MEMBERS

Kathy Albain, M.D.
James E. Krook, M.D.
Kim A. Margolin, M.D. (p.m. session)
Derek Raghavan, M.D., Ph.D.
Victor M. Santana, M.D.
Richard L. Schilsky, M.D.
Richard M. Simon, D. Sc.

CONSUMER REPRESENTATIVE

E. Carolyn Beaman, M.H.S.

VOTING CONSULTANTS

Jan Craig Buckner, M.D. (a.m. session)
Carol B. Miller, M.D. (p.m. session)
Stacy Nerenstone, M.D.
Esperanza B. Papadopoulos, M.D. (p.m. session)
George Sledge, M.D.

VOTING PATIENT REPRESENTATIVE

Craig Lustig (a.m. session)

FDA

Martin Cohen, M.D. (a.m. session)
Steven Hirschfeld, M.D. (p.m. session)
John Johnson, M.D. (a.m. session)
Robert Justice, M.D.
Robert Temple, M.D.
Grant Williams, M.D. (p.m. session)

C O N T E N T S

**A.M. Session**



**NDA 21-029 and NDA 21-050, Temodal (Temozolomide)**
**Schering Corporation**
**Indicated for the Treatment of Adult Patients with Malignant Glioma (Glioblastoma Multiforme and Anaplastic Astrocytoma) at First Relapse**

C O N T E N T S (Continued)

**P.M. SESSION**

P R O C E E D I N G S

**Call to Order and Introductions**

DR. DUTCHER: We are going to get started. This is the 60th meeting of the Oncologic Drugs Advisory Committee. So if that is where you are supposed to be, you are here. We are going to go around the table and introduce the members of the committee. We will start with Dr. Santana.

DR. SANTANA: Victor Santana, Pediatric Oncologist, St. Jude's Children's Research Hospital in Memphis, Tennessee.

MS. BEAMAN: I am Carolyn Beaman, Sister's Breast Cancer Network, consumer rep to the committee.

DR. RAGHAVAN: Derek Raghavan, Medical Oncologist, University of Southern California.

DR. NERENSTONE: Stacy Nerenstone, Medical Oncologist, Hartford Hospital, Hartford, Connecticut.

DR. BUCKNER: Jan Buckner, Medical Oncologist, Mayo Medical School, Rochester, Minnesota.

DR. SLEDGE: George Sledge, Medical Oncologist, Indiana University.

DR. DUTCHER: Janice Dutcher, Medical Oncologist, New York Medical College, New York.

DR. TEMPLETON-SOMERS: Karen Somers, the Executive Secretary to the committee, FDA.

MR. LUSTIG: Greg Lustig, brain tumor survivor and

patient rep to the committee.

DR. SCHILSKY: Rich Schilsky, Medical Oncologist, University of Chicago.

DR. ALBAIN: Kathy Albain, Medical Oncologist, Loyola University, Chicago.

DR. JOHNSON: John Johnson, Clinical Team Leader, FDA.

DR. COHEN: Martin Cohen, FDA.

DR. JUSTICE: Bob Justice, Acting Director, Division of Oncology Drug Products, FDA.

DR. KROOK: Jim Krook, the Duluth CCOP, Medical Oncologist.

DR. DUTCHER: Thank you. Remember to use your microphones when you are speaking, for the recording secretary.

Dr. Somers has a conflict of interest statement and some other remarks and then we will go to the open public hearing.

**Conflict of Interest Statement**

DR. TEMPLETON-SOMERS: First of all, we would like to welcome our guests and patient representatives, and I would like to also mention that Dr. Sledge and Dr. Nerenstone are attending as incoming members of the committee. We are in the process of expanding the committee roster to thirteen members, and they will be full members by the next meeting. Today they are full members for everything except being on

the other side of the page of the roster.

There is also one change in the agenda from that which was published in the Federal Register. The original NDA for Temodal has been split for administrative reasons and is now covered under two different NDA numbers, as shown in the agenda. It is a change from the FR notice. The division of the NDA occurred because the proposed indications were in different review classes. So, it is just an administrative thing.

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

In accordance with 18 USC, Section 208(b)(3), waivers have been granted to Dr. Victor Santana, Dr. Derek Raghavan and Dr. George Sledge. The waivers permit them to participate in all matters concerning Temodal. A copy of these waiver statements may be obtained by submitting a written request to the FDA's Freedom of Information Office,

Room 12A-30 of the Parklawn Building.

In addition, we would like to disclose for the record that Dr. Richard Schilsky and Dr. Kathy Albain have reported interests in Bristol-Myers Squibb which do not constitute a financial interest in the particular matter within the meaning of 18 USC 208, but which could create the appearance of a conflict. The agency has determined, not withstanding these interests, that the interest in the government and Dr. Schilsky's and Dr. Albain's participation outweighs the concern that the integrity of the agency's programs and operations may be questioned. Therefore, Dr. Schilsky and Dr. Albain may participate fully in today's discussion and vote concerning Temodal.

Further, we would like to disclose that in 1997 Dr. Jan Buckner did a one-day consult with Schering to review the product development for Temodal.

In the event that the discussions involve any other products of firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record. With respect to all other participants, we ask in the interest of fairness that they address any current or previous involvement with any firm whose products they may wish to comment upon. Thank you.

DR. DUTCHER: Thank you. We have a participant here to speak at the Open Public Hearing, and also a letter to be read, and the first speaker is Laura Gipson. Please state your name and whether there is any support from the sponsor.

**Open Public Hearing**

MS. GIPSON: You will have to excuse me, I am a little nervous. My name is Laura Gipson, and I would like to thank Schering for making it possible for me to be here today, in more ways than one.

Of course, in the most obvious way, they have paid my travel expenses but also, in a much bigger way, I am a cancer patient. I was diagnosed in February of 1997, at the age of 17, with a glioblastoma multiforme--not exactly what I needed half-way through my senior year in high school, with the California State Academic Decathlon competition coming up.

Of course, I took the traditional treatment routes first, with multiple surgeries and countless chemotherapies--I have lost track of how many--and then, of course, radiation. All of these have been limited successes but in the end I was still in a bind with the recurrence of my fast-growing brain tumor.

It was then that I was attracted by the thought of taking an oral medication instead of the lengthy infusions I had been used to previously, and I was hoping that the side

effects of nausea and exhaustion would be less and I wasn't disappointed. I was able to start to resume my daily activities instead of not being able to do much more than sit on the couch and watch cartoons. And, I was hoping that I could go back to UCSF and finish my biology major that I had started there.

Even better than all of this was the results that I had. After only two months or two rounds of being in the study, my MRI showed a 50 percent reduction in imaging tumor. I wanted to throw a party but--!

My case is exceptional in that the tumor response is not usually that quick. It may take four or five months, or whatever, but I wasn't complaining. So, I really hope that this drug can be more available for others in my same situation. So, I guess I would just like to thank Schering again for helping me to still be around. Thanks.

DR. DUTCHER: Thank you very much. We now also have a letter from Linda Lee that Dr. Somers will read.

DR. TEMPLETON-SOMERS: To whom it may concern: Since I will be unable to attend the FDA meeting concerning the Temodal treatment, I appreciate this opportunity to include my success story in your report.

Following a 40-year lifetime of good health, I experienced a seizure in March, 1997 that would change my life forever. An MRI was performed indicating a growth in

the right frontal lobe. Within two weeks a large portion of the lobe was removed and proved to be an anaplastic astrocytoma grade III. This was closely followed by 33 radiation treatments which were completed in June, 1997. I became a subject in a clinical study at UCSF, with PCV as my chemotherapy. This treatment involved many harsh side effects for me and ended in February, 1998 when tumor recurrence was noted on the MRI. Since the tumor had moved into the left portion of my brain it was necessary to take quick action.

I was immediately enrolled in the Temodal study since I met all of the qualifications. Beginning March 1, 1998 I would take 320 mg daily for 5 days followed by repeat dosing 28 days later. After the first 8 weeks the MRI indicated that the tumor had stayed the same without further growth. The second 8 weeks would reveal that the tumor had shrunk to almost half its size. This area was originally comprised of a 1 cm area enhancement in the left cingulate gyrus with abnormality and edema in the adjacent white matter tracts and corpus callosum. By September 10, 1998 the MRI report stated total disappearance of the enhancing nodule in the left cingulate gyrus. No new lesions are seen. Success!

I am now finished with ten treatments and will begin my final two cycles on January 13, 1998. I look healthy--no hair or weight loss, and continue to walk for exercise.

There are no outward signs that I am receiving chemotherapy and this has been a positive mental factor. Although I tire more easily, the major fatigue was experienced during the earliest cycles. By keeping a journal, I was able to plan my schedule around the treatments and prepare myself for normal discomforts.

I suffered mostly from a feeling of heartburn and upper digestive pain but found that keeping a small amount of food in my stomach before and after ingesting the Temodal seemed to help. I also got relief from 20 mg of Prilosec as needed. The most serious complaint throughout has been constipation. I keep a great deal of fiber and fluid in my body and take cascara segrada or docusate sodium each night, but the worst time I must avoid impaction is from the third day of Temodal to the first week after.

I have found the most convenient time for me to take my treatments is at night. My routine stays the same all five nights as follows, a small meal finished near 6:00 p.m., fasting until Zofran at 7:00 p.m., fasting again until Temodal at 8:00 p.m. and a light snack with Dilantin between 9:00 and 9:30 p.m. When I kept my stomach empty, it felt like there were holes burning inside and this schedule has vastly decreased that feeling. I typically awaken at night with severe stomach cramps, especially on the first night. This leaves me waking with less energy but I just allow for

more rest during the day. I expect the fatigue and try to plan my life around it during those days. I have also experienced some treatment delays due to low blood counts but have gotten back to the necessary range within a one- to three-week period of time.

I feel fortunate to have taken part in this study which has certainly brought precious time to my life. I would wish the same opportunity for any other brain tumor patient that needs treatment. My case clearly documents that success has been achieved. Sincerely, Linda A. Lee.

Thank you.

DR. DUTCHER: Thank you. There not being any others who wish to speak from the audience, we will proceed with the sponsor's presentation. Dr. Speigel?

**Schering Corporation NDA 21-029 and NSA 21-050 Temodal (Temozolomide), Indicated for the Treatment of Adult Patients with Malignant Glioma (Glioblastoma Multiforme and Anaplastic Astrocytoma) at First Relapse**

**Introduction**

[Slide]

DR. SPEIGEL: Good morning, ladies and gentlemen, and members of the FDA advisory committee. I am Dr. Robert Speigel, Senior Vice President of Medical Affairs and Chief Medical Officer for Schering-Plough Research Institute.

On behalf of the Schering-Plough Corporation and my

colleagues in attendance here today, I want to thank you for considering our accelerated application seeking NDA approval for temozolomide or Temodal.

We believe the development of Temodal represents an important advance in the challenging treatment of malignant glioma, particularly in the setting of relapsed patients who have failed primary treatment.

Temodal was licensed to Schering-Plough from the Cancer Research Campaign Technology of the United Kingdom based on early encouraging results in brain cancer preclinical models and Phase I studies involving glioma patients.

It is a cytotoxic alkylating agent with excellent oral bioavailability, and is quite well tolerated. Throughout the day you will learn more about the safety and efficacy of Temodal in the relapsing glioma population who will benefit most from its use.

We are grateful to the FDA for the partnership we have enjoyed in developing this drug, and in permitting us to bring our data to you today, which we believe will provide a valuable new therapy for glioma patients and the physicians who care for them.

[Slide]

With us today are a number of attending consultants, all of whom have worked with Schering during the development

phase of Temodal. Dr. David McDonald is Associate Professor of Neuro-Oncology at the University of Western Ontario, and Dr. McDonald has published extensively on the evaluation of treatments for brain tumors.

Dr. Alfred Yung is Professor of Neurology and Deputy Chairman of the Department of Neuro-Oncology at M.D. Anderson Cancer Center. Dr. Yung also serves as the principal investigator of the North American Brain Cancer Consortium.

Dr. Henry Friedman is Associate Professor of Medicine and Surgery and Co-director of the Clinical Neuro-Oncology Program at Duke University Medical Center. Dr. Friedman has also worked throughout his career in the evaluation of new drugs for malignant glioma.

Finally, Dr. Nancy Yue is Assistant Professor of Radiology at the Johns Hopkins University Medical Center, and Dr. Yue served as the independent reviewing neuroradiologist for all the studies that we will be discussing today.

[Slide]

Our agenda for approximately the next hour will be the following: Following my introductory comments, Dr. McDonald has been asked to give a brief disease background in the setting of malignant glioma.

Dr. Sara Zaknoen, from our Research Institute, will

review the clinical data that has been provided to you in your briefing book.

We have asked Dr. Yue to give some brief comments on MRI imaging in this setting. Dr. Alfred Yung will then give a clinical perspective and expert critique on the glioblastoma multiforme data that has been presented. Dr. Friedman will similarly critique the clinical perspective of the astrocytoma study.

[Slide]

To set the stage properly, I want to state that the indication sought in our NDA is the following, that Temodal capsules are indicated for the treatment of adult patients with malignant glioma (glioblastoma multiforme and anaplastic astrocytoma) at first relapse.

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Briefly, I would like to review the regulatory history of this product. An IND was initially filed by the NCI in May of 1993 based on data available from the CRC in the United Kingdom. Subsequently, during that year when Schering-Plough obtained the licensing rights to the product, we filed our own IND in December of 1993.

Somewhat less than a year later, in November of 1994, we had a pre-NDA, pre-pivotal meeting with the agency and also had a number of ODAC present at that meeting in November of 1994, where we reviewed Phase I data and

reviewed the strategy for clinical development that we intended to proceed with. That strategy was agreed to and, shortly thereafter, in early 1995 the three studies that we will be discussing today were all initiated.

In October of 1996 we requested another meeting to review with the agency the results of the planned first interim analysis. At that time, I would note that the two open-label trials had completed enrollment. We reviewed the data of the ongoing C94-091 randomized trial, and were advised by the FDA to continue the study as planned and to keep the agency informed of ongoing results.

We proceeded to do that and, in the summer of 1997, we shared with the agency again the planned second interim analysis results, and we were advised by the FDA at that time to continue the study to completion, which was done.

Based on those completed results, we had a meeting with the agency in June of 1998 to review what we considered to be an NDA package which would include both results in the two glioma indications, GBM and anaplastic astrocytoma, as well as the results of a parallel trial and program that was ongoing in malignant melanoma.

We were advised by the agency to separate the malignant melanoma claim from the glioma indication, which we have done, and we were also encouraged that the glioma data could support an accelerated review, particularly based

on the results in anaplastic astrocytoma. Based on that, a submission was made in August of 1998.

[Slide]

This is my last slide, and I just wanted to spend a moment giving an overview of the three studies you will be hearing about this morning. These are all well described in your briefing book but I would like to make a few points about them.

C94-091 is a randomized, open-label study of Temodal and procarbazine for the treatment of glioblastoma multiforme at first relapse. I would note that this is a study with an active comparator, procarbazine. This is in contrast to the study that is referred to in some of the questions that you will be addressing later regarding the glioma development program which was compared to a placebo. This pivotal trial compared Temodal to an active comparator.

In I94-122 we conducted a Phase II study of Temodal for the treatment of glioblastoma multiforme at first relapse, and a similar trial, 123, was conducted with Temodal for the treatment of anaplastic astrocytoma at first relapse.

I would just like to make a few points about these studies. First, of course, is the overall size of the program. We believe that we bring forward today the largest program ever developed for the development of a single agent

in the treatment of malignant gliomas. These studies on the screen describe over 500 patients, over 400 of whom were treated with Temodal at the dose and schedule for which we seek approval.

Secondly, although I have noted that the primary endpoints of all these studies were progression-free survival, we believe it is important that the advisory committee note that there is a consistency of effect throughout the trials. Consistency includes activity in both GBM and AA, and it also includes the fact that while six-month progression-free survival and overall progression-free survival were achieved with statistical significance, there are very positive trends which confirm this activity in six-month survival and overall survival. There also is consistent effect in all the populations and subgroups that were studied both prospectively and retrospectively.

We believe that together this presents to you very strong weight of the evidence for consistent activity of Temodal in malignant gliomas and a very favorable benefit to risk ratio.

I would now like to introduce Dr. McDonald who will proceed to give an overview of the disease setting of malignant glioma.

**Disease Background**

[Slide]

DR. MCDONALD: Thank you, Dr. Speigel. I am Dr. David McDonald. I am a neurologist and a neuro-oncologist at the London Regional Cancer Centre in London, Ontario, Canada.

I would like to present a brief overview of the clinical problem of malignant glioma and to make a few comments on clinical trial design in this disease.

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Primary brain tumors constitute an important problem in clinical oncology. Although these diseases are not as common as breast cancer and lung cancer, nevertheless, they have a similar incidence as Hodgkin's disease and malignant melanoma, and constitute a major cause of cancer deaths in children and young adults. About two-thirds of all primary brain tumors are gliomas, and these include astrocytomas, oligodendrogliomas and ependymomas. When these tumors have components of more than one cellular type they are referred to as mixed gliomas, such as oligoastrocytomas. Half of all primary brain tumors are malignant gliomas, and these include the anaplastic or malignant astrocytoma and glioblastoma, and these are the diseases under consideration for use with Temodal.

[Slide]

There are a number of classification schedules that have been proposed for use in malignant glioma. The classification scheme used by the study, which is a standard

classification scheme, is that described by Burger and Nelson. Based on standard histologic criteria, astrocytoma tumors are divided in three categories of increasing growth potential and malignancy. Astrocytomas are also referred to as low grade astrocytomas and are equivalent to World Health Organization grade II tumors. Anaplastic astrocytomas are equivalent to grade III, and glioblastoma, which are the most aggressive and malignant of the tumors, are grade IV. Between the various classification schemes there is close correlation.

[Slide]

Glioblastoma is the most common primary malignant tumor in adults. The annual incidence is 4-5 per 100,000 per year, and this means 8,000 to 10,000 new cases in North America each year. The median age of onset is in the 50s, and the survival is very short from initial diagnosis even with aggressive therapy. Typical survival is 6-12 months.

Anaplastic astrocytomas are less common than glioblastomas. They occur at an incidence of about one-fifth to one-quarter that of glioblastoma. This means 2,000 to 3,000 new cases in North America a year. These occur in patients who are somewhat younger than glioblastoma, typically 40 to 50 years of age, and the median survival is somewhat more favorable than for patients with glioblastoma, typically 2 to 3 years from initial diagnosis with

aggressive therapy.

[Slide]

In consideration of any of these tumors, one must keep in mind that there are a variety of prognostic factors that are found to be important in these tumors. These are features either of the patient or the tumor that seem to influence how the patient does and how the patient responds to treatment.

The best established prognostic features for malignant glioma include age, in which younger patients do better than older patients; histology, in which patients with anaplastic or grade III tumors do better than glioblastoma or grade IV tumors; Karnofsky performance status, in which patients who have a high performance, typically 70 or above, do better than those with a poor performance, typically 60 or below; and degree of resection, in which patients who have gross total resections of their tumor at their diagnosis do better than those with minor resections or biopsies.

[Slide]

Over the years standard treatment for these tumors at initial diagnosis has evolved. Currently standard treatment involves accurate neuroimaging of the tumor based on contrast-enhanced MRI scans or CT scans, and in general MRI is preferred over CT.

Maximum feasible resection to remove the tumor,

followed by cranial radiation which is given focally to the tumor and surrounding margins, and a typical radiation prescription would be 6,000 centi Grays in 30 fractions over 6 weeks. Often this is followed by adjuvant chemotherapy, certainly in North America. For glioblastoma the typical adjuvant chemotherapy is a single agent, nitrosourea chemotherapy, either carmustine, which is BCNU, or lomustine, which is CCNU. For anaplastic astrocytomas the typical adjuvant chemotherapy is a 3-drug combination, called PCV. This is procarbazine, CCNU and vincristine.

In addition to these treatments, supportive therapies, such as dexamethasone to control cerebral edema and anticonvulsants, such as phenytoin to control seizures are given depending upon the individual needs of the patient. Despite these aggressive therapies with surgery, radiation and chemotherapy, malignant gliomas almost invariably recur and, unless there is effective therapy given to the patient, increasing disability and death then result.

[Slide]

At time of recurrence there is really no standard therapy that is available for all patients. When one is faced with a patient with a recurrent malignant glioma, the clinician has several options to consider. The first consideration is whether or not the patient is suitable for repeat surgery. This is dependent upon the location of the

tumor and the clinical status of the patient, and repeat surgery can be done either alone or with placement of Gliadel wafers which, as the committee knows, are BCNU impregnated wafers. Due to our limitations of surgery in this patient population, fewer than 20 percent of patients generally are suitable for repeat surgery.

The next consideration is whether or not one can repeat the radiation therapy. In general, one cannot repeat wide field radiotherapy due to concerns of radiation toxicity and radiation injury in these patients. In highly selective patients, however, those with very small tumors, very localized tumors, it may be possible to repeat the radiotherapy using highly focal, conformal or radiosurgery techniques. Again, this is suitable for only a very small proportion of the patients that have recurrent malignant gliomas.

For most patients, the major option for active therapy at recurrence is chemotherapy. Nitrosoureas, such as BCNU or CCNU, are considered if the patient has not been exposed to these drugs before. Due to concerns about developing resistance and particularly due to the cumulative toxicity of nitrosoureas, it is generally not appropriate to retreat patients with nitrosoureas if they have had previous treatment with these agents before.

In this situation then, a variety of other currently

available chemotherapeutic agents can be considered. These include procarbazine, cisplatin or carboplatin, etoposide, tamoxifen and a variety of other agents. In general, the use of these agents is based on anecdotal experience of treating oncologists in very small and often older clinical trials.

Patients with recurrent tumors may be considered for treatment with an experimental agent as part of a Phase II trial, but not all patients are suitable for these treatments. And, of course, supportive care measures, such as hospice care, may be the best option for some patients, depending upon their clinical situation. It is clear that there is a pressing need for more active effective therapies in this disease.

[Slide]

In consideration of any new therapy one always looks to the medical literature for guidance in terms of evaluating whether the new therapy is a development in comparison to older therapies. Unfortunately, the medical literature on malignant glioma has many limitations.

Many of the older studies lump together patients with glioblastoma and anaplastic astrocytoma even though the outcome and responsiveness of these tumors can be quite different. Small samples sizes are common in the older studies. Some of the studies reported have as few as 10

patients or even less.

Prognostic factors such as age and performance status either are not controlled, not mentioned or not reported. There may be selection bias in the choice of patients for studies, and in some studies the effect of selection bias on entering patients onto study is as large or even greater than the effect of the treatment under question.

Many of the older studies had highly variable evaluation methods, and highly variable response criteria, such that the comparison from one study to the next is very difficult, if not impossible, and certainly comparison of older studies using these limitations to new studies which correct these limitations is very difficult.

Finally, many of the older studies have not addressed quality of life issues which are increasingly important to patients.

[Slide]

In this setting, I would like to comment on the clinical trial design of the studies under question. There were three studies, and I will concentrate initially on the pivotal study, which is the 091. These studies were designed prospectively to recognize and correct some of the limitations of the medical literature in trial design for malignant glioma.

These trials were histology dependent. 091 and 122

were glioblastoma only; 123 was anaplastic astrocytoma only. They were prospective studies, not retrospective. 091 was randomized to Temodal and an active reference agent, which was procarbazine. The sample sizes were large so one could have confidence in the results, and very strict inclusion and exclusion criteria were used to regulate entry onto trial.

In particular, there were very rigorous response and progression criteria that were set up at the beginning of the trial. These were based on MRI evaluation as well as clinical evaluation, and the radiologic responses were confirmed by central radiologic review which was blinded to treatment allocation.

A variety of endpoints were evaluated. The primary endpoint was progression-free survival at six months, and secondary endpoints included response rates, health-related quality of life and overall survival. This general trial design is uniform throughout these trials.

[Slide]

Gadolinium-enhanced MRI was chosen as the imaging modality of choice for several reasons. This is an objective measure of the tumor. It is the most accurate imaging technique available at this time. Multiplanar imaging is available so that one can visualize the tumor. Although it is recognized that there may be infiltrating

cells beyond the margin of the enhancing tumor, it is generally considered that a Gadolinium-enhancing or Gadolinium-positive mass represents active tumor. As such, increases in the size of the enhancing mass or decreases in the size of the enhancing mass represent growth or regression of the tumor. The use of Gadolinium-enhanced MRI is widely accepted in the medical community by neurologists and oncologists, and really sets the current gold standard for brain tumor imaging.

[Slide]

For all these trials very vigorous progression criteria were used. This outlines the criteria that were used in this trial, and I should say that these are widely accepted criteria, which I was privileged to be part of the development of, and these are based on similar criteria in general use in oncology.

These take both radiologic and clinical considerations into factor. A complete response was described as complete disappearance of all enhancing tumor, with the patient clinically stable or improved and the steroid dose stable or reduced; a partial response as a 50 percent or greater reduction in the cross-sectional area of the tumor, with the patient stable or improved and the steroid dose stable or reduced; and, progressive disease was defined as greater than a 25 percent increase in the area of enhancing tumor,

or clinically worse with the patient on a stable dose of steroids or an increased dose of steroids. Stable disease is really all other situations. These response criteria have clearly met widespread acceptance and are widely used in the neuro-oncology field in evaluation of brain tumors at this time.

[Slide]

A variety of endpoints are possible in evaluating new therapies. Response is certainly the traditional endpoint in terms of objective growth or regression of the tumor. However, as I have mentioned, in the past literature a variety of different response criteria and response assessments have been used which makes it difficult to compare the current experience to older experience.

Response in the past has been poorly correlated with survival. It is also known that while tumor growth is either accompanied by clinical deterioration or is very soon followed by clinical deterioration, tumor regression is not always accompanied by clinical improvement because these patients may have fixed neurologic deficits caused by the tumor. Thus, a clinical response alone is not accurate and it is necessary to use radiologic response criteria as an important part of assessment.

Overall survival is certainly an important endpoint. It is certainly accurate. Nobody questions the date of

death. However, it has limitations as well. In particular, overall survival might be influenced by subsequent uncontrolled supportive therapies given to patients at time of tumor progression, and these are therapies that are beyond the control of any study or evaluation of the treatment under question.

Progression-free survival, as I have mentioned, is the endpoint used in these trials. This is a reliable and measurable endpoint when one uses modern imaging modalities and modern criteria, and it is a clinically significant endpoint. Malignant glioma are progressive and ultimately fatal tumors, and a treatment that will prolong useful function, useful survival for months can be an important benefit for patients and their families, giving them time to do important things, accomplish things in their life.

Progression-free survival is not influenced by subsequent therapies that may follow progression, and progression-free survival is an increasingly important and widely accepted endpoint used in clinical trials, including those of the NCI-supported consortium.

[Slide]

As I mentioned before, there were three clinical trials. The 122 trial is also glioblastoma only; the 123 trial is anaplastic astrocytoma only. So, these were histology-specific trials. These were single-arm trials,

and they had the same general design features as the randomized trial.

In summary, I would like to say that these were among the best designed and best executed clinical trials in evaluation of brain tumor, and really they set the standard for the clinical trial development in this disease at this time.

Thank you very much for your attention, and I would like to turn the podium over to Dr. Sara Zaknoen, from Schering-Plough, who will present the clinical results of these trials. Thank you.

**Clinical Data**

DR. ZAKNOEN: Thank you, Dr. McDonald.

[Slide]

Members of the committee, I will be presenting the efficacy and safety results of our program in recurrent glioma.

[Slide]

I would like to structure my talk by first reviewing the clinical pharmacology. It has been very well reviewed in your briefing book so I will only hit the highlights; and then review the efficacy and safety results of our 2 trials in recurrent glioblastoma, and our trial in anaplastic astrocytoma.

[Slide]

For the clinical pharmacology, I would like to briefly review the mechanism of action, the metabolism of Temodal, the rationale for our regimen selection, and review with you the relevant pharmacokinetic data.

[Slide]

As you have heard, Temodal is an oral alkylating agent that methylates DNA at the $O^6$-guanine and $N^7$-guanine positions. Methylation at the $O^6$-guanine position results in mismatch repair and ultimately in single- and double-strand DNA breaks leading to cytotoxicity.

[Slide]

Temodal is non-enzymatically hydrolyzed from its native form, its active form, MTIC, in a pH-dependent manner. MTIC is then rapidly and non-enzymatically hydrolyzed in a pH-dependent manner to its inactive form, AIC. Because enzymatic metabolism plays such a small role, there is low inter- and intra-patient variability in clearance and in half-life.

[Slide]

Preclinical as well as Phase I clinical data support the five-day regimen selected for these trials. A murine lymphoma model suggested multidose regimens improved survival rates in mice over a single dose. In addition, a five-day regimen maximizes depletion of $O^6$-MGMT which is the primary cellular resistance mechanism to Temodal.

Phase I clinical data reported by the CRC demonstrated no response in patients treated with a single-dose regimen. However, if that dose was divided over five days there were complete responses and partial responses reported in this patient population of advanced cancers, including patients with recurrent glioma and melanoma.

[Slide]

Temodal has a dose-related and predictable AUC and $C_{max}$. There is no accumulation with multiple dosing. It has a short half-life of about two hours. It is 100 percent orally available, and food lowers the bioavailability by nine percent.

[Slide]

It penetrates well into the central nervous system and cerebral spinal fluid with about 30 percent of the concentration seen in plasma. The clearance is unaffected by coadministration of commonly prescribed drugs in this population, including steroids, anticonvulsants and anti-emetics. Clearance was also unaffected by age, renal function or mild to moderate hepatic insufficiency.

[Slide]

I would now like to present the data on our randomized, open-label study of Temodal and active reference agent, procarbazine, in the treatment of patients with recurrent glioblastoma multiforme.

[Slide]

As stated, the population was recurrent glioblastoma and gliosarcoma. The design was that of a randomized, open-label reference-agent controlled study. It took place in 21 sites, 19 domestically and 2 sites in the U.K. It enrolled 225 patients from January of 1995 to October of 1997. As stated by Dr. McDonald, there was central neuropathology and central neuroradiology review.

[Slide]

The primary efficacy endpoint was progression-free survival at 6 months. More specifically, it was to demonstrate that the progression-free survival rate at six months was significant greater than 10 percent, with 10 percent considered the threshold of effectiveness. It was also to determine the activity of the active reference agent in patients enrolled in this trial. The 10 percent level of effectiveness was determined after reviewing the literature, discussing with expert neuro-oncologists and analyzing a historical data base acquired from the University of California at San Francisco.

[Slide]

On this slide we show the analysis of 93 patients from the UCSF database who were treated with a variety of single agents in protocols that were similar in design to our trial. The progression-free survival rate for those

patients at 6 months was 10 percent, and ranged from 0 to around 20 percent for procarbazine patients. However, the number of patients analyzed in this trial was quite low, 10.

We were also able to acquire from M.D. Anderson their data on patients treated in recurrence with procarbazine, and the progression-free survival rate with those patients was about 14 percent.

[Slide]

Secondary study objectives included overall survival, response rate and quality of life.

[Slide]

The key inclusion criteria are shown on the next two slides, and I will go through them briefly. As stated, patients must have had histologically proven GBM or gliosarcoma. They must have had enhancing residual tumor on Gadolinium-enhanced MRI, and in a small percentage of patients contrast-enhanced CT scans, after failing standard first-line radiation therapy. They could have had no more than one prior chemotherapy regimen which must have contained a nitrosourea. They could not have had prior interstitial radiotherapy or stereotactic radiosurgery. If they underwent surgical resection for recurrent disease, there must be residual enhancing tumor evidence on an MRI scan done 72 hours after surgery.

[Slide]

They must have had a Karnofsky performance status of greater than 70, a life expectancy of greater than 12 weeks, and to have signed informed consent.

[Slide]

The study schema is shown here. Patients were prospectively stratified for age, prior chemotherapy and prior surgery at initial diagnosis, and randomized to receive Temodal or procarbazine at the doses and schedules listed. The dose and schedule for procarbazine is that used standardly in recurrent patients.

Patients were evaluated monthly with a performance evaluation, neurologic examination, clinical evaluation and a quality of life questionnaire. Tumor was evaluated every two months with either Gadolinium-enhanced MRI or contrast-enhanced CT scan.

[Slide]

The study populations I will be presenting are the intent-to-treat population of all 225 patients randomized, and a safety population of 220 patients. Five patients did not receive study drug.

[Slide]

The demographic characteristics are shown on this slide, and are balanced between the two groups, with a median age of 52 for Temodal and 51 for procarbazine. The majority of patients had a KPS of greater than 80.

[Slide]

Previous therapies were also well balanced between the groups. The majority of patients had surgery at initial diagnosis. All patients had failed prior radiation therapy. Two-thirds of patients had nitrosourea-containing chemotherapy, and 20 percent of patients had surgery at first relapse.

[Slide]

The primary efficacy endpoint is shown here. For Temodal the six-month progression-free survival was 21 percent, with a confidence interval of 13-19 percent.

[Slide]

In addition, when compared to procarbazine there is a statistically significant greater six-month rate for Temodal, 21, compared to procarbazine, with a p value of 0.016 and a hazard ratio of 0.147, which means that on procarbazine 47 percent more patients were likely to have progression than on Temodal.

[Slide]

Our secondary endpoint of overall survival, although not statistically significant, has a trend in favor of Temodal with a six-month overall survival rate of 60 percent compared to 48 percent for procarbazine, and a p value of 0.067 and a hazard ratio of 1.15.

[Slide]

Response rates were similar between the two groups for objective response rates, five percent each for Temodal and procarbazine. However, a higher number of patients on Temodal obtained stable disease. It is traditional in the glioma literature to include stable disease in listings of overall response rate. So, the overall response rate for Temodal is 46 percent compared to 33 percent for procarbazine.

[Slide]

To look at the effect of known prognostic factors, such as KPS and age, on the treatment outcome a Cox regression analysis was performed. In the presence of these factors the effect of treatment on progression-free survival remained significant.

[Slide]

In addition, subgroup analyses were performed based on each of these factors. The analyses demonstrate the remarkable consistency of the advantage of Temodal on progression-free and overall survival. Regardless of the subgroup for progression-free survival, the hazard ratio is always greater than 1, and for overall survival all but two of the hazard ratios are greater than one.

[Slide]

Quality of life was assessed with the EORTC QLQ C30+3 and a second validated brain cancer model, the BCM20. A

quality of life response was defined as a 10-point improvement from baseline maintained for at least two months.

[Slide]

This slide shows for both Temodal and procarbazine the percent of patients achieving such a quality of life response in each of 7 quality of life domains, considered by a panel of clinical experts, to be or most clinical relevance.

Two observations can be made from this data: Quality of life improvement was consistent across multiple domains, and in all seven of the domains more Temodal than procarbazine patients achieved this quality of life response.

[Slide]

The quality of life data collected in the trial was also useful in showing the benefit of delaying MRI-based progression. This slide and the next will show that in six of the seven of the quality of life domains the quality of life scores declined at the point of MRI-defined disease progression, as shown. However, if one looks at one month before disease progression quality of life is stable.

[Slide]

This slide shows symptoms of visual disorder, motor dysfunction, communication deficit and drowsiness. Again,

at the time of progression a decrement in quality of life; however, at the month prior, stable quality of life.

[Slide]

I would now like to briefly review the results of I94-122, which is the supportive trial in recurrent glioblastoma. It was similar in all ways to the design of the 091 trial. It recruited patients with recurrent glioblastoma as well as gliosarcoma. It was a Phase II single-arm trial which took place in 26 international sites, enrolling 138 patients. It had as well central neuropathology and neuroradiology review.

[Slide]

The progression-free survival for the 122 patients was very similar to those seen in 091, with a progression-free survival rate of 19 percent compared to 21 percent, and a confidence interval of 12-26 percent.

[Slide]

Responses were also seen in this population. There were two complete responses and nine partial responses for an objective response rate of eight percent, and including stable disease an overall response rate of 51 percent.

[Slide]

To summarize then our efficacy in the recurrent glioblastoma population, progression-free survival at six months was significantly higher than ten percent on Temodal

in both of the trials, 091 and 122. Progression-free survival at six months was significantly higher with Temodal compared with procarbazine, 21 percent for Temodal, 9 percent for procarbazine. In addition, overall progression-free survival with Temodal was also significantly longer than with procarbazine.

[Slide]

For our secondary endpoint of overall survival, although not significantly different from procarbazine, favored Temodal with a median of 7.3 months versus 5.8 months, and a six-month overall rate of 60 percent versus 48 percent. The quality of life domain scores confirmed that clinical deterioration at MRI progression can be detected, and that there were quality of life benefits seen with Temodal.

[Slide]

To briefly review the safety, over 90 percent of Temodal patients were still on treatment after two months, compared to procarbazine where the majority of patients had dropped off the study after the first 2 months. The doses were generally at the protocol specified dose level, and there was a small percentage of patients in both arms who required dose reductions, primarily for hematologic toxicity. The number of patients discontinuing treatment was less for Temodal, 3, compared with 11 for procarbazine.

[Slide]

Overall adverse events for the two treatments were similar when one looks at all patients and all cycles. If one looks at grade 3 and 4 adverse events, again for all cycles the incidence was similar between the two drugs, with the highest reports of headache, thrombocytopenia, vomiting, convulsions, hemiparesis, gait abnormality and somnolence. With the exception of thrombocytopenia and vomiting, it was felt by the investigators that the majority of the adverse events were related to disease progression or concomitant medication rather than study drug.

[Slide]

Because so many of the procarbazine patients dropped off after the first 2 months of trial, we looked at the adverse events reported during the first 56 days or two months of the trial, which was one cycle for procarbazine and two cycles for Temodal. Here, one can see that there is a smaller number of reported grade 3 adverse events for Temodal, 26, versus procarbazine, 35.

[Slide]

Myelosuppression was of low incidence, 11 percent of patients on Temodal had neutropenia; 15 percent had thrombocytopenia compared to 13 and 19 percent for procarbazine.

[Slide]

To summarize the safety then, adverse events were generally mild to moderate and were readily reversible. Temodal was administered more often at full dose levels and with fewer dose reductions or dose delays compared with procarbazine. Discontinuations due to adverse events were infrequent, 3 with Temodal and 11 with procarbazine.

[Slide]

Myelosuppression was of low incidence and occurred in the first few cycles of treatment and was not cumulative. Nadir platelet and neutrophil counts occurred late in the 28-day cycle and resolved within 14 days.

Although I have not shown the data for the safety of the 122 patients, it is very similar to the safety profile seen in the 091 patients, and is included in your briefing books.

[Slide]

Next I would like to turn to the Phase II study of Temodal in the treatment of patients with recurrent anaplastic astrocytoma.

[Slide]

The population was recurrent anaplastic astrocytoma and anaplastic mixed oligoastrocytoma. The design was a Phase II, single-arm study which took place at 15 sites in the U.S. and 17 sites internationally, and enrolled 162 patients from February of 1995 to June of 1996, and had

central neuropathology and neuroradiology review, and, as you have heard from Dr. McDonald, was in all ways identical in design to the glioma trials.

[Slide]

The primary efficacy endpoint was progression-free survival at six months. Secondary endpoints were overall survival, response rate and quality of life.

[Slide]

The study conduct was identical in inclusion and exclusion criteria, with the exception of histology. The Temodal dosing schedule was the same, as was the schedule of the clinical and Gadolinium-enhancing scans.

[Slide]

The three populations to be discussed are, first, the intent-to-treat which includes all 162 patients enrolled; the eligible histology population which includes only those patients with AA or AOA as deemed by the central neuropathologist; and 158 patients for safety. Four patients did not receive study drug.

[Slide]

The demographic characteristics are shown here. The median age was 42, which is a decade younger than the median age of the glioma population. Around 70 percent of patients had surgery at initial diagnosis. All had failed prior radiation therapy. Although 60 percent of the overall

intent-to-treat patients had prior chemotherapy, 80 percent of those patients from the domestic sites had prior chemotherapy and 36 percent at the international sites. Similar to the recurrent glioma population, 20 percent of patients had surgery at first relapse.

[Slide]

The primary protocol endpoint, progression-free survival, is shown here as 46 percent, the median progression-free survival of 5.4 months.

[Slide]

Overall survival, our secondary endpoint, is here, six-month overall survival rate of 75 percent and a 12-month survival rate of 56 percent. The median overall survival was 13.6 months.

[Slide]

Perhaps most encouraging results were seen in response rates. If one looks at the overall intent-to-treat population of 162 patients, there were 13 complete responses and 44 partial responses for a combined objective response rate of 35 percent. If one includes stable disease, the overall response rate was 62 percent. If one looks at the eligible histology population, that is, those patients with AA of AOA, there were 8 complete responses and 31 partial responses, again, for an objective response rate of 35 percent and an overall response rate of 64 percent.

[Slide]

Responses occurred in patients regardless of prior nitrosourea-containing chemotherapy. In patients who received prior chemotherapy there were 6 complete responses and 23 partial responses for an objective response rate of 30 percent, overall response rate of 58 percent. As would be expected in patients who hadn't received prior chemotherapy, the response rate is somewhat higher, with an objective response rate of 43 percent and an overall response rate of 69 percent.

[Slide]

I would just like to review briefly some of complete the responses that we had. They ranged from 4 months to greater than 26 months, and occurred in patients who had radiation therapy alone as well as radiation therapy and PCB.

[Slide]

These data show that patients who received an objective response, in the yellow, or had stable disease, in the blue, achieved greater quality of life responses than patients who did not, those patients who had progression disease, shown in green, for all seven quality of life domains I presented previously.

[Slide]

To summarize efficacy in the recurrent astrocytoma

population, Temodal as a single agent demonstrated efficacy in relapsed AA patients, with an objective response rate of 35 percent and an overall response rate of 62 percent. The progression-free survival at 6 months was 46 percent, with 24 percent of patients remaining progression free at one year.

[Slide]

Median overall survival was 13.6 months, with 56 percent of patients alive at one year. Progression-free status and response, either CR of PR, was associated with quality of life benefits.

[Slide]

To briefly review the safety, the grade 3 and 4 adverse events most common are listed here, and are very similar to the glioma population. Again, with the exception of thrombocytopenia, nausea and vomiting, they were reported to be unrelated to study drug and related to disease progression or concomitant medications. Nine patients discontinued on this trial due to adverse events.

[Slide]

To review our overall safety database of over 1000 patients, including 500 patients on melanoma trials as well as other Phase I and Phase II trials, in general the overall AE profile is very similar to the glioma experience that I just described to you. There were no unusual or unexpected

adverse events or organ toxicities.

[Slide]

I would just like to take a moment to address a concern raised in the questions from the FDA on the incidence of thromboembolism in this population. It is well reported that patients with malignant glioma are at high risk for the development of thromboembolic phenomena, including deep venous thrombosis and pulmonary embolism. The number of these events, listed in your Table number 7, reflect the number for the overall 400 patients in the glioma population. If we break them down and look at them individually, we see that the incidence is about the same for pulmonary embolism and DVT for glioma patients on all cycles of the Temodal patients in 091 and the procarbazine patients of 091, the Temodal patients of 122 and 123.

In addition, in 151 patients randomized to the Temodal arm of a large melanoma trial there were no reports of pulmonary embolism or DVT. If one looks at the first 56 days or the 2 months when the majority of procarbazine patients were still on trial, again, there is a very low incidence in all of the trials.

We, therefore, believe that the incidence of venous thromboembolism represents the disease rather than the study drug.

[Slide]

To summarize then, we have demonstrated the efficacy of Temodal in the treatment of gliomas at first relapse in three large trials involving over 400 patients.

There has been a significant benefit for glioblastoma patients at six months as compared to procarbazine in the randomized trial, and a high rate of meaningful objective responses in recurrent AA patients.

[Slide]

Consistent effects were seen in all subgroups, and there were positive confirmatory survival trends in the randomized trial.

Temodal is very well tolerated and has a very acceptable safety profile. Response, CRs and PRs, or delay of progression is associated with a quality of life benefit for these patients. Overall, we feel this drug has a very positive benefit-risk profile.

Thank you for your attention. I would now like to introduce Dr. Nancy Yue who will be making comments on the MRI imaging in this trial.

**MRI Imaging**

DR. YUE: Good morning.

[Slide]

I am Dr. Nancy Yue. I am an Assistant Professor of Radiology at Johns Hopkins, in the Department of Radiology in the Division of Neuroradiology. I also served as the

head of the committee of neuroradiologists who reviewed the MRI scans on these patients. I have to add that the reviewers were blinded as to the clinical arm of the trial of these patients. They were also blinded as to the clinical status and to the investigator's assessment of the MRI results at the individual sites.

[Slide]

I am here to answer the question of whether progression can really be reliably detected by contrast-enhanced MRI-based criteria. It is well accepted in neuro-oncology that there are variable amounts of glioblastoma which do not enhance with contrast. However, as stated by Dr. McDonald, contrast-enhanced MRI does remain the standard for assessment in neuro-oncology since it is sensitive to response and progression in active tumor.

The use of two-dimensional areas is the accepted standard for progression or response not only in neuro-oncology but also in all of oncology. Now, as an adjunct study in these patients, we did collect volumetric data, three-dimensional data, both utilizing maximal perpendicular diameters and also traced volumetric data. A preliminary interim analysis of these results indicates very similar response percentages to that indicated by the use of axial areas.

We also looked at the scans to see if the progressions

could be considered to be subtle. In fact, in this study two-thirds of the patients progressed with a greater than 50 percent increase in the enhancing tumor area. So, these are not subtle responses.

I have also been told that of all the progression, 85 percent of the patients had scan-based progression, and there was a small number that progressed without having an MRI scan, and in most of the patients it was because they were unable to have an MRI scan either due to clinical progression or due to death.

[Slide]

We designed the MRI methodology to be very rigorous so that we could compare the scans from patient to patient and also from scan to scan. This is part of the prescription that was sent out to each of the sites, and also the sites were told to call me for questions about methodology, which they certainly did.

I also want to show you some of the scans on these patients. These scans were selected randomly from the database just to demonstrate the degrees of progression, and I remain blinded as to the clinical arm of the trial and also to the clinical status of these patients.

[Slide]

This is the first patient. This scan demonstrates from before to after a 26 percent increase in the area of

the tumor and, as you can see, this is not a subtle response although it does barely meet our criteria for progressive disease by MRI criteria.

[Slide]

The second patient is more representative of the typical type of tumor progression. This particular patient showed a 78 percent increase in the percentage of increase of axial areas.

[Slide]

The third patient is representative of the patients that were considered to be non-measurable. This patient was considered to be non-measurable because there were 3 or more enhancing areas but, as you can see, the enlargement in the size of the tumor, again, is not subtle.

So, in summary, we consider MRI to be the most sensitive modality presently available for evaluation for progression or response in glioblastoma. It is accepted throughout the neuro-oncologic community and is utilized by both the pediatric and adult brain tumor consortia in every one of their clinical trials.

So, if you have any questions, I would be happy to address them after this session. I would like to now introduce Dr. Alfred Yung from M.D. Anderson.

**Clinical Perspective: Glioblastoma**

DR. YUNG: Thank you, Dr. Yue.

[Slide]

I am Alfred Yung. I am from the M.D. Anderson Cancer Center, in Houston. There, I am the Medical Director of the Multidisciplinary Brain Tumor Clinic and we see over 600 new patients with brain tumor a year. I am also the director of clinical trials for our brain tumor center, and we enrolled the most number of patients into both the glioblastoma and AA trial on Temodal.

In the last 20 years as a neuro-oncologist seeing patients with glioblastoma and doing clinical trials and trying to identify a better regimen for these patients, I am constantly frustrated because we haven't found any wonderful drug for them. We still have BCNU and procarbazine. The latest Gliadel entry also represents BCNU in a slow-release wafer.

[Slide]

The two trials presented to you for glioblastoma and anaplastic astrocytoma with Temodal share the same strengths. They are prospectively designed trials. The glioblastoma trial is randomized. There is straight pathology and radiology central review to assure the quality of the entry. There are straight exclusion/inclusion criteria. Above all, the sample size is large compared to other reported Phase II trials with new drugs. They usually have only 10-15 patients. More importantly, the response

and progression criteria are prospectively defined, and also blind-reviewed by a group of central radiologists.

[Slide]

When a patient with recurrent glioblastoma, after primary treatment, comes to my clinic, what do I have to offer them? There are three options. One option is going to supportive care or hospice care, and do nothing. The second alternative is to go onto a Phase II trial that we have ongoing. The number of patients that are eligible for a Phase II trial is not the majority. The majority of them fall into this group where we have to use non-protocol regimens including radiation therapy, surgery with or without Gliadel, or chemotherapy.

Radiation therapy is really not a good option because they already have external-beam radiation. The only alternative is radiosurgery.

As to surgery, 20 percent of patients are eligible for re-resection, and those patients have the option of receiving Gliadel and then afterwards they can follow with systemic chemotherapy.

[Slide]

Since there is no standard agent for systemic chemotherapy, for the 80 percent of patients that do not qualify for re-resection these are the commonly used drugs that we can offer them: procarbazine, carboplatin,

carboplatin plus etoposide.

[Slide]

What do we offer these people with these regimens? These are the response rates and six-month progression-free survival rate that we can get from the literature and from our own experience at M.D. Anderson.

Procarbazine offers a response rate, including CR, PR and stable disease, of 28 percent; 14 percent progression-free survival at 6 months; and 9 weeks of median time to progression. Carboplatin, 40 percent response rate, CR, PR and stable disease; 14 percent six-month progression-free survival and 9 weeks of median time to progression. Carboplatin and etoposide offers only 21 percent for CR, PR and stable disease. In the randomized trial with Temodal, Temodal offered 46 percent in response rate of CR, PR and stable disease, and a six-month progression-free survival of 21 percent, which is better than procarbazine or carboplatin; a median time to progression of 13 weeks, which is also better than carboplatin and procarbazine. In the reference arm it is 32 percent and 9 percent at 9 weeks, which is comparable to the other data in the literature.

[Slide]

What about the side effects? What does the patient feel? The side effects for a patient on Temodal are similar and slightly better than for procarbazine in hematologic

toxicity as well as non-hematologic toxicity, and definitely better than carboplatin and carboplatin and etoposide when it come to hematologic toxicity.

[Slide]

What about Gliadel? Gliadel is applicable for patients that can go to re-resection with a complete resection of a tumor and putting a Gliadel wafer in after surgery. These patients generally represent a selected group of better quality patients, and 40 percent of the patients in a trial receive systemic chemotherapy, and analysis of the trial shows benefit for glioblastoma patients.

[Slide]

How does Temodal compare to Gliadel? When you look at the six-month survival, Gliadel is 56 percent and Temodal has 60 percent. If you look at overall mean survival, Gliadel has 6.5 month while Temodal has 7.3 months.

[Slide]

Is progression-free survival an appropriate endpoint for this kind of trial? I think so. Progression-free survival allows us to look at the study drug specifically in that period. It also takes into account all responders, including the patients who achieve CR, PR and stable disease.

When we look at six-month progression-free survival,

we look at the majority of patients since they all failed very early. In this trial that was presented, progression-free survival correlates with prolongation of overall survival. It remained consistent with all the subgroups that were looked at and analyzed. More importantly, patients that remained progression free also remained stable with quality of life. So, they enjoy stable or better quality of life during the time that they were progression free. It is being used as an endpoint in many of the North American Brain Cancer Consortium trials that we are organizing now.

[Slide]

So, in summary, from the data that we have, Temodal is an active drug. It offers a greater than six-month progression-free survival and a favorable trend in six-month overall survival than procarbazine. The patients that remain progression free enjoy stable and better quality of life and, more importantly, it is convenient. Patients only get sick for about five days of a month as compared with procarbazine where they may remain sick for the entire month.

As I told my patients, Temodal is not a wonder drug that will cure a tumor that we are looking for. We are still looking for that agent. But it offers the best choice that we have now compared to procarbazine and carboplatin.

Thank you. Let me introduce Dr. Friedman now to present his perspective on anaplastic astrocytoma.

**Clinical Perspective: Anaplastic Astrocytoma**

DR. FRIEDMAN: Good morning.

[Slide]

I am Henry Friedman. I am Co-director of the Clinical Neuro-Oncology Program at Duke Medical Center. We see approximately 50 patients new to Duke each month with brain tumors. I think each year we wind up seeing a few more than M.D. Anderson.

[Laughter]

[Slide]

Let's first talk about anaplastic astrocytoma, newly diagnosed patients. Standard of care: surgery, radiotherapy and a chemotherapeutic regimen called PCV, known as procarbazine, lomustine or CCNU and vincristine. With that intervention the median survival is approximately 36 months. It is a better disease to have clearly than GBM.

[Slide]

Unfortunately, patients with recurrent anaplastic astrocytoma do not have the same outcome. There is no standard of care for these patients. The median survival is measured in six to nine months.

[Slide]

The options that are available for patients with a

recurrent anaplastic astrocytoma: We, of course, think of Phase II trials or Phase I trials even with recurrent AA. The majority of patients do not qualify for that. We certainly have access to nitrosoureas and procarbazine, but the majority of patients will have seen these agents, precluding their use. Carboplatin, irinotecan, also called CPT11, tamoxifen have in small trials shown some activity but their activity borders so far on the anecdotal.

[Slide]

If you look at the published literature from which you can extract those patients who had AA as opposed to glioblastoma, you can see response rates that range from as low as 6 to the current study of Temodal at 35 percent. But if you look at the numbers, many of these studies are very small in numbers. This is clearly the largest trial using a single agent or a combination agent for the treatment of recurrent anaplastic astrocytoma, and only Levin's trial using multiple agents, with more toxicity, had a response rate approximating that and, of note, no CRs.

[Slide]

If you look at it a different way, evaluating activity or efficacy, in this case efficacy, you can look at the database that has come out of M.D. Anderson with 150 patients in eight different Phase II trials where you see a progression-free survival of 31 percent versus 46 percent

for the Temodal trial; a time to progression of 13 weeks versus 22 weeks for Temodal. To reiterate what has been said, time to progression or the absolute documentation radiographically of progression is the standard in every trial in this country, pediatric or adult.

[Slide]

The strength of the Temodal study has been stated, and I will just simply reiterate it. It was limited to AA and AOA. It is the largest study that has been done, with very strict criteria for inclusion and exclusion; very rigorous response and progression criteria; the use of Gadolinium-enhanced MRI, which is the standard of care in this country for neuro-oncology; central radiology/pathology review; and the same endpoints as the GBM trial.

It is not a flawless study. If one were to critique the AA study conducted with Temodal, the major concern has to be that it is not a randomized, 2-arm study. The question is could such a study in recurrent AA have been conducted? Should it have been conducted? The problem in this country is that the standard of care--surgery, radiation and adjuvant chemotherapy, PCV is the usual intervention. It is simply inconceivable that one should or could have run a trial with a placebo control. You have no standard arm to control to. So, despite any consideration as to how the trial should have been done, it is impossible

in this country to do that, at least for recurrent anaplastic astrocytoma. Seventy-eight percent of the patients in the U.S. trial had a prior nitrosourea-based chemotherapy. It is not a perfect world, folks; it could not have been done.

[Slide]

So what are the conclusions that we can derive then for AA? Patients with recurrent disease have no meaningful options--none. Temodal is safe. It is active in recurrent anaplastic astrocytoma.

Finally, I am unaware of any trial that has been conducted with recurrent malignant glioma or, for that matter, newly diagnosed tumors that have any meaningful numbers with systemic chemotherapy that failed to show that those patients with AA didn't do better, far better than those patients with GMB. So the fact that you have such strength of the GBM randomized trial only increases our belief and conviction that the agent will have better activity, if anything, in recurrent anaplastic astrocytoma.

Thank you.

**Questions from the Committee**

DR. DUTCHER: Thank you. Are there questions from the members of the committee for the sponsor? Dr. Krook?

DR. KROOK: I believe when I first became a member of ODAC this was one of the first formal conversations that I

was involved in, and I remember--and there are certainly people in the audience who were there--the issue of the reference and how to set up a study in GBM. I believe that this is a Phase II where it is not truly a randomized trial; it is not a double-blind trial. I think as I look at the literature that we are not really comparing procarbazine with Temodal, but we all look at it that way. So, if I am correct, this was not really, truly a randomized trial in a true Phase III. Am I right? It is a Phase II with two agents.

DR. SPEIGEL: Well, it was randomized but I think your characterization is correct.

DR. DUTCHER: It was a randomized Phase II design.

DR. KROOK: Right, because we had a long discussion about just exactly what my colleague from Duke said, that we could not do a double-blind study, and we needed to do something, and procarbazine was another oral agent.

My second question is if a patient was randomized to procarbazine on the 91 study, could they cross over to 122 and get active drug? If they were on procarbazine they could not because, as I remember reading, some of the same institutions participated in both.

DR. SPEIGEL: The answer to the second question is that you are correct. Some institutions, in fact many institutions had both trials open, however, they were not

permitted to cross over or have any inducement to go off of 091 so they would be able to get Temodal on 122.

But let me address your first point, and I also wanted to make an opening statement saying that as sponsors we certainly agree with the assessment Dr. Friedman made about the difficulty of doing a randomized trial in relapsed AA. However, I should state that in our pre-NDA conversation with the agency we have agreed that as a condition of accelerated approval for Temodal we would be very willing, and very pleased to do a randomized Phase IV commitment in newly diagnosed AA, and that is one of the conditions of our being here today, our agreement and actual enthusiasm to do further study in front-line treatment in a randomized way of AA.

Let me address what we expected to be a very obvious question about this unusual trial design, if I could have slide number 127?

[Slide]

What I would like to do is take you back to 1994 and the assumptions at that time which, as Dr. Krook said, he participated in as an ODAC representative--and I am sure, in retrospect, he was very pleased by that opportunity--in our discussions with the agency.

What was our rationale for what we are calling a randomized reference agent controlled study design? We have

a group of statisticians here who would be glad to speak statistical language to the members of the committee who would like that; I will try to translate it as a clinician. A study size to demonstrate an absolute 10 percent superiority to an active comparator would require 300 patients per arm or 600 patients. So, if we assume that procarbazine, in the literature, had a true six-month progression-free survival rate of 14 percent, and we had the confidence in our Temodal from the Phase I trial that it would have a 24 percent six-month progression-free survival, with the power that we projected to be necessary and a p value of 0.05 required at the time the study was completed, it was projected that that would require 600 patients.

Obviously, a study designed to demonstrate equivalence would be even larger. As everyone I think can appreciate, a placebo control in the classical sense was not considered feasible or perhaps even ethical at that time.

With an active reference agent design, it would allow an attainable N, in our opinion, in a reasonable period of time with sufficient statistical power if we had a 20 percent progression-free survival at six months to exclude what we considered from looking at the literature and discussing it with the agency to be a historical database that showed that there are ineffective agents that would have less than 20 percent progression-free survival.

So, we proceeded to initiate study 091 with the commitment to the agency that it would be our obligation today, when the study was all over, to show an adequate historical experience that would confirm that there are truly ineffective agents that wouldn't reach this point, and that our study was sized to show an active reference agent, procarbazine in this case, for comparison purposes. But the true endpoint of the 091 study was to complete the study with large numbers and, therefore, a small confidence interval that would exclude it being seen as an ineffective agent.

[Slide]

Now I am going to get on more dangerous ground, talking statistically. This is another way to present some assumptions that could be made depending on what you expected your drug to do. If we said we would go from 14 percent--if we knew we were going to go from procarbazine coming in a 14 percent to 20 percent with Temodal, that would be projecting a hazard ratio of 1.2, which again would have required, if we had set it up as a direct comparator study, 962 events.

Now, it turns out that Temodal performed very well and procarbazine performed pretty poorly compared to what the literature would have predicted. So, we actually came in closer to a hazard ratio of 1.5, which only required 195

events.

[Slide]

This shows you the overall survival curve that Dr. Zaknoen presented earlier. If I can draw your attention to the right-hand side, that shows the six-month overall survival outcome, which was 60 percent for Temodal versus 48 percent for procarbazine as a six-month overall survival rate. That actually has a hazard ratio of 1.46 and it came close to a significant p value of 0.67. However, that is six-month overall survival. That is an endpoint that Gliadel was able to hit when it was compared to placebo.

If we look at our overall survival results on the left-hand portion of the bar, at the bottom, we are looking at Temodal having a median overall survival of 7.3 months versus 5.82 months, about a 1.5 month increment produced by Temodal, but the hazard ratio is only 1.15 and the p value is 0.337, all of which is to say that it takes a very large study to be powered to show a survival difference in this setting.

Dr. Krook, I think that really reiterates where we were in 1994, and the outcome has only shown that. Because of the outcome of the study, although we designed it and we said repeatedly that the intent was not to do a direct comparison to procarbazine, we felt that it would be asked very likely how do you look compared to your comparator

agent. We made this comparison, and it is only because procarbazine in this type of rigorous design performed poorly and Temodal performed even a little better than we expected that we are much closer to statistical significant in at least six-month overall survival than we had initially anticipated.

DR. DUTCHER: Dr. Raghavan?

DR. RAGHAVAN: I have three quick questions. The first is to Dr. Zaknoen. I notice, looking at the demography of the patients, that there are about 2.5 times the number of non-Caucasian patients treated with procarbazine as compared to Temodal. Understanding the numbers are small and you didn't look at race as an outcome determinant, do you think that influences the outcome at all?

DR. ZAKNOEN: Yes, you are right. The vast majority of the patients were Caucasian, and we did not look at the efficacy in the subsets of non-Caucasians.

DR. RAGHAVAN: Thank you. My second question is to Dr. Yue, and I may have this wrong but in trying to marry the various bits of data it seems to me that you presented two CT scans from patients who were less than 60, had previously been treated with MRI scans and had previously undergone surgery, and one who was less than 60 who had had chemotherapy but not surgery. And, that is based, from what

I understand, as your numbering system.

My question is, was there any mechanism for you to identify which arm the patients were in? So, for example, if you had a patient numbers 015 or 019, that means less than 100 and, were the first 50 numbers allocated to procarbazine and the second 50 numbers in a series allocated to the study drug so that you could actually look at the numbering system and identify what treatment the patient had had? You can characterize quite a lot about the patients just by the numbering. Were you able to identify what the treatment was?

DR. YUE: Actually, if there was a systematic numbering method I am not aware of it. So, no. The only way we could tell by looking at the cranial changes on the MRI to assess whether there had been prior surgery.

DR. RAGHAVAN: Thank you. My final question is to Dr. Friedman. It must have hurt you to comment that you see more cases than the M.D. Anderson does. I could feel the pain!

[Laughter]

But I also noticed that you entered less than a third the number of cases that they did--

[Laughter]

--and my question is what are the selection biases for entry at Duke? Is there a particular type of case that gets

entered into this type of trial?

DR. FRIEDMAN: The accrual at Duke during the last four years has gone from 100 to 200 to approximately 400 and now 600 patients annually referred. So, I suspect that the accrual to the Temodal trials reflect the number of patients we were actually seeing at that time, during those years. The reasons for the accrual increasing are really beyond the scope of this although I would be glad to talk about that. The selection criteria at Duke are in general that those trials which represent a translation from laboratory pursuits to the clinic, that is, a lab clinic pathway, are the protocols that we consider our highest priority, and we have had extensive laboratory work both with the activity and the mechanisms of resistance to Temodal which reflects our interest in working with the agent now.

DR. DUTCHER: Along these lines, in terms of a question, Dr. Yung presented that approximately 20 percent of relapsed GBM patients would actually be eligible for Phase II. Could you give us some estimate of what percentage of relapsed AA patients would be eligible for experimental therapy--by meeting eligibility criteria, not just because there is nothing available but that would meet the strict criteria that are presented in a clinical trial?

DR. FRIEDMAN: Well, it depends on the nature of the trial so it is hard and it is going to be institution by

institution. For example, at Duke, because there are a number of regional therapy protocols using, for example, radiolabeled monoclonal antibodies, that is much more restrictive eligibility with a resectable tumor. But in general for patients with anaplastic astrocytoma who would be considered Phase II eligible in general, you are probably talking about somewhere between 20 and 40 percent of patients who would be eligible for a clinical trial with that kind of eligibility based on Kornofsky, size of tumor, etc.

DR. DUTCHER: Dr. Buckner?

DR. BUCKNER: Yes, I have a couple of questions for Dr. Zaknoen. First, on the pivotal study, I believe that you mentioned that progression was defined either by MR imaging or by clinical criteria. Do you have the breakout by arm of what proportion are procarbazine versus Temodal patients, what proportion was by clinical track criteria only?

DR. ZAKNOEN: Yes.

DR. BUCKNER: And, if you don't have that now we could receive it later. We can come back to that.

DR. ZAKNOEN: We do have that.

DR. BUCKNER: And, just one other piece of information I would like in terms of the AA study, these are patients with anaplastic astrocytoma or anaplastic oligoastrocytoma

who were included in this trial. Do you have a breakout of response based on the different histologic types, please?

DR. ZAKNOEN: Yes, I do. May I have slide 312?

[Slide]

This is for the AA trial. What I have added to this is an arm or a column at the very end in which we looked at AA alone. So, the intent-to-treat is all the eligible histologies, AA and AOA. The AA arm alone, with AOAs factored out, had a complete response rate of six percent and a partial response rate of 28 percent, for an objective response rate of 34 percent.

DR. BUCKNER: And similarly, do you have progression-free survival data by the same criteria by AA versus AOA?

DR. ZAKNOEN: No, I have it for AA plus AOA compared to the intent-to-treat but not for the AA alone.

DR. SPEIGEL: Dr. Zaknoen might actually have the specific data you requested for procarbazine versus Temodal. I think we might want to show slide 170. In response to some of the questions that we have had in our interactions with the FDA and also some European authorities, there has been some question about whether the MRI-based scan is accurate; is the best measure of what a new drug can do. Although all of our experts told us initially, and our clinicians continue to say that clinical deterioration is an uncertain science--it depends on where the tumor is growing

and you wouldn't expect in many patients clinical signs to improve upon response, you can take a look at whether clinical deterioration correlated with the MRI-based scan, which was the primary endpoint. So, this wasn't even intended as a secondary endpoint of our study but we have looked at it in response to some questions from regulatory authorities.

[Slide]

This slide shows what is the time to clinical worsening, defined as a KPS score decreasing to less than 60. Remember that we needed a performance score of 70 to get into the trial. If you look at the time to worsening to 60, there is a clear separation of the Temodal versus the procarbazine over time.

And, we have a series of other analyses along this line as well that show any way that we looked at clinical worsening, if we also looked at what time did the patients have an absolute decrement from wherever they started, it shows a similar outcome. It separates.

[Slide]

So, I just wanted to bring that to your attention, that we have looked, although it wasn't an intended analysis, at time to clinical deterioration independent of MRI scans being called progressive.

I don't know if Sara wants to talk specifically about

your question about Temodal versus procarbazine.

DR. ZAKNOEN: No, I am actually still trying to find a slide.

DR. DUTCHER: All right, we will go on. Dr. Schilsky?

DR. SCHILSKY: I have another question about the central MRI review. Can you tell us what was the concordance rate between the central reviewers' assessment of the scans and the assessment done by the radiologists at the sites?

DR. ZAKNOEN: I am sorry, please repeat the first part of your question.

DR. SCHILSKY: What was the concordance rate between the assessment of the MRI scans done by the central reviewers and that done by the radiologists at the participating sites?

DR. ZAKNOEN: Yes, it is the concordance between the central reviewer and the site reviewers.

[Slide]

Unfortunately, I don't have that specific number with me. That is something that I would be very happy to send back to you. There was good concordance between the site and the central reviewer.

What is shown here is the curves when we look at just the central reviewers' analysis. This is the Kaplan-Meier curve.

[Slide]

If one looks at the central reviewer and when he or she determined progression, the progression-free survival rate at 6 months for Temodal is 21 percent and for procarbazine 9 percent, with the medians at 3.49 and 2.11.

DR. SCHILSKY: So, just to be clear, the data that you presented during your formal remarks was based upon the progression as defined at the sites?

DR. ZAKNOEN: Yes, that is correct, the site review because the endpoint, as Dr. McDonald talked about, needed to correlate their clinical as well as their steroids. So, that was best served at the site.

DR. SCHILSKY: Do you have any sense as to whether there was any relationship between progression defined by a scan and progression that was determined clinically? That is, you know, when the scan got worse was the patient also doing worse?

DR. ZAKNOEN: That is a very good question. Actually, in about 60 percent of the patients the patients were clinically progressing at the time that their scan was progressing. In about 20 percent of patients the scan progressed and the patients were not progressing clinically.

DR. SCHILSKY: I have another question about the quality of life analysis. I am curious to know how you accounted for what appears to be a much higher dropout rate

in the procarbazine arm because at 2 months, which is when the quality of life analysis was sort of done, I think you said 90 percent of the patients were still on Temodal but only 33 percent were still on procarbazine. So, how did you account for that?

DR. ZAKNOEN: That is a very good question and I am going to ask Dr. Dave Sugano, from our quality of life group, to address that for you. Thank you.

DR. SUGANO: If you are referring to the quality of life data that Sara presented in the presentation, those quality of life analyses primarily tried to define a quality of life response in a similar way that you would define a radiologic response of at least two cycles or two months of improved response or comparison to baseline. That kind of an index is, as you pointed out, to some extent confounded by the duration that a patient is, in fact, on study. I think regardless of whether or not there is actually improved--at a given time point, whether a patient on Temodal is significantly better functioning prior to progression than someone that is on procarbazine is not totally clear.

We think they are, in fact, better but I think when you look at the total time that the patients are on study prior to progression, the time point at which we can see a real discernable degradation in their quality of life

regardless of the scales, we thought it was important to make sure that everyone understood that when you looked at that time prior to progression the patients enjoyed a higher quality of life response time on the Temodal arm. Does that answer your question?

DR. SCHILSKY: Well, I guess not exactly but at least I understand your thinking about it a little bit better.

DR. DUTCHER: Could you just comment on the reasons for dropout? I mean, was it drug intolerability or was it disease for the procarbazine arm?

DR. SUGANO: No, this is due to progression. So, the vast majority of people, obviously, had no quality of life data once they progressed because they were off study.

DR. SPEIGEL: In response to Dr. Schilsky, I want to be clear that this study was designed with the best of intentions to have a randomized design with longitudinal analysis of quality of life in both arms. That was our intent and that was the primary protocol-specified quality of life analysis that we had hoped to do. Because of the heavy censoring it became unfeasible to do that, and we admit and agree with what the FDA will be presenting in their presentation, that the analyses you are seeing are more post hoc to try to see if there is useful quality of life data, but it is not the prospective longitudinal analysis that it was intended to be because of the high

dropout rate.

DR. SCHILSKY: Just one other question on a different subject, I am curious since you have told us consistently about how these trials represent such a large, well-defined database for these patients, I am curious to know whether or not in the course of the trials there were tumor blocks collected. It seems to me that, given the high quality of the clinical trial database, there is an enormous opportunity here to do correlation studies between biologic characteristics of tumors and outcomes.

DR. ZAKNOEN: The sites were instructed to send unstained slides and I believe blocks to the central pathology review. I think though that it was also mandated that when those were finished they would be sent back. So, there is no bank of these blocks that is being kept at M.D. Anderson where the central pathology review was done.

DR. SCHILSKY: That is most unfortunate.

DR. DUTCHER: Dr. Santana?

DR. SANTANA: I guess as a corollary to that question, I mean, this agent seems to work in a very particular way and impact on mismatch repair enzymes. So, have there been any ancillary studies that were done during the trials that would address issue, and can we see that data if it is available?

DR. ZAKNOEN: There were no studies that were done to

look at mismatch repair specifically in these studies, or to look at the levels of the $0^6$-methyl guanine, methyl transferase. There a certainly a number of trials that are ongoing looking at those, and Henry Friedman may want to comment on some of those. He is involved in some of that.

DR. FRIEDMAN: Well, I think as you know, we published last month in the Journal of Clinical Oncology a report detailing the activity of Temodal in patients with newly diagnosed glioblastoma multiforme and a handful with AA, did exactly the kinds of correlations that I think you are talking about, specifically looking at alpha-transferase and looking at DNA mismatch repair. I think it is clear that this agent will not work in a DNA mismatch repair deficient population but that, of course, is relatively rare from what we have found so far in the malignant glioma population. On the other hand, AGT is a more ubiquitous problem and does appear to be able to predict for Temodal activity.

It is certainly food for thought for the issue in that larger body of patients, which is the possibility of looking retrospectively because the paraffin-embedded tissue still is a major resources for looking at alpha-transferase and mismatch repair by immunohistochemistry, and it could easily be done, and add additional information for another JCO paper.

[Laughter]

DR. SANTANA: My last question, since you are on the podium, Henry, obviously, I am a pediatrician and glioblastoma and astrocytoma are also devastating diseases in children. Can the sponsor briefly review for us the ongoing work in pediatrics in terms of this agent, but in particular as it relates to pharmacodynamics or toxicity in children maybe being different from the indication that is being sought in adults?

[Slide]

DR. ZAKNOEN: We do have experience in pediatrics with Temodal. Our experience is in three trials, listed here: our Phase I study, I93-125, which enrolled 27 patients; a Phase II extension of that which is currently ongoing in the U.K. and France, that has enrolled 60 patients; and we are supporting a CCG, Children's Cancer Group, trial, a Phase II trial in children with recurrent CNS malignancies of 6 different histologies. There are 87 patients currently enrolled to that and 120 patients planned to be enrolled.

[Slide]

The objectives of our Phase I study in pediatrics--it was a classic dose-finding study of Temodal in pediatric patients with advanced cancers with very standard objectives of dose-limiting toxicity and maximum tolerated dose to characterize the pharmacokinetics of Temodal in the pediatric population. As a secondary objective, we were

interested in looking at any preliminary evaluation of anti-tumor effect in these children.

[Slide]

Just to summarize the pharmacokinetic data, it was as in adults, rapidly absorbed and eliminated. The maximum tolerated dose was similar to the adult dose, 1000 $mg/m^2$ in patients who had not received prior nitrosourea or cranial-spinal irradiation. The dose-limiting toxicity occurred at 1200 $mg/m^2$ and was hematologic toxicity. There were no unusual events in children.

[Slide]

Just to summarize the safety, there was, again, headache, nausea, vomiting and myelosuppression which were seen in the adults, and no evidence of cumulative myelosuppression except in 2 patients where they had had previous nitrosourea.

[Slide]

This shows the response in the patients who had good risk gliomas. Those were intrinsic brain stem glioma and high grade glioma and glioblastoma. In these children we saw 1 complete response and 3 partial responses, as well as 7 disease stabilization.

DR. SANTANA: Thank you.

DR. DUTCHER: Dr. Nerenstone?

DR. NERENSTONE: Just briefly getting back to the

clinical endpoints, I think there is some concern because six-month progression-free survival is a somewhat subjective endpoint. Can you briefly discuss what would neurologic progression be in terms of definition besides, obviously, dropping Karnofsky score, and were there any patients where neurologic progression was not matched with the MRI, and how were those patients coded?

DR. ZAKNOEN: The neurologic exams were prospectively defined and described in the protocol, and they were ranked on a system where the investigator was to evaluate the patients on seven different criteria and rank them as -2, definitely worse; -1, probably worse or possibly worse; 0 is unchanged; +1 was possibly or probably better; and +2 was definitely better. To accept a neurologic endpoint we looked for a -2, so a drop to a definitely worse neurologic exam.

DR. NERENSTONE: If you got a -2, would that trigger a scan?

DR. ZAKNOEN: They got their scans every two months, and if they had a -2, say, at the first month, are you asking if it triggered a scan at the first month? There was a very small number of patients who did not get their scans at the defined times. So, it generally did not trigger a scan.

DR. NERENSTONE: If somebody got -2 at month three,

were they considered progression as of month three or were they considered progression as of month four when they got their scan?

DR. YUNG: If I may add to that question, at the site when the patient called and said "I'm worse," they generally called and asked to come to the clinic for an exam. The exam was whether it was month three or month five. They got a scan to evaluate whether they were worse or not. If the scan was worse they called it progression. If the patient's clinical condition was very bad even though the scan might show not much change, they would still be called clinical progression.

DR. NERENSTONE: But when you say "very bad," if they hit -2--

DR. YUNG: Yes, -2.

DR. NERENSTONE: So, no matter which of the seven categories, if they hit -2 by a neurologic exam, even though the CT or MRI was unchanged, they would still be progressing?

DR. YUNG: Right.

DR. FRIEDMAN: Can I just add one point to what you are saying? Because there is one more factor that I think all the centers do, which is that it is very clear in a brain tumor patient that any insult--a urinary tract infection, a febrile illness, any of those kinds of insults

can produce a prodigious clinical deterioration. So, when we have a patient who has a clinical deterioration and a scan that does not support a progression of the tumor, all of the programs look very carefully for whether they have a febrile illness or, frankly, most commonly a UTI to explain that clinical deterioration. If that deterioration reverses with appropriate intervention it would not be considered a progression, only if you really have no other explanation.

DR. DUTCHER: Dr. Albain?

DR. ALBAIN: Yes, I would like to come back to the statistical design a bit, and I need a little bit more help in understanding what is being presented here. You prospectively designed this as a randomized, controlled Phase II, and achieved your endpoints, and conducted it in an exemplary fashion. But what we are seeing here, it seems to me, is a lot of p values of comparing the two arms which I didn't understand to be appropriate in a controlled Phase II--we are really seeing a small Phase III trial where your p value of 0.016 for the six-month progression-free survival is, obviously, significant but you still have the boundaries of your confidence intervals that overlap each other even for that endpoint. Could you comment why you chose to present it this way, which was different than how you prospectively designed the trial?

DR. SPEIGEL: Before I begin, could you just clarify

what you were referring to as overlapping boundaries?

DR. ALBAIN: C-41 in your slides, the 4-15 percent and the 13-29 percent confidence interval range around the six-month progression-free survival endpoint.

DR. SPEIGEL: Okay.

[Slide]

The protocol that was written and submitted to the FDA and that we proceeded with defined the primary objective and the primary endpoint of the study to be the point estimate of six-month progression-free survival, and we set a threshold for ourselves that the study would be successful if we could exclude the 10 percent lower confidence interval because we had said that that would be the threshold for an effective or ineffective agent. So, throughout the protocol, and it should have been clear in our clinical study report submitted to the agency, that was the primary endpoint that we had agreed to live or die by. If the lower estimate had been below 10 percent we wouldn't have been able to say we had met the primary objective of the protocol.

In Dr. Zaknoen's presentation we hoped to be straightforward in showing that as the primary endpoint, and in her first efficacy slide it said that the objective of the study was met. Having said that, it is an unusual study design. It is an unusual target for the demonstration of

efficacy of a new drug, and we thought it was very clear both in our interactions to date with the FDA and with other international regulatory bodies that it begs comparison to procarbazine, which was a randomized, blinded comparator that was put in the study. For that reason, we have shown p values and made comparisons.

DR. ALBAIN: Blinded?

DR. SPEIGEL: I am sorry, it is open-label. I am sorry. Randomized but not blinded.

DR. DUTCHER: Dr. Buckner?

DR. BUCKNER: Yes, do you have--back to Dr. Zaknoen, I believe, on prognostic variables time from initial diagnosis to study entry between the two treatment arms of the pivotal trial?

[Slide]

DR. ZAKNOEN: What you are specifically asking for is here, time from initial diagnosis to first relapse--

DR. BUCKNER: Actually, that is not what I am asking.

DR. ZAKNOEN: Oh, I am sorry.

DR. BUCKNER: Not to first relapse--that was in the material you provided--but actually to study entry because there could be a difference between first relapse and study entry between the two arms.

DR. ZAKNOEN: We have from radiation to first relapse, time from initial diagnosis to first relapse, time from

surgery at first relapse to study drug.

[Slide]

This would be time from surgery at first relapse, which only is in 20 percent of the patients, unfortunately.

I do though have the answer to your first question. Slide 144, please.

[Slide]

This is a breakout of what actually happened to the patients by arm. So, 83 of the Temodal patients had their progression on scan, 74 on procarbazine; 10 Temodal patients had their progressions on the clinical basis and 9 for procarbazine. Then the others are the other events, dropping out for adverse events, completing treatment and so on. Does that answer your question?

DR. BUCKNER: So there is about a 10 percent difference, roughly, in scan-based progressive disease.

DR. ZAKNOEN: Yes.

DR. DUTCHER: Dr. Sledge?

DR. SLEDGE: A question of any of the three clinicians, Dr. Friedman, Yung or McDonald. When I look at the study what I see as a clinician, in the pivotal trial, is a five percent partial response rate and a one-month improvement in progression-free survival. Is this what in the brain tumor world is considered a significant therapeutic signal?

DR. YUNG: Let me address the response rate first. In the brain tumor world we see very little response, PR and CR. Conventionally, we often explain it because the brain does not clear that tissue very well. So, even though the tumor may remain dormant, it is not shrinking. So, we see very few responses in this situation, but we see more stabilization in the Temodal study. If you look at the patients who remained stable, more patients remained stable on Temodal versus those patients who remained stable on procarbazine. We often tell the patients that achieving stable status is good because they live longer--sorry, they may not live longer but they remain in good quality and in good neurological condition longer. That is why it was mentioned earlier by David that if we can offer a patient one month, two months or their median survival overall of six-nine months, which is quite a bit of time for them to stay with their family to do the things that they want to do.

DR. SLEDGE: So, if I am seeing it correctly, what you have added is one month.

DR. YUNG: Well, in this study it is one and a half months.

DR. SLEDGE: Well, 1.97--

DR. YUNG: Yes--

DR. SLEDGE: Yes, 2.99, one month. Again, I guess my

question is, is this a significant therapeutic signal for brain tumors?

DR. YUNG: Consider that this one month is over procarbazine, which we consider as a drug that already offers something to the patient, and Temodal one month over and above procarbazine--I think this is a significant signal, even though I said earlier that it is not the wonder drug that we are looking for yet. I am still looking for another drug. But given the alternative I have, this is a good alternative that I have right now.

DR. FRIEDMAN: I agree. If this was Temodal versus a placebo it would be difficult to get extremely enthusiastic, but it is against, in truth, one of the few agents that has some activity in the field. Procarbazine is an agent with activity so that if you now are demonstrating any improvement, and I do accept the small improvement as a real improvement, it is definitely a drug that I think, for those of us in the neuro-oncologic community, are excited about because we have had no drugs in 20 years that have done anything in this field, and we have made extremely little progress and this is the beginning of a step forward. It is not the answer. We are not going to name it "resurrecting" but it is definitely a drug that will help us move forward both alone and in the combination trials which are unequivocally going to flourish and start as soon as we have

access to this agent in a commercial venue.

DR. DUTCHER: Do we have any more pressing questions? Go ahead.

DR. KROOK: One of the questions that we are going to have to deal with is the issue of what progression-free survival means at various times, and one of the things that enters in here, and I guess I am speaking as a clinician, we all like tumors to shrink and go away, and we like the PRs and the complete responders, but one of the issues is the classification of stable. I guess my question is anybody who is stable for a period of time, and here it is six months, enters into that progression-free survival. So following on Dr. Sledge's question, is the stability measured at the same time in both groups at day 56? So, if at day 56 I am stable, I go into that--and if I look at C-43 between the study drug and procarbazine, that really comes down to the difference in the response criteria. So, I think that is one of the things that we as a committee have to deal with as we are going to be asked what progression-free survival at various times means versus overall survival. But day 56 is the day and 112, and everybody is measured at the same time? Although on the study arm they are seen at day 28 again?

DR. ZAKNOEN: Correct.

DR. DUTCHER: Could you use the microphone?

DR. MCDONALD: Well, maybe I can address that. On the study, it is true that patients on Temodal were seen monthly at each cycle. Patients on procarbazine were seen at least every two months--every month as well. The cycles were shorter--a cycle for Temodal was two treatments; a cycle for procarbazine was one month on trial, one month between trials. But patients were evaluated at the same frequency and had equal opportunity. If anything, maybe the Temodal patients had greater opportunity to fail earlier on this trial.

To address the issue about stable disease, however, and progression criteria, it is my opinion that stable disease in this disease is an improvement endpoint because what you are doing when you induce stable disease is that you are staving off progression, and you are maintaining clinical function. All the patients that went on these trials had good quality life to go in.

So, what we want to do in clinical oncology with brain tumor is maintain and prolong useful life. Sure, we would like to cure tumors but, unfortunately, we are not. Sure, we would like to make tremendous advances in survival but, unfortunately, we are not yet. But, in the face of that, we want to prolong useful function and get patients a better time, and in these diseases when you can stave off progression you can maintain function and that is a clear

clinical benefit for patients and their families. So, I think that in these trials showing stable disease has been showing benefit for patients.

DR. DUTCHER: I think we are going to take a break now, 15 minutes.

[Brief recess]

**FDA Presentation**

DR. COHEN: Good morning. My name is Dr. Martin Cohen, and I am going to present the FDA review of temozolomide for first relapse gliomas.

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As you see on the slide, there were two NDAs submitted, NDA 21-050 for glioblastoma multiforme and NDA 21-029 for anaplastic astrocytoma.

NDA 21-050 for first relapse glioblastoma consisted, as you heard this morning, of 2 trials. The pivotal trial, C94-091, was a randomized Phase II trial in which patients received either temozolomide or procarbazine. Twenty-one sites participated, 19 in the United States.

The supporting trial was I94-122. It was a single-arm, uncontrolled trial in which all patients received temozolomide. There were 26 sites; none in the United States.

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The second NDA, number 21-029 was for first relapse

anaplastic astrocytoma. It consisted of a single pivotal trial, C-I92-123. It was an uncontrolled trial. All patients received temozolomide. There were 32 sites altogether, 15 in the United States.

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In terms of how we did our study analysis, the sponsor submitted to us many tables of quantitative and qualitative tumor responses. This data came from the central reviewer and from the site reviewer. Because of the many tables, we queried the sponsor as to how to do the analysis, and we were told that the sponsor used site reviewer tables for progression and central reviewer tables for response. So, we did our review the same way.

I would assume from this morning's discussion that the central reviewer tables for response were blinded but the site reviewer tables for progression were probably not. And, whenever possible, we used primary data rather than summary data.

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The FDA analysis differed from the sponsor's analysis primarily in three ways. The first was criteria progression. As the sponsor told you this morning, for them the Gadolinium-enhanced MRI was the gold standard for declaring progression, and the sponsor would wait until the Gadolinium scan was performed before assigning that date as

the date of progression. In the FDA review, neurologic exam was considered equivalent to Gadolinium-enhanced MRI, and whichever occurred first was used to define the date of progression.

The second area concerned death. In the sponsor's analysis death was considered a progression event, and the date of death was declared the date of progression. In the FDA analysis if a patient had not progressed at his last evaluation before death and then died, the patient was censored at that last evaluation.

The third area was delayed evaluations indicating progression. For example, usually if a patient was progressing clinically the MRI scan was gotten shortly after the clinical progression. However, there were some patients though in which the MRI was delayed more than 30 days after clinical progression. In that case, the sponsor used the date of MRI for progression and in the FDA analysis, if a scan was delayed more than 30 days the patient was censored at the last evaluation.

I should say here that despite these differences in analysis our results are comparable. The FDA results and the sponsor's results for progression-free survival, overall survival and response rates are all pretty much the same.

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In terms of my presentation of the efficacy results, I

am going to follow this order: First, we will discuss regulatory issues if any regulatory issues are involved. The primary reason for doing this is to seek ODAC consideration and advice for how we should handle these issues.

Secondly, I will present a brief study overview and patient characteristics. In terms of clinical results, I will present response rates, progression-free survival, both median and six months, and overall survival, both median and six months, the same as the sponsor did.

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The first issue with regard to the glioblastoma trial like, I guess, with all the trials is the definition of the primary efficacy endpoint. You have heard this morning the sponsors tell you that the primary efficacy endpoint was progression-free survival at six months and, more specifically, that the lower bound of the 95 percent confidence interval for that progression-free survival be greater than 10 percent. Secondary clinical endpoints were overall survival and health-related quality of life.

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The principal regulatory issue is what is the most appropriate study endpoint for these high grade glioma trials? Is it progression-free survival or is it overall survival?

The sponsor told you that in a placebo-controlled trial Gliadel was shown to significantly improve survival. Secondly, increased survival is a requirement for approval of three ongoing pharmaceutical industry glioma trials. The third point, and I will go more into detail on this third point in the next slide, is whether accurate determination of progression-free survival is possible. The purpose of the next slide will be to show that we think that it is difficult to accurately determine progression-free survival. The fourth point is that even if you could determine progression-free survival, is that of any clinical value?

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Summarized here are three patients who participated in the anaplastic astrocytoma trial. In all three of these patients, during therapy the patient progressed on therapy yet, despite that progression, for reasons unknown to the FDA, the patient was continued on treatment and then developed a long-term response.

So, the first patient is a 40-year old woman who, 4 months into treatment, had an MRI that showed progression. As I said, despite the fact that she progressed she was continued on treatment. Two months later she became a complete responder, and the complete response lasted for 12.5-plus months when she was lost to follow-up.

The second patient is a 24-year old male who, 3.5

months into treatment, had an MRI that showed progression. Again, treatment was continued. Five months later the patient became a complete responder and that complete response lasted seven-plus months.

The third patient, a 35-year old female, again is similar. Thirteen months into treatment her MRI showed progression. Treatment was continued. Two months later she became a responder and this patient alternated between a PR and a CR for the next 12.5 months when she was lost to follow-up.

Like the treating physician, the FDA in its analysis of these results also discounted the progression and considered all of these patients as long duration responders.

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Turning now to study results, this is study 92-091, the pivotal glioblastoma study. We are going to be talking about two patient populations, the intent-to-treat patient population and the eligible histology patient population. As you saw earlier this morning, there were 112 temozolomide-treated patients, 113 procarbazine-treated patients, and the eligible histology was 104 and 108 in the FDA analysis.

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Patients in this trial, the temozolomide and

procarbazine patients, were comparable for nearly all prognostic factors. You heard this morning that age and Karnofsky performance status are probably the two most important prognostic factors for these patients. The median ages were 51 and 51 for temozolomide and procarbazine respectively, and the median performance status was 80 for both. The only difference between these two groups was in time from initial diagnosis to relapse, and that favored patients in the procarbazine arm.

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As was indicated earlier, in the sponsor's intent-to-treat analysis and the FDA's intent-to-treat analysis and the eligible histology analysis, for both temozolomide treatment or procarbazine treatment there were no complete responses, and the partial response rate was in the range of 5 percent for all except the procarbazine-treated patients in the FDA analysis, where it was 2.7 percent.

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Again, as you heard earlier today, in the sponsor's intent-to-treat analysis we are talking about three months versus two months for median progression-free survival, with a highly significant p value, and the results in the FDA intent-to-treat analysis and the FDA eligible histology analysis are basically the same, with a strong indication that temozolomide might produce superior median progression-

free survival compared to procarbazine.

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Six-month progression-free survival--again, in the three analyses, the sponsor's analysis and the two FDA analyses, the results are relatively comparable. Only in the FDA eligible histology analysis where the six-month progression-free survival rate was 17 percent versus 7 percent did the lower bound of the 95 percent confidence interval for the 17 percent reach 10 percent. In all the other analyses the lower bound was greater than 10 percent.

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We turn to median survival in the sponsor's analysis. It was 7.34 months for temozolomide and 5.82 months for procarbazine. The p value was 0.337. In the FDA's eligible histology it was 7.3 months versus 5.86 months, and the p value was 0.61.

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In terms of six-month survival, in the sponsor's analysis, as you heard earlier today, it was 60 percent versus 48 percent, and comparable numbers are achieved in the FDA analysis. The p value in the sponsor's analysis was 0.067 and in the FDA analysis it was 0.07.

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Turning now to the supporting glioblastoma multiforme trial, I94-122, the intent-to-treat population comprised 138

patients. The eligible histology population comprised 131 patients. The median age of study patients here was 54, relatively comparable to C94-091, and the median performance status was 80.

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As you heard earlier this morning, for response rates there was one percent CRs in all analyses and between four-seven percent partial responses in all analyses.

It should be noted--I specifically picked out this analysis but it holds true for all the other analyses, that the majority of responders had received no prior chemotherapy.

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In terms of progression-free survival in this study, in the sponsor's analysis it was 2.1 months and a little bit better in the FDA analysis; it got to 2.24 months. We will come back in subsequent slides and contrast the outcomes in I94-122 with the outcomes in C94-091.

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Six-month progression-free survival, again, in all analyses was in the range of 20 percent. In all cases the 95 lower bound and 95 percent confidence interval was greater than 10 percent.

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Median survival was 5.4 months in the sponsor's

analysis and 5.33 months in the FDA eligible histology analysis.

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Six-month survival, again, was comparable, 46 percent and 44.5 percent.

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Now, to try and contrast the results of C94-091 and I94-122, when we looked at prognostic factors, all the regular prognostic factors--age, performance status, sex, race, initial therapy, type of surgery, etc, were all comparable. The things that were different, that were statistically different between the two groups were, one, that patients enrolled in C94-091 had smaller tumors than patients enrolled in I94-122. Median tumor size was 12 $cm^2$ versus 18.04 $cm^2$.

Favoring I94-122 patients was the fact that 66 percent of the I94-122 patients had no prior chemotherapy versus 26 percent of the C94-091 patients. Also, there was a longer time from diagnosis to first relapse, 274 versus 232 days, suggesting that the I94-122 patients would have had some slower growing tumors.

All in all, my impression was that based on these above factors patients in I94-122 should have had a longer progression-free survival and overall survival than C94-091 patients.

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When you look at progression-free survival--and this is the eligible histology population in the FDA analysis--in C94-091 median progression-free survival was 2.7 versus 1.88 months. For I94-122 temozolomide-treated patients it was 2.24 months. Six-month progression-free survival is relatively comparable between C94-091 temozolomide-treated patients and I94-122 temozolomide-treated patients.

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Median survival times in C94-091 were 7.3 months for temozolomide versus 5.86 for procarbazine, and was 5.33 for patients in I94-122. Similarly, six-month survivals were 61 and 48 percent in C94-091 and 44.5 percent in I94-122. That completes the response part of the discussion for glioblastoma multiforme.

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Turning now to the anaplastic astrocytoma trial, C-I94-123, the regulatory issue here is that the sponsor indicated that a randomized trial was not feasible in patients at first relapse because patients would have already received all active drugs. We were told earlier today that the standard of care is a 3-drug regimen that includes both nitrosoureas and procarbazine. So, we assume that nitrosoureas and procarbazine have to be considered the active drugs for this patient population.

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If one looks at prior chemotherapy for the intent-to-treat population, which comprised 162 patients, we see that 62 patients had no prior chemotherapy, 38 patients or 23 percent had nitrosoureas but not procarbazine, and only 59 patients or 36 percent of the eligible histology population actually had both drugs. So, we wonder why a randomized trial might not have been possible.

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This is the same data for eligible histology patients. I guess our evaluation of eligible histology is different from the sponsor's evaluation of eligible histology because we have somewhat more patients in our eligible histology population than they did. But, nevertheless, 40 percent of our eligible histology population had received no prior therapy. Only 54 patients or 38 percent had received both a nitrosourea and procarbazine.

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Patient characteristics--median age of patients in this study was about a decade lower than the median age of patients in the glioblastoma study. As we heard this morning, that is pretty much what is expected. Karnofsky performance status, the median value again was 80.

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Response rates for anaplastic astrocytoma patients

were considerably better than were the response rates for the glioblastoma multiforme. Here, there was a relatively significant percentage of complete responses. In the sponsor's intent-to-treat analysis it was 8 percent; in the FDA's analysis it was a little bit lower but still present. PRs were 27-28 percent in the various analyses, and the total response rates were in the range of 33-35 percent.

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This is response rate by prior therapy. As you can see, patients who had no prior therapy, there were 57 of eligible histology patients. Their response rate was 39 percent. For patients who had prior nitrosourea and procarbazine the response rate was 22 percent. For patients who had nitrosoureas without procarbazine the response rate was 37 percent. Once patients responded, the response duration didn't appear to be affected at all by prior therapy so that the response duration for patients who received nitrosoureas plus procarbazine therapy was at least as good as the response durations for patients who had no prior therapy or who had nitrosoureas alone.

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Looking specifically at the complete responses, there was a total of 13 complete responses. Five of those complete responders had received prior nitrosoureas and procarbazine. The median response duration was 448 days,

with a range of 367-797 days. One patient that received just nitrosoureas, median response duration was 667 days. Seven patients had received no prior therapy and their median response duration was 266, with a range of 173-626.

So, my conclusion from this is that meaningful complete responses do occur in patients who have received prior nitrosoureas and procarbazine.

[Slide]

Median progression-free survival in the sponsor's intent-to-treat analysis was 5.4 months. In the FDA's intent-to-treat analysis it was 6.18. In the FDA's eligible histology it was 6.64. The median progression-free survival for patients with prior nitrosourea and procarbazine therapy was 3.85 months.

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Six-month progression-free survival was 46 percent in the sponsor's intent-to-treat analysis, 51 percent in the FDA's intent-to-treat analysis; 52 percent in the FDA's eligible histology analysis, and 39 percent for eligible histology patients who had received prior nitrosoureas plus procarbazine.

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Median overall survival in the sponsor's analysis is 13.6 months, 14.61 months in the FDA analysis, and for prior nitrosoureas plus procarbazine patients the median overall

survival was 15.86 months.

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Six-month survival rates were comparable across the various analyses in the range of 75-77 percent.

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Turning now to the health-related quality of life which was a secondary endpoint in all trials as was mentioned previously, in the pivotal glioblastoma multiforme trial a longitudinal analysis was specified in the protocol. For reasons that were also detailed this morning, a longitudinal analysis could not be done, and what was actually performed was another series of analyses including a QTwist analysis for the four patients in the pivotal glioblastoma study. All of these analyses were performed either with small numbers of patients or with unknown numbers of patients. There was no statistical analysis done on any of this quality of life data.

So, the FDA conclusion regarding the quality of life evaluation was that the protocol-specified analysis could not be done in the case of the pivotal trial and that any other results claimed from quality of life evaluation must be viewed with caution.

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In terms of toxicity of treatment, this slide indicates hematologic toxicity in the 94-091 trial which

compared temozolomide with procarbazine. As you can see here, anemia was relatively similar for the 112 temozolomide patients versus the 110 procarbazine patients. Both neutropenia and thrombocytopenia appeared to be more common in temozolomide-treated patients, but what one must remember is that there were 1.6 times as many doses of temozolomide administered as there were doses of procarbazine. So, one might expect about 1.6 times more toxicity. In fact, you see a little bit more toxicity than that, but not strikingly more.

There were five deaths related to hematologic toxicity. Two of the deaths, one temozolomide and one procarbazine-treated patient, were associated with leukopenia. There were three deaths, all in the temozolomide-treated patients, associated with thrombocytopenia.

[Slide]

The sponsor made note of this slide in their remarks. This was just something that was noticed in going through the trial results, that 11 patients, 9 temozolomide-treated, had developed pulmonary emboli, and there were 16 patients, 15 temozolomide-treated, who had developed venous thrombosis and, therefore, there is a possible indication that temozolomide might induce hypocoagulability but I would agree with the sponsor that more data is obviously needed

regarding this point. But it is something to watch out for in future trials.

[Slide]

Deaths within 30 days of treatment--this data came primarily from sponsor tables. As you can see, most of the deaths were thought to be related to disease. Only a relatively small number of deaths related to treatment. The causes of deaths are indicated here. I hope everybody can read that; it looks small to me.

[Slide]

Turning now to a summary of the clinical data, you will see in several of these summary slides that I have included a literature estimate of median response rate and ranges of response rates. The literature that I reviewed for this estimation came primarily after 1990. So, it is relatively modern literature.

The eligibility criteria for the literature trials was not that much different from the trials we have been discussing this morning. That is, the median Karnofsky performance status in the literature was around 70, and patient age in the glioma trials was generally in the 50s, and in the anaplastic astrocytoma trial generally in the 40s to early 50s. So, they are not that different patient populations. As I said, all I am trying to do is to get some ballpark estimate of what you might expect in this

disease.

For this response summary I reviewed 22 reports, and those reports included a total of 367 patients with what the authors claimed was histologically confirmed glioblastoma multiforme. There were no anaplastic astrocytoma patients in this data, as best as I could tell. As you see, response rates in the literature, the median is 7.5 percent which is in the same ballpark as the response rates observed for temozolomide in C94-091 and for temozolomide in I94-122. Response durations were not given in the literature, and you see the response durations for temozolomide and procarbazine on the right of the slide.

[Slide]

In terms of progression-free survival, we all agree that temozolomide gave a longer progression-free survival than did procarbazine. We are talking about a one month difference, from three months to two months, as has been mentioned previously.

In terms of six-month progression-free survival, again, temozolomide treatment was superior to procarbazine treatment, and the p values are listed.

[Slide]

In terms of overall survival, in the sponsor's analysis and the FDA's analysis we are talking about 7.3 months versus almost six months for procarbazine. The p

value is 0.337 and 0.61. And, for six-month progression-free survival the p values were 0.067 and 0.07 for the two analyses.

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In terms of median survival comparing C94-091 and I94-122, for temozolomide-treated patients in C94-091 it was 7.3 months versus 5.86 months for procarbazine. In I94-122 the median survival was 5.33 months.

In the literature, the median survival of the literature trials, which included 21 trials with 402 patients, was 6 months and the range was 3.9-10.2 months. Six-month survival, 61 percent for temozolomide-treated C94-091 patients, 48 percent for procarbazine-treated patients, and 44.5 percent for temozolomide-treated glioblastoma patients in I94-122.

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Now going to anaplastic astrocytoma response rates summary, and this is by prior therapy again--with no prior therapy the response rate was 39 percent. For patients who had prior nitrosoureas plus procarbazine the response rate was 22 percent. Five of the 12 responders though were CRs in this category. Response durations were fairly impressive I think for these 5 CRs, 448 days with a range of 367-797 days. Overall response durations, at least on the high side, appear to be relatively good for temozolomide

treatment of anaplastic astrocytoma patients. In the literature the median response rate was 22.5 percent, with a range of 0-100 percent.

[Slide]

In terms of progression-free survival for all patients with eligible histology, it was 6.4 months versus 3.85 months for patients with prior nitrosourea and procarbazine, and the median progression-free survival of the 11 reports with 216 patients in the literature was 7.4 months with a range of 3.7 to 19.8 months, and figures for progression-free survival are indicated.

[Slide]

For overall survival, median survival for FDA eligible histology anaplastic astrocytoma patients was 14.6 months. For patients who had received prior nitrosourea and procarbazine it was 15.86 months. Six-month survivals were in the range of 75 percent. In the literature, in 21 reports with 255 patients, the median survival was 10.2 months and the range was 3.9 to 22.2 months.

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I anaplastic astrocytoma is granted accelerated approval, this was the proposed Phase IV anaplastic astrocytoma trial that was submitted to the FDA. This proposal was for an inter-group study led by RTOG. It was for newly diagnosed, histologically confirmed procarbazine.

Patients would be stratified by age, performance status and extent of surgery. They would receive standard radiotherapy to 59.4 Gray delivered conventionally, and they would be randomized to receive either temozolomide or the three-drug combination that was talked about this morning, procarbazine, CCNU and vincristine, or the PCV regimen. The primary endpoint would be survival, and the sample size would be 284 patients.

That concludes my presentation. I would be happy to answer questions.

**Questions from the Committee**

DR. DUTCHER: Any questions from the committee for Dr. Cohen? No questions? Thank you. Oh, one question. I knew we would have one question. Dr. Raghavan?

DR. RAGHAVAN: I got a little bit tangled up reading your assessment of the regulatory events and the sponsor's, and I just wondered if someone can clarify for me, is there some dispute between the agency and the sponsor about the endpoint that was regarded as acceptable for this trial, or is everybody hunky-dory about it?

DR. COHEN: Well, I wasn't present for those discussions so I might not be the right person to ask that question. But my impression from reading the minutes was that those issues were never really adequately discussed and settled. The sponsor presented progression-free survival as

the primary endpoint. I don't think FDA either formally objected to that or formally accepted that. There is just nothing in the minutes to indicate that it was discussed. Other people might want to comment on that.

DR. JUSTICE: Well, I was there but it was five years ago and the minutes aren't entirely clearly on the issues that were discussed. But I don't think I would characterize it that we have a disagreement about their plan. They did what they did and apparently we agreed with them at the time.

DR. RAGHAVAN: So, therefore, do I draw the conclusion from that if you set the bar at a particular level, the level has been defined in terms of progression-free survival and I think they have shown, and you agree or your agency agrees, that they have identified a set level of progression-free survival, then does that mean that they have gotten over the bar? Is that what I interpret from what you have just said?

DR. JUSTICE: No. I mean, I think that is what you are here for, to let us know whether or not that bar is reasonable. I mean, Dr. Krook pointed out that was his first meeting, not that it has anything to do with the issue here but it is really whether or not you think or you agree with the position that we took. We are asking your advice.

I think one thing that I do remember about the meeting

is that there was a lot of discussion about how we were pushing time to neurologic progression as a potential endpoint and we were told by the investigators that was not possible; that was not reasonable, and we were surprised to see that it was on one of the slides. So, I guess you did at least make some attempt to look at time to neurologic progression.

The issue of survival, as far as I know--I think pretty much most of the meeting was spent discussing whether or not a randomized, controlled trial would be required, and I am not sure we ever adequately covered survival.

DR. RAGHAVAN: And, one more question to Dr. Cohen. You have had a chance to look at the raw data. One of the difficulties when you are doing this sort of randomized Phase II design is to dissect out what happens after the initial responses and initial failures. Can you help us at all in terms of what are the things that may have brought the curves together? If we can go back in time when mitazantrone was approved for prostate cancer, overall survival was never the endpoint because the patients who got prednisone crossed over with mitazantrone failures. So, can you take us through what the events were, what the pattern of management was after failure of the procarbazine, after failure of the drug patients? Do you have any data on that?

DR. COHEN: I don't have data; I have an impression.

I think that in the glioblastoma trial the progressions were occurring so rapidly that once failure was documented the patient was near death and nothing further was done. If anything further was done, I don't have any data to indicate what was done.

In the anaplastic astrocytoma patients where there was longer survival, generally patients were censored at last follow-up and I have no idea what happened to them subsequently.

DR. DUTCHER: Dr. Speigel?

DR. SPEIGEL: Let me see if I might be able to help Dr. Raghavan in his question. If I could have slide 112?

[Slide]

At least for glioblastoma multiforme we have done a plot of time from progression to death. And, what this shows is that from the time of progression there was no separation and, unfortunately, as characterized by our consultants, there is a predictable, very rapid decline in time to death. In fact, I think about 35 percent of the patients are dead by month 4 after progression was documented.

[Slide]

This is the time to progression curve that you have seen before. It shows from time of randomization to time of progression, and there is a good separation.

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This slide is the overall survival. There really isn't a collapse of the separation. I would posit that the separation was, in fact, maintained. The improvement or delay that was seen in time to progression is actually maintained with a 1.5 month improvement in survival time.

So, it is not that after progression the curves for overall survival come together; they actually maintain their separation but they don't have the statistical power to show a meaningful statistically significant difference at that time.

The other thing is there have been some questions about perhaps differences in the outcome in the international study that was done in 122, and there probably is some difference in standard of care after progression. If patients are simply sent to hospices or no further treatment is given, it can affect survival time compared to those patients who are heroically either maintained on steroids or other supportive care. But in our study the two curves were identical for the outcome of procarbazine and Temodal from the time of progression.

DR. DUTCHER: Dr. Albain?

DR. ALBAIN: I am really intrigued by those patients who progressed and then had a CR. In your analysis regarding those three patients, did you look at the prior

treatment in greater detail? For example, when they had most recently had radiotherapy? Or, are we positing a flare reaction a la bisphosphonates, or something?

DR. COHEN: I am sorry, I don't have that data.

DR. DUTCHER: Could some of the investigators perhaps comment as to what they think was happening?

DR. SPEIGEL: Sure. We don't have the details on those three specific patients.

[Slide]

This slide reviews the progressive disease criteria. It says progressive disease was defined as a 25 percent or greater increase in any measurable lesion or any new lesions on MRI scans, and steroid use was to be stable or increased with or without neurologic progression. So, you would assume and, you know, the FDA has been very thorough and has found three patients out of the 130-plus in the AA study where, if you look carefully at their time to progression there were these three patients who technically had progressed by MRI. The physicians taking care of these patients called our study monitor and asked for permission to allow them to stay on the study, which was granted, and they actually went on to become responders.

We don't know the details today. These patients could have had their steroid dose decreased. The doctor might have tried to titrate and decrease their steroid dose, which

can result in a transient or apparent worsening of the MRI scan. I don't know the details. I don't know if Dr. Yue wants to comment further on that.

DR. COHEN: I would comment that I specifically looked at steroid doses and that, in fact, did not have--

DR. SPEIGEL: Okay. I don't know if we have any other experience that would say why you might find an occasional patient who was in apparent progression but is able to stay on study.

DR. BUCKNER: I would just like to comment that what Dr. Albain mentioned is certainly a possibility, that patients who we think are having progressive disease actually do not. They have a delayed reaction to radiation which may occur either prior to going on study or after going on study, which subsequently resolves spontaneously. We do not know the magnitude of that effect in this population of patients.

DR. DUTCHER: Dr. Schilsky?

DR. SCHILSKY: I have a question. I just want to clarify something you said in the beginning of your presentation. Is it correct that progression was determined at the sites but response was determined by the central review?

DR. COHEN: That is correct.

DR. SCHILSKY: Okay, and progression, of course, was

not blinded.

DR. COHEN: I believe that is correct.

DR. SCHILSKY: But going back to some comments that were made earlier, one might anticipate that there would be a relationship between stable disease which is part of the response criteria and, therefore, would have been reviewed by the central reviewer, and progression or freedom from progression which would have been reviewed at the sites. Do you have a sense as to whether there is, in fact, a relationship between duration of stable disease and freedom from progression?

DR. COHEN: I am not sure that is an issue.

DR. SCHILSKY: Except that basically they may be more subject to bias than the other because progression, if it was assessed in an unblinded fashion and stable disease was assessed in a blinded fashion--you know, there may be just a very subtle difference.

DR. COHEN: No, I think all patients, no matter whether they were responders, stable disease, or what, were evaluated by a site reviewer for progression, and the central reviewer had nothing to do with that. The central reviewer only called PRs and CRs.

DR. SCHILSKY: So, the central reviewer didn't define if someone had stable disease?

DR. COHEN: That wasn't one of the requirements for

the central reviewer.

DR. DUTCHER: Any other questions? Just one moment, we have a comment from Dr. Yue.

DR. YUE: Can we clarify those issues because I am not sure what I am supposed to as here?

DR. COHEN: Well, let me tell you, you know, when we received the data we queried the sponsor. You know, we got your tables for both response and progression measured by perpendicular diameters or by volumes, and we got the central reviewers' data, both quantitative and qualitative for responses and progressions. So, we didn't know what to do with all that data. So, we queried the sponsor and we were told by Schering that we were to use only the site reviewer tables for progression determinations and only the central reviewer tables of perpendicular diameters for response determinations. And, that is what we did.

DR. ZAKNOEN: Yes, the progression dates were based on the site investigator's clinical and MRI and steroid assessment of the patient. The site investigators also made an assessment that they felt that there was a complete response or a partial response or stable disease. They made a call that was entered. The central reviewer reviewed all scans for all patients. I showed you the data using just the central review assessment of progression-free survival and it is really the same as the site. But, for purposes of

reporting, the objective responses were taken from the central reviewer who had no idea of the clinical state of the patient or what arm they were on, but the dates for progressive disease came from the site reviewers, although our central reviewer reviewed all of the scans. Does that answer your question?

DR. SCHILSKY: Yes, I think that comes fairly close, but can I ask you to clarify one thing again because I think certainly what I am grappling with here is that we are dealing with fairly small differences between temozolomide and procarbazine. Granted that it may not even be appropriate to make the comparison, but the differences are small and they are based upon assessments of progression that were done in an unblinded fashion at the sites. So, the importance of precisely defining what is progression I think becomes critical.

Again, you just said that at the sites the investigators used scan results, the clinical status of the patients and steroid use. But I thought that what was said earlier was, in fact, that it was the scan result that really made the call as to whether somebody had progression or not. So, even if somebody was clinically deteriorating and required an increase in their steroid dose, until the scan result was known it wasn't determined whether, in fact, they had progression or not. So, could you clarify that

again?

DR. ZAKNOEN: I can try. More weight was based on the scan results, and in the slide that I showed previously the vast majority of patients had their progressions documented by scan, usually with neurologic and clinical deterioration at the same time. There were patients, as Dr. Yung and Dr. Friedman have said, where they did have neurologic or clinical deterioration either with or without a scan being run, or with a scan that showed stable disease. If, in the opinion of the investigator that patient was progressing, that was the date that was entered.

DR. DUTCHER: Dr. Nerenstone?

DR. NERENSTONE: Getting back to those three patients, and I do agree that they are interesting but I think it underscores the difficulty in having an unblinded study and I wonder if these patients had been on the procarbazine arm, if those patients would have been off study. So, in my understanding they would have been protocol violations, and significant protocol violations at that, but, yet, they were coded actually as responders so they were kept on study and it was retrospectively said, "well, you progressed but now we're going to call you a responder and we're going to throw that away." My question is if you throw those patients out does it change your conclusions?

DR. COHEN: No.

DR. DUTCHER: Any other questions for Dr. Cohen?

[No response]

Thank you. Is there any further discussion amongst the committee before we go to the questions? If not, we can discuss the questions. Dr. Johnson?

**Committee Discussion and Vote**

DR. JOHNSON: I just wanted to respond to Dr. Raghavan that the FDA has consistently advised pharmaceutical companies that a favorable effect on survival would be required in this situation, and maybe I should make an exception because it isn't clear that we consistently advised Schering of that. But we have advised three subsequent companies of that. So, we want to find out from the committee whether we have been giving the wrong advice and setting the wrong standard. That is a very important thing that we want to find out.

DR. DUTCHER: Dr. Simon?

DR. SIMON: I just want to make a comment about the design because I think it is complicating our life here, and I am hoping that it doesn't complicate our life in future submissions. I don't know whether it really directly affects the questions, however. My view is that this design is a confusing design and an inappropriate design for a licensing setting.

The purpose of the design is to outline what the

analysis is going to be so that the analysis doesn't consist of a rummaging through the data to find significance. This design doesn't provide us with that because it looks like a randomized, controlled trial but it is stated that each arm will be compared to some historical control, the relevance of which is really unknown. Then it comes out that you can compare the arms directly and get what looks like statistically significant, although a very small effect with regard to progression-free survival, and so that is done even though it wasn't really part of the original design. So, we don't really know how to interpret that.

We can't really go with the original specification of the 10 percent threshold because that is not necessarily relevant. We get to survival and we are tantalized with a borderline significance level because when you look at it at six months, well, what is the relevance of looking at survival at six months? Well, the relevance really is just because it makes a good story and it is borderline significant. The standard statistical approach would be to compare those two arms with a log-rank test, and there is no evidence at all that there is any benefit of survival.

DR. DUTCHER: Dr. Krook?

DR. KROOK: I guess I just want to comment on Dr. Johnson's remarks. I don't have any minutes that I kept from the '94 meeting but the Gliadel came through in about

'96, if I remember correctly, and most of that meeting, as my recollection is, we talked about survival. I am not sure we talked about six months progression-free survival and the majority of the discussion was trying to either not do the study medication only as a single arm but that we needed--and I will go back to what I started with--a reference control.

What I believe the sponsor wanted to do, and there are probably other people at that meeting who wanted to use historical data, particularly the University of California San Francisco, and the people who were there did not feel it was appropriate to use that. But I think it is a timing issue because when that meeting went on survival was not really talked about until '96 when the Gliadel came along, John. So, I think it is historical partially that we have to deal with.

DR. DUTCHER: Dr. Buckner?

DR. BUCKNER: I think one of the first questions is the relevance of the progression-free survival as an endpoint. I would like to make several observations. There are some pros to it, as has been mentioned by the sponsor, in that it avoids confusion with post-progression treatment influences on overall survival. So, that is a potential advantage.

However, there are numerous problems with it. First

of all, how do you get into the study? Patients must have had a progression following radiation, and we realize that this is not necessarily a 100 percent reliable eligibility criterion. There are conditions that mimic tumor progression, most specifically delayed treatment effect; less commonly withdrawal of corticosteroids. So, even getting into the trial, there will be a certain percentage of patients likely who do not have true tumor progression. We do not know what that percentage is.

Second of all, since neurologic worsening was also considered progression, there are some pitfalls there. There are other factors, other than tumor growth. Some have been alluded to--concurrent medications, particularly anticonvulsants, other co-morbid conditions; Dr. Friedman mentioned infection. Anything that causes a diffuse encephalopathy can mimic tumor progression--withdrawal of corticosteroids and the treatment itself. We should remember that procarbazine can cause encephalopathy, particularly at the higher doses. So, it may not be possible to sort out tumor progression neurologically from the effect of the procarbazine.

Further, there can be further deterioration from prior radiation that can occur after the initial "progression". Similarly, scan worsening can result from factors other than tumor growth, again including withdrawal of corticosteroids

or progressive deterioration from prior radiation.

There is another problem in that the mix of the patients is a bit heterogeneous both in the GBM study and the AA study to use progression-free survival. Either patients that had an initial diagnosis of glioblastoma and then went on to progress, or patients who had some other lower grade histology and then, upon progression, had biopsy which showed a glioblastoma evolution were also eligible. We do not know the mix of those types of patients in this randomized trial, and we do not know if they have a similar course following progression. There is certainly evidence that they do not. There is a concept of a primary versus secondary glioblastoma. There is preliminary evidence that there are genetic differences between the tumors and that there are clinical differences between the tumors. So, there is definitely risk of tumor heterogeneity.

I have already asked previously about the issue of lead time bias when patients enter the study. That is, the length of time from tumor progression to study entry may vary. It is interesting that the only statistically significant difference in the procarbazine versus temozolomide arms was this particular factor. One interpretation is that it favored procarbazine because it was longer in the procarbazine group. However, we really don't know whether it makes a difference or not. It may be

not relevant, and the sponsors have looked at that in a multivariate analysis and found it not to be relevant.

There is an alternative interpretation, that in fact the patients who apparently progressed earlier on, and there were more of those in the temozolomide arm, a greater proportion of those patients in fact were a delayed radiation effect and it would resolve spontaneously without treatment.

So, I think there is some question about the whole issue of not only progression-free survival but, unfortunately, survival as well in the recurrent disease setting.

Finally, we have mentioned the issue--actually, it was mentioned obliquely, the issue of investigator bias. Modesty will keep me from saying how many patients with brain tumor we see at the Mayo Clinic compared with M.D. Anderson or Duke--

[Laughter]

--suffice it to say we, unfortunately, see enough to realize the devastation that this disease brings on patients, often young patients, and the extremely frustrating experience of having no truly effective agents available. So, consciously or unconsciously the best intentioned physicians may wish for one therapy to be more effective than the other, and may hope to discover a new and

improved therapy for patients with this disease.

Furthermore, when there is a doubt of tumor progression, and I think we have all acknowledged that there is often a doubt the patient is possibly worse but not definitely worse; a scan is possibly worse but not definitely worse--we want people to do well, and all of us at some point will perhaps give the benefit of the doubt and say this is not necessarily tumor progression. So, there could be imbalance in that judgment in two treatment arms, not with any necessarily ill intent on the part of anyone but just because humans are humans.

Furthermore, there is the issue of conflict of interest that can influence clinical judgment when physicians are paid to put people on study on a case by case basis. That does not necessarily mean that there is bias but it does provide the opportunity for bias.

So, basically to summarize, endpoints which rely on human judgment are likely to be influenced by human nature, and I think we cannot completely ignore that particular aspect of this trial.

So, those are my comments on the difficulties of progression-free survival as an endpoint not only in this study but for future studies as well.

DR. DUTCHER: Thank you. Dr. Raghavan?

DR. RAGHAVAN: Could I ask Dr. Buckner a question

because I am having trouble with this whole thing because I don't treat brain tumors? I am sort of a lay person, I guess.

When you listened to the presentations from both teams today, were you impressed, as someone who knows this field, by the fact that it appeared that in the Temodal-treated patients there were more alive at certain time points as defined? I mean, I am getting a sense that there isn't a conflict really in the actual production of the data as defined; it is kind of the interpretation. So, you know, when you looked at the survival curves, overall progression-free survival, mostly overall, it looked like there were more live bodies at the landmark of six months with drug A than with drug B. Is that important in this--I mean, it is obviously important but in the context of what happens in the treatment of brain tumors? It is the same question as George asked, I guess. How big a deal is what we have seen because it looks kind of like it is an active agent and, yet, there are reasons why we could get tangled in methodology and miss the fact that it is potentially a pretty useful drug. I wouldn't like to make that mistake.

DR. BUCKNER: Sure. I am much more reassured by survival per se as an endpoint than progression-free survival. It is not controversial in terms of when does it occur, and it does not depend on the frequency of scanning,

and it does not depend on a number of the other variables that can influence the interpretation of progression-free survival. So, from my standpoint, if this truly represents a difference in survival, if we are comparing apples with apples here which we haven't gotten to here but if we are comparing apples with apples and patients live longer and the toxicity profile is modest, which I believe it is, then I see no reason to withhold this drug from people. A month on average of increased life with good quality of life is a month, and I think that the sponsors have adequately shown the safety of this particular agent.

So, overall survival I think is important if we are convinced that we are comparing apples with apples. Unfortunately, it is not of the magnitude that we would like to see but, in general, in oncology we do not hit home runs; we hit base hits and if it is a base hit it ought to be called so.

DR. DUTCHER: Dr. Simon?

DR. SIMON: I believe the appropriate p value for survival is either the 0.337 that the sponsor proposed or the 0.65 which I believe is what the FDA recalculated it as when you compare the two survival curves with regard to the log-rank test. It was not specified in advance that six months was going to be a time for comparing survivals. I don't believe that any secondary treatments after

progression have much of an effect on survival, and I think it is really unreliable to sort of compare the curves at six months because you get a small p value there and ignore the fact that the overall hazard ratio is 1.12, which is totally nothing, and the data really suggest that there is no survival effect.

DR. ALBAIN: Richard, wasn't the primary prospective endpoint at six months though?

DR. SIMON: That was for progression-free survival.

DR. DUTCHER: Other issues? Okay, if you look at the questions, there are a number of tables that are brief presentations of the data that we have just discussed. I will give you a minute to look at that. Has everyone had a chance to look at that?

The first question is, is an improvement in six-month progression-free survival or overall progression-free survival sufficient as the principal basis of regular approval for drugs indicated for the treatment of relapsed malignant gliomas or should an improvement in survival be required?

Just for clarification, is this to include the anaplastic astrocytomas or is this strictly glioblastomas?

DR. COHEN: There are separate questions--

DR. DUTCHER: It includes anaplastic astrocytoma. Okay. So, the first question is whether six-month

progression-free survival or overall progression-free survival can be used as a basis for evaluating and/or approving drugs indicated for the treatment of relapsed malignant gliomas, including both glioblastoma multiforme and anaplastic astrocytoma, or should an improvement in survival be required? Comments? Dr. Santana?

DR. SANTANA: Can I clarify that? Obviously, this is a very important question because it relates to the subsequent discussions. So, I need to get a sense. If we are going to hold this whole discussion to this standard does it invalidate the rest of the questions that we have to discuss?

DR. DUTCHER: Can I just say I think there are some of us who would like to separate the issue of this particular application of glioblastoma from a discussion of anaplastic astrocytoma.

DR. BUCKNER: I would agree with that.

DR. JUSTICE: Just to clarify, the question of anaplastic astrocytoma is focused on accelerated approval and this question is talking about regular approval. So, it would have potentially applied if they had a trial design for anaplastic astrocytoma that was using progression-free survival as a primary endpoint. You know, in a theoretical way it still applies but it doesn't apply to the anaplastic astrocytoma indication.

DR. DUTCHER: Okay, so the issues are regular approval based on six-month progression-free survival in relapsed brain tumors.

DR. BUCKNER: I have given my spiel on that. I think you have heard my concerns. I would just point out one other thing, it is not in the literature a validated endpoint at this point. That doesn't mean it is not valid; it just means that using multiple databases it has not been a reproducible endpoint that has been studied.

DR. DUTCHER: Yes, sir?

MR. LUSTIG: Just a couple of points, first, I am painfully aware of the struggles that the scientists face in achieving progress, particularly with glioblastoma. However, thinking about this issue of progression-free survival, I really feel it puts us on a slippery slope and that concerns me. It fails to take a holistic view of patient care, and I realize, especially with glioblastoma, that we struggle to give people a day more of life and I respect that.

But I do think that using what seems to me, from what I have heard, to be somewhat unclear data about progression is defined as and how we measure it, and what will happen if this drug is approved--physicians will need to, I hope, at least in my experience, take a look at what is going on for the patient, what is going to be the best for them and,

hopefully, continue to be cognizant of whether simply achieving a reduction in their tumor size or whether they need to think more about some of the end of life issues that they may be facing and how to give them the best quality of life for however many days they have, and maybe more days with a lousy quality of life is not really that valuable.

While I certainly believe in my dealings with clinicians that they have generally been sympathetic and brought the appropriate emotion to the table, I think, unfortunately, what happens when we go down this slippery slope which is perhaps always going to be part of this process is that cold numbers and statistics, which are really human beings--the human side of this sort of gets lost, and that concerns me, particularly with brain tumors. Someone said to me that unlike other types of cancer, because of where a brain tumor is, it affects the soul. And, I have been to a number of these meetings and, certainly, patients dealing with cancer always have great alarm and great concern but brain tumors are a different animal. And, I just think that looking at real survival is very important.

DR. DUTCHER: Should we vote on question number one?

Is an improvement in six-month progression-free survival or overall progression-free survival sufficient as the principal basis of regular approval for drugs indicated

for the treatment of relapsed malignant gliomas?

I think we should leave it as a yes/no question. All those who would say yes?

[One hand raised]

One. All those who would say no?

[Show of hands]

Eleven no.

The added on part is that improvement in survival is required. All those who would vote yes to the second part of that question? Go ahead. Comment?

DR. BUCKNER: Yes. There are other potential endpoints, other than survival, and we have not discussed those.

DR. DUTCHER: So, would you like to discuss those before we discuss the vote?

DR. BUCKNER: It is up to you, Madam Chair.

DR. DUTCHER: Do you want to hear other potential endpoints?

DR. JUSTICE: Yes, please.

DR. DUTCHER: They are asking for some help in how to analyze this data.

DR. JUSTICE: Yes, I guess the question of or should survival be required wasn't particularly well worded. I think if there are other alternatives that the committee recommends we are certainly open to considering them.

DR. BUCKNER: I think that that is to be discussed actually in questions concerning objective response. So, I would just submit that there is a rationale for using objective response as an endpoint.

DR. COHEN: Are you suggesting objective response for both glioblastoma and anaplastic astrocytoma?

DR. BUCKNER: Yes, I think that there is room for discussion at least on using objective response as an endpoint for approval, depending on what the magnitude of that response might be.

MR. LUSTIG: I am sorry, I am not really sure I understand the terminology "objective response".

DR. BUCKNER: There are some advantages to using objective response. First of all, as we have seen in the study, it can be validated by blinded reviewers. Okay? There are MRI criteria. We have to accept along with it, however, that there are some patients who are classified as tumor progression who probably don't have tumor progression. I can give you from my own practice example after example after example of patients who I thought really had tumor growth and their PET scan was worse, and their thallium SPECT was worse, and we didn't do anything and they got better. Okay?

So, we don't know the magnitude of that. Is it 5 percent? Is it 10 percent? Is it 15 percent? It is

probably not 80; it is probably not 50; it is probably not 40 or 30. It is probably low. Unfortunately, that is where most of the response rates in gliomas range, in the low range, and is this phenomenon that we see in terms of resolution of treatment effect--how does that confound the interpretation of response? If we do set some arbitrary level, say 20 percent for example, if an agent exceeds that and if there are other supporting data in terms of quality of life or survival data that would tend to support that response rate as being a valid endpoint, then I think it should not be ignored.

DR. DUTCHER: Do you think it is easier to make that assessment than non-progression?

DR. BUCKNER: I do. Well, in this case non-progression includes both radiologic and non-radiologic endpoints. Okay? And, I think that also if the bar can be set at some level, then perhaps the background noise of this delayed treatment effect can be overcome.

DR. DUTCHER: And, in terms of response, you are talking about partial or complete response--

DR. BUCKNER: Right.

DR. DUTCHER: --not stable disease?

DR. BUCKNER: And, in fact we have today an example. In one case we see a very low response rate and in another we see a substantial response rate. That is also true in

other situations in neuro-oncology. It is not that it is impossible to tell if a patient is responding or not. We are reasonably confident that patients with anaplastic oligodendrogliomas respond very well to chemotherapy. There is evidence that patients with anaplastic oligoastrocytomas probably also respond. There is certainly evidence that patients with medulloblastoma, primary CNS lymphoma, central nervous system germ-cell tumors are responsive tumors and that can be picked up. So, I do not think that completely ruling out any imaging evaluation as a means of approving drugs is appropriate.

DR. SCHILSKY: This is getting a little bit ahead but since we are discussing it now, I can accept the notion that we can reliably determine by scan whether a tumor is shrinking or not, but the question that you haven't addressed is whether that is an adequate surrogate for benefit for the patient. If the scan shows the tumor is getting a little smaller, based on your experience, are you prepared then to conclude that the patient is getting better?

DR. BUCKNER: Most of the time I think the answer to that is yes. I think it is helpful if it is supported by some other quantitative data of quality of life, as our colleague across the table is suggesting. I mean, really in medicine it is do people live longer or do they live better

or both. And, we are pretty good at measuring that people live longer. The issue of do they live better is much more difficult. I think response is certainly a surrogate endpoint of living better, and supportive data such as quality of life data that show that people do live better is strong supportive evidence.

DR. SCHILSKY: Let me just pursue that for a minute. In this patient population, would you consider living better to be absence of neurological deterioration? Because it is conceivable to me, given the unique anatomy and physiology of the brain, that someone who has a mass that is shrinking might still have fixed, persistent neurological deficits that might not improve. But if they don't worsen that might be considered to be some evidence of benefit.

DR. BUCKNER: I agree. Time to neurologic progression and, as the sponsor showed, time to performance score deterioration I think are strong supportive evidence of benefit.

DR. DUTCHER: Dr. Nerenstone?

DR. NERENSTONE: One of the questions that keeps coming up is the quality of life assessment. I have to say that looking at their data I was very surprised that as soon as the patient stopped taking the drug they were off study and, therefore, not followed. Certainly, in the GOG quality of life continues. Even if the patient is off study drug

quality of life is still required to be gathered for that patient. I think that would capture some of these bigger issues of what is the quality of life? Do they do better when you stop the drug? Do they get worse? How fast? So, that all needs to be written into the study. But just to say somebody is off drug and stop getting quality of life means you have no data, but it is there and it probably can be obtained.

DR. DUTCHER: Let's go on to question number two. Do the results of the randomized, controlled trial in patients with relapsed glioblastoma multiforme, Tables 1-3, provide evidence that Temodal is effective for this indication?

Comments? I think that by putting it in this phraseology you are not requiring it to be better than procarbazine. You are assuming that procarbazine is an active drug, and if you think that this is comparable, is that effective in this indication? Dr. Simon?

DR. SIMON: Well, given that the response rates of both of these were so low, I don't see how you could assume really that procarbazine is benefitting these patients. So, I really don't see how you could make a judgment that because their drug is equivalent to procarbazine in this situation that, therefore--and because the assumption would be that procarbazine would be effective in these patients--I think that is a very slippery slope. You could approve

practically anything on that basis.

DR. DUTCHER: Dr. Albain?

DR. ALBAIN: But I think you do again have to come back to the population and the importance of stabilization of disease, and all these other endpoints that Jan brought up. Response rate in and of itself, while that is what we hope for in that ideal drug that was alluded to before, there are other things that were happening with this population that were very, very important to the clinicians.

DR. SIMON: Well, I think that the quality of life stuff is really unevaluable here because basically quality of life--if you go off study as the procarbazine patients did after one course of therapy, you can't have a quality of life response because quality of life requires, as I understand it, for it to be maintained for two months. So, the fact that the procarbazine patients--so, quality of life here really is essentially a surrogate for time to progression and going off study. That is why, if for no other reason, you would get more of a quality of life response rate for the study drug than for procarbazine, just because the procarbazine patients, for the most part, couldn't have a quality of life response by the definition of it because they went off study after one course. So, I don't think quality of life is measured here, given that the instrument was not utilized after the patient went off

study.

DR. BUCKNER: Just a clarification in my own mind. My understanding was that the entire survival distributions between the procarbazine and temozolomide arms--the p value was 0.067, or was that a chi square at six months? That was just the six months? Okay, thank you.

DR. SCHILSKY: I guess the problem I am having with this is that if you forget about the procarbazine, because I think there are concerns raised about whether it is reasonable to do a comparison, but if you just take sort of the sponsor's stated goal for the study, which was that there be at least 10 percent of patients at 6 months who had not progressed on temozolomide, the difficulty I am having is, given all that we have just discussed about the problems with assessment of progression, I don't know that one can say with a high degree of confidence that in fact that goal of at least 10 percent progression-free survival at 6 months has been met.

DR. DUTCHER: Any other comments? No? Do the results of the randomized, controlled trial in patients with relapsed glioblastoma multiforme provide evidence that Temodal is effective for this indication?

All those who would vote yes?

[Show of hands]

Four.

All those who would vote no?

[Show of hands]

Eight.

Question number three, 94-122 is a single-arm, uncontrolled trial in patients with relapsed glioblastoma multiforme. Without a concurrent control it is difficult to attribute the progression-free survival and survival results to Temodal. While objective responses could potentially be attributed to drug effect, the observed response rate was low, 6 percent, and the endpoint suffers from the previously mentioned concerns about the reliability of response assessments in this disease. Do the results of the Phase II trial provide confirmatory evidence that Temodal is effective for this indication?

I guess in this setting, does the response rate provide more comfort in terms of assessing a benefit or an effectiveness. Any comments about the Phase II study? Do you want to review the tables a moment? This gets back to the issue of whether response is an easier assessment of benefit. Any comments?

DR. BUCKNER: I will just make a comment here. Personally, I would be much more comforted had there been a much higher response rate witnessed because I am not sure that the methodology is capable of sorting out other interpretations with this low a response rate in GBM.

DR. DUTCHER: So, a vote?

Do the results of the Phase II trial in patients with relapsed glioblastoma multiforme provide confirmatory evidence that Temodal is effective in this indication?

All those who would vote yes?

[No response]

Zero.

All those who would vote no?

[Show of hands]

Twelve.

Anybody want to comment about safety? I don't know that we have to vote on this, do we? No.

Okay, number five, is Temodal approvable for treatment of relapsed glioblastoma multiforme?

All those who would vote yes?

[No response]

Zero.

All those who would vote no?

[Show of hands]

Eleven.

Abstain?

[One hand raised]

One.

The next section is regarding anaplastic astrocytoma. The applicant indicated to the FDA that a randomized,

controlled trial in patients with relapsed anaplastic astrocytoma was not possible because almost all patients would have already been treated with all effective drugs, especially nitrosoureas and procarbazine. In the Phase II anaplastic astrocytoma study, however, 89 of the 143 eligible histology patients had not previously received both a nitrosourea and procarbazine. Fifty-seven of 143 patients had received no prior chemotherapy. Thus, there would have been patients eligible for a randomized, controlled trial.

The applicant is requesting accelerated approval for treatment of relapsed anaplastic astrocytoma based on progression-free survival and a commitment to conduct a Phase IV study. although the FDA does not generally consider progression-free survival in a single-arm trial to be interpretable, a meaningful objective response rate in patients unresponsive to other therapies could provide a basis for an accelerated approval.

The 54 patients with relapsed anaplastic astrocytoma who have received both a nitrosourea and procarbazine could be considered unresponsive to other therapies. Does the committee agree? Do we have enough data to agree?

DR. BUCKNER: I think it is fairly clear that there is not a broad spectrum of agents that are active in this disease. A nitrosourea and procarbazine seem to be the most commonly used. There are not other agents that have a

consistent track record.

DR. KROOK: If I remember the slide, there were 5 CRs in this group, which was the largest group of CRs in this group if we use an objective response.

DR. BUCKNER: I would like to point out as well that time to progression from initial diagnosis in this cohort was considerably longer and, in most cases, likely beyond the threshold that we would still expect to see radiation effect.

DR. DUTCHER: Does the committee agree with question six? All those who would vote yes?

[Show of hands]

Twelve.

Given the problems with determining objective responses in patients with recurrent gliomas, is objective response an adequate surrogate for clinical benefit for the purpose of accelerated approval of a drug in refractory malignant gliomas?

Do we want to make this astrocytomas or do we want to leave it as malignant gliomas?

DR. BUCKNER: I think it could be either one.

DR. DUTCHER: Either one. So, given the problems with determining objective response, is an objective response an adequate surrogate for clinical benefit for the purpose of accelerated approval?

Dr. Sledge?

DR. SLEDGE: I don't know that this is a yes/no question because it doesn't give us any parameters. Are we talking about 5 percent, 10 percent, 20 percent, 40 percent? What? In terms of objective response. I think if there is a signal of sufficient magnitude we are all going to be reasonably impressed by that. The question is where do we draw the line for that, and I don't think this question tells us.

DR. RAGHAVAN: The other problem is it doesn't really define what we mean by response, and Jan Buckner has already said that it is somewhat hard to define. There doesn't seem, from what I have been listening to today, to be a universal definition of what constitutes response. So, even if we vote yes we are going to have to put on a coda that says what the FDA defines as response for future purposes, otherwise you have an anarchical situation.

DR. DUTCHER: Dr. Justice?

DR. JUSTICE: I am sorry, response here means CR plus PR. It doesn't include stable disease.

DR. RAGHAVAN: No, I understood that, but I mean we have been listening about the difficulty of defining when does a PR happen. We have seen progressions that would normally have mandated patients going off study, and they haven't and they have done well. So, we have a term

definition problem.

DR. TEMPLE: You have to give us advice about whether you thought the way response was defined was a meaningful way of doing that.

This is more a theoretical question. Is there some kind of objective response and some rate that would be considered a reasonable surrogate for effectiveness in accelerated approval terms?

DR. DUTCHER: Well, I think we have heard some discussion that that can be measured. Correct? Dr. Schilsky?

DR. SCHILSKY: I guess I at least was persuaded that the criteria that Dr. McDonald presented earlier this morning are, to me, both reasonable and seem to be fairly widely accepted in the neuro-oncology community. So, it seems to me that there are criteria that the community has agreed on.

Now, I think the issue is, I guess, how reproducible are the measures because the criteria depend primarily on reduction in tumor size by scan and, you know, as someone who doesn't read these scans for a living it is hard for me to make a judgment about that, although I think in a study in which complete or partial response was an endpoint with blinded central neurology review by expert radiologists I think I would probably be willing to accept those type of

data.

DR. RAGHAVAN: But if I can respond, I mean, the thing that always worries me is the shifting bar phenomenon. You know, the company has put a lot of money into R&D and because the technology five years ago was different from what it is now somebody now reasonably says, well, what we said before doesn't necessarily apply. And, the thing that I think is hard is the fact that you have an emerging PET technology; you have Gadolinium MRI; you have changing sophistication, maybe not improvement but changing sophistication of quality of life measures.

It seems to me that we could make maybe a statement today that response is good and that tumor doubling in size is bad, but that is probably not going to help in the future and what we probably need to do is, if we make that recommendation as a coda, we need to say that the FDA needs to commission a specific definition to be created by people who are a whole lot more expert in this domain than you and I are. You know, you need to get Buckner and Friedman and the various experts in the field to sit down and get a gold standard. But, at the moment, the sort of ubiquitous 50 percent reduction in area--although if you read the discussion, as you have done, there was discussion about do we mean area; do we mean volume. I mean, just to say response I don't think is going to help the FDA for the 500

drugs that are circling the FDA.

DR. SCHILSKY: I couldn't disagree with anything you have said, but what you said applies to virtually every area in oncology and every contemporary test. It certainly is our hope that as time goes on, in everything we do we will be able to more precisely define patient benefit.

DR. RAGHAVAN: I think that is true, but in the other domains there is a better, more defined global experience.

DR. SCHILSKY: There is an international committee right now that is redefining objective response criteria for most solid tumors. So, it will be different in a few years.

DR. RAGHAVAN: I know that but in the brain tumors it just seems to be even--I mean, I don't hold us up as paragons but I think in the brain tumor area we have come into it at a time when there is such a change, and there is such background uncertainty and that is what has come out today. You know, with all the tables that were listed there was very little information about natural history. We have the natural histories for many of the tumors that you and I routinely treat. So, I am just trying to avoid problems for the committee in five years. It seems to me that if we acknowledge response as a good thing, which is fine, then we need to at least let the FDA hear that maybe there is some debate about what really is an acceptable response.

DR. DUTCHER: Well, what we are talking about here are

criteria for accelerated approval. So, we have accepted surrogate endpoints in other diseases. So, the question is what surrogate that is reasonably reproducible can be used as a basis for the next randomized trial so that an assessment can be made. I mean, we have just now sort of trashed progression-free survival. So, is the ability to assess response in these particular diseases sufficiently reproducible that that could be the basis for us to decide that there has been some benefit? Dr. Nerenstone?

DR. NERENSTONE: I believe if you look at the patients who survived who had responses, their survival was meaningful in terms of the time; certainly very long in the anaplastic astrocytoma patients and significantly longer in the GBM patients as well for the responders. So, frank response did seem to correlate with prolongation of survival or prolongation of response. So, once you got a CR you did have some time of survival before progression.

I don't think that is where we have the problem. I mean, I think we could come up with a number. Here the numbers are 9 percent response rate. We are unimpressed with that. Twenty-five percent response rate, CR plus PR radiographically with clear-cut endpoints? Could we agree that that probably is meaningful? Probably.

I think the real problem is that is not what we are going to see. It is the much more subtle things, and I

think there is the problem with the accelerated approval, that you really need to do the work of the Phase III and look at your quality of life, and look at your overall survival before you can get an answer about whether the drug is helping you. But I think we probably could come up with a number. If 10 percent is maybe underlying noise, then 25 percent in a large study of 200 patients--maybe that is worthy of an accelerated process.

DR. SIMON: There is substantial literature sort of pointing out that because you have responders living longer than non-responders doesn't mean that the response caused them to live longer. They may be prognostically better or they may have less tumor bulk. So, that in itself doesn't permit you to conclude that response is a good thing. The response may just be a marker of patients--I mean, the median survival for anaplastic astrocytomas was substantial even from the literature so it just may be a marker.

I guess the other thing that I didn't see in the presentation today is any real data of a quality of life type that sort of demonstrated baseline and follow-up, what kind of improvements in quality of life do we see for responders. I saw only one figure that showed that we had a higher rate of percentage improvement in responders than non-responders but that, to me, is not interpretable because the non-responders tended to go off study and, therefore,

they couldn't qualify as having an objective improvement in quality of life. But I didn't see an analysis that showed us what kind of quality of life improvements, at least with this data, we saw with the responders.

So, the impression is, is response reasonably viewed as a surrogate for patient benefit, but I haven't seen any data today that indicated that it is.

DR. DUTCHER: Dr. Schilsky?

DR. SCHILSKY: Maybe I could just frame this question in a slightly different way because my understanding is that the agency and we, as a committee, have generally accepted response rates, CR and PR, as a surrogate for clinical benefit in the setting of accelerated approval. You know, we have recommended other drugs for accelerated approval based on those criteria.

So, the question, I suppose, to my colleagues on the committee is, is there anything different about brain tumors that would lead us to conclude that objective response should not be viewed in the same way as we have used it in other tumors?

DR. BUCKNER: I would say too that the issue does get back to one of definition, and if we could move on to say that an agreed upon definition of objective response, or something, or by using McDonald criteria, or whatever--if that would help clarify us and get us off the time.

I think that response does tell us something. I think it has not been as clearly worked out in the brain tumor literature as it might be because of confounding variables, but I still think that it does mean something and that when appropriately defined is appropriate for accelerated approval.

DR. DUTCHER: Dr. Temple?

DR. TEMPLE: Perhaps for people who haven't been part of this, our accelerated approval rule specifically allows us to rely on a reasonable surrogate, a surrogate endpoint reasonably likely to predict clinical benefit. But it quite explicitly doesn't say that clinical benefit, for example improvement in quality of life, has to be demonstrated. It allows us to do that. The application in oncology has generally said that we will do this for refractory disease but not necessarily for other diseases, and this committee has recommended approval in quite a number of situations where that was found, where there was a reasonable objective response. So the committee needs to give us advice on whether it is sufficient. It is also relevant whether in this particular disease objective response does appear to be a reasonable surrogate for likely clinical benefits. The discussion is all entirely relevant. I just wanted to touch on some of the terminology.

DR. RAGHAVAN: To answer Dr. Schilsky's question, I

think there are some really quite important differences in the two domains that we talk about. Understanding that they are going to be changing the rules--may change the rules. You know, we have had in SWOG and elsewhere criteria that preclude using a heavily irradiated lesion as a primary index of response.

I mean, the neuro-oncologists have an impossible task. This is in no way critical of the work they do because it is just awful what they have to face, but they have patients where you have a mass that arises in an operative field that may have necrosis, that may have abscess formation, that has been irradiated. It either gets bigger or smaller with steroids. There is a bunch of other drugs that are given to stop you having seizures which, at the same time, can blunt your quality of life and make you think less well. So, it just seems to me that, therefore, this is real tiger country.

You know, the index that we trashed today I didn't actually think was that bad an index given the impossibility of dealing with this whole situation. So, I didn't come here today thinking the FDA had goofed in the past. I think the discussion today has taken us away from that direction, but I am not sure that I have heard anything today that makes me disagree with Richard Simon. You know, there aren't data that are being presented where we have defined

what is real response, and does it correlate with outcome. You know, a lot of the stuff that related to astrocytoma today may well be a natural history thing that relates to differentiation and growth rate rather than necessarily response to an individual drug.

So, it leaves us in a jam, and the problem is that what we do today puts the FDA in a position of perhaps having to approve things where the committee next year will say, "this is nonsense; it doesn't make sense." So, I would rather sit on the dime than move in a direction that might be going backwards, I guess.

DR. JUSTICE: I would just like to clarify. Perhaps the question is being interpreted too precisely. I mean, what we are really asking is, is there an objective response rate of sufficient magnitude for the patient population that would be an adequate surrogate. We are not asking you do define that. We are just talking about the general principle of using objective response in brain tumors as a surrogate endpoint.

DR. BUCKNER: With regard to some of the factors you mentioned, Derek, and I can see how they certainly can affect the natural history and other biological features, it is a little harder for me to imagine, other than resolution and postoperative radiation changes, how it can actually affect the appearance of the scan, some of the prognostic

variables in terms of host or tumor variables.

Certainly, I think it is more problematic when it comes to discussing progression-free survival or overall survival following progression, but there are not that many things that actually cause the tumors to reduce in size. So, I think the list becomes very short and our job is just to make sure that those factors aren't somehow accounted either in the percentage response rate required or control for steroids or taking into account previous therapies when we are defining what a response means.

DR. DUTCHER: But I think also in these two subsets of patients that we are seeing here we might answer this question one way for glioblastomas and another way for the anaplastic astrocytomas. And, an adequate surrogate for clinical benefit--I mean, I am not sure we were seeing clinical benefit in the glio group but maybe in the astrocytomas there might be clinical benefit if anything, defined by time; hopefully, defined by function. But whether just response can be used as that surrogate I think is very difficult. I think we are having difficulty with that. Dr. Temple?

DR. TEMPLE: Can you say what the difficulty is? How are you distinguishing between shrinking of brain tumor and shrinking--I don't know--a bowel tumor. Why is one surrogate reasonably likely to predict benefit even if it

doesn't show benefit by itself, and the other not? Help us understand what the difference might be.

DR. DUTCHER: I think it is in part what our patient rep. has said, that the brain is the soul and if a person is no different but has a shrinking tumor, is that clinical benefit? I mean, the clinical benefit is the whole person. It is function; it is survival; it is steroid reduction; it is, you know, no seizures. The clinical benefit is a fairly global thing when you are dealing with a brain tumor. I mean, I defer to the neuro-oncologists on this but it seems to me that something that makes that person more of a person is what we want to see, which is what we are all asking for but which may be unrealistic.

DR. TEMPLE: Of course, that is what you want to see but in the design of this study they didn't provide a setting in which they could have seen it if it was there. Again, the principle of accelerated approval, whether it is appropriate or not and you need to tell us, is that you use a surrogate that you think will correspond to clinical benefit and then after approval they demonstrate that it is there, and if it is not there they lose their approval. You know, that was a highly debated rule. Not everybody is happy with that approach but that was what it was done, and it has been done by this committee in a whole lot of settings, some of which now have been confirmed; some of

which are still going on.

I guess the question is what the difference is between this and, say, a bowel tumor. I mean, you need to help us.

DR. NERENSTONE: I think the question that needs to be asked to the neuro-oncologists is do you ever see patients where the tumor is objectively responding to treatment and, yet, the patient deteriorates significantly, where it is not related to intercurrent illness, infection or other non-contributing things but where clearly the MRI is getting better and the patient is getting worse? Because I think that is your question.

DR. BUCKNER: I think the answer to that is we do see patients whose masses on MRI get better while the patients continue to deteriorate clinically, and over time it become apparent that probably we weren't treating progressive tumor but we were probably treating some delayed effect which continues to get worse. And, it just is a matter, I think, of magnitude of overcoming the background noise, and I think that there are levels that can be set that would take that phenomenon into account, and there is other supportive evidence in addition to the MR response that can reassure us that what we have seen is actually tumor shrinkage rather than resolution of radiation effect. So, I think the answer to the question is yes but that is not a reason not to use response rate as criteria for accelerated approval.

DR. DUTCHER: What is that noise level?

DR. BUCKNER: It is probably in the range of 10-15 percent maybe. I would be very comfortable with a response rate of 20 percent for accelerated approval.

DR. DUTCHER: Dr. Raghavan?

DR. RAGHAVAN: Jan, as a maybe more universal endpoint, what about one-year survival of X percent? That is something that could be done fast. Given that we have heard all day about how nothing works, except maybe Temodal, one-year survival of X percentage would be quantifiable, reproducible, not subject to bias. It would allow companies to generate data pretty quickly from point of entry to one year--alive or dead. I mean, it sounds very blunt.

DR. DUTCHER: For which disease?

DR. RAGHAVAN: For either one. I mean, I am struck by the fact--I am less enthralled by the difference between GBM and AA because it sounds, from what I have been hearing, that the difference may be what Richard Simon said, a natural history difference; that the AAs would live longer untreated. I don't know. But you could define from the domain of experience. It sounds like no published series has had a one-year survival with a to-be-defined X percent. I am not trying to be polemical; I am just asking a question. Is that going to be a quantifiable thing that we can take back to the FDA and say, "we would view having a 30

percent survival for GBM at one year as earth-shattering, and for AA and 80 percent." I don't know. You would have to set the numbers. Is that going to be something that is less controversial for when we meet next year for drug X than response?

DR. BUCKNER: Well, you never know what is going to be controversial, but I think that is not a perfect endpoint in this entity either because it has not been clearly worked out what factors, what non-treatment variables influence survival at one year. For example, does extent of surgery at recurrence influence survival? What about MIB-1 labeling? What about EGFR expression? What about time from initial diagnosis to study entry? What about a number of factors. So, it is not a perfect endpoint.

I would say, however, it is acceptable, but I don't think it is necessarily more acceptable than response rate. I think actually both of them would be acceptable endpoints.

DR. DUTCHER: Dr. Temple?

DR. TEMPLE: I just need to be sure of what we are hearing. There probably is some one-year survival that would be obviously different from the natural history, but you are really advocating use of a historical control based on appropriate data. Usually you need a control group to get an answer on whether you have improved one-year survival. Why do you think in this case you wouldn't?

DR. RAGHAVAN: I am not sure that I do think that you wouldn't. In other words--I mean, again, I would ask Richard for input on this but, you know, you may be able to define in the context of historical controls--I mean, again, as I said maybe before you came in, I know nothing about this field and I have acknowledged that publicly.

In this context, from what I read, you know, there is no published series of GBMs that has, I guess, a 25 percent one-year survival, 30 percent, whatever you want the number to be. So, therefore, what you might say is that the documentation of a 10 percent improvement and one-year survival in a Phase II design, understanding that Phase IIs are not normally done that way, might be a useful endpoint. It seems to me this is an area where we need to be creative because of the nature of the beast.

As our chairman said philosophically, you know, this is the seat of the soul. If you then become more pragmatic, it is also an area that gets chopped open, irradiated, and there are a bunch of other drugs that make it very hard to assess many things. I take Jan's point that there are not any of those factors that make disappearance of mass effect an artifact. I accept that. But the problem is if we just say response--I didn't hear us say complete response--we then start to get into the realm of real difficulty.

And, doctor, you showed three very good scans which

showed exactly why it is hard to use response as an endpoint. There are wiggly, little blotchy things which are dense in one area and not in another, and I just would like to avoid reading in a cancer report that this happened--

DR. DUTCHER: But isn't that why we have the experts here, to tell us what they consider a response. I mean, we have some fairly notable neuro-oncologists here who have made definitions for us to use, and at least in this situation of accelerated approval, it seems to me we have to rely on some of that expertise. I mean, relapsed brain tumors is not a well studied area. Most of those people--20 percent are eligible for Phase II trials after recurrent disease.

So, it seems to me we are really trying to make this tighter than it is going to be possible to do. If there are criteria that get above the noise of the variability of radiation effect and other effect that can give us a real response rate that we can use as a surrogate marker for benefit, and then we can go on and do a comparative trial, we are ahead of where we have been for a long time. I mean, you know, I don't have a problem with that. If the neuro-oncologists can define the noise level that they all agree exists and makes the field difficult, but if you get beyond that they really will accept this, you know, clinically and physiologically, I think we have to accept that they know

what they are talking about. Dr. Simon?

DR. SIMON: I just want to clarify you can go on and do a randomized trial either way. I mean, doing the accelerated approval doesn't permit you to do a randomized trial. The randomized trial that was proposed was using survival as an endpoint and it was for first-line treatment. I guess what the accelerated approval does is say that we believe that there is sufficient reproducibility of this response rate, and we have sufficient comfort that it corresponds to patient benefit that we want to make the drug available while that subsequent trial is being done.

DR. ALBAIN: Being relatively new to ODAC, and trying to understand the accelerated approval process, does accelerated approval require reproducibility, or will one Phase II trial suffice?

DR. TEMPLE: Usual standards are said to apply. The rule doesn't change the level of evidence; it just changes the kind of evidence. So, ordinarily, that would require evidence of independent substantiation. To me, that goes to the question of in a series, as opposed to a controlled trial, what exactly is the study? Where you cut a series off is kind of arbitrary. It is almost as if each patient is its own evidence of a response rate, in contrast to a trial where you are looking at mortality in two groups. So, it is a little hard to say what constitutes replicability in

a series. That has never been addressed in any really systematic way. But ordinarily you need to expect that the rate is well defined, and would be likely to show up in another setting. There is more than one center in here.

DR. ALBAIN: So there is precedence for an accelerated approval with one well-conducted Phase II trial.

DR. TEMPLE: Well, particularly if the data arise from more than one center and are consistent across. In this one you have three groups of patients you could look at and reach that conclusion. But it is highly judgmental and there is not a strict rule. But the accelerated approval route is not meant to change the quantitative standard of evidence, which usually means we want evidence from one appropriately controlled study. That is what it usually means.

DR. SLEDGE: I must say, I think we are being a little too tough on this drug in this disease. I mean, what we have is three responses in previously treated patients and four response in previously untreated patients. I have heard nothing from any of our experts, either on or off the panel, to suggest that this isn't something that is significantly above the noise level, and it sounds to me like it is. And, we are requiring of them that they do a prospective, randomized trial against the standard combination for the disease. Those all sound very

reasonable to me.

DR. SIMON: Can you clarify, what was your denominator?

DR. SLEDGE: How do you mean? I am sorry?

DR. SIMON: In terms of how many responders, what are you talking about?

DR. BUCKNER: He is talking about roughly 30 percent or 40 percent.

DR. SLEDGE: Yes, for the AAs, not for the GBMs.

DR. ALBAIN: I guess in particular I am struck that 12 out of 54 patients who had prior nitrosourea and procarbazine.

DR. DUTCHER: We have discussed whether response is a surrogate, and I don't think we have to vote on that for the second part of it. There is some sense that you can use response if you define it and have a noise level.

Does the Phase Ii study in anaplastic astrocytoma show that Temodal is effective for the treatment of relapsed anaplastic astrocytoma in patients who have had prior treatment with a nitrosourea and procarbazine?

DR. BUCKNER: Yes.

DR. KROOK: Yes.

DR. DUTCHER: All those who would vote yes, please raise your hand.

[Show of hands]

Twelve yes; zero no.

If so, is the safety of Temodal acceptable for this indication?

DR. BUCKNER: Yes.

DR. KROOK: Yes.

DR. DUTCHER: All those who would vote yes?

Twelve yes; zero no.

Last question, should Temodal be given accelerated approval for the treatment of relapsed anaplastic astrocytoma in patients who have had prior treatment with a nitrosourea and procarbazine?

DR. BUCKNER: Yes. I would answer yes.

DR. KROOK: Yes.

DR. DUTCHER: Those who would vote yes?

Twelve yes; zero no.

I hope the discussion was of some help to you in terms of future directions. Thank you all. We are going to adjourn and we are going to try to start on time at 1:45.

[Whereupon, at 1:05 p.m. the proceedings were recessed, to be resumed at 1:55 p.m.]

# AFTERNOON SESSION

## Introductions

DR. DUTCHER: There are new people at the table so, I guess, I would like to have everyone once again introduce themselves. Dr. Krook?

DR. KROOK: I am Jim Krook. I am a medical oncologist, Duluth CCOP.

DR. SANTANA: Victor Santana, pediatric oncologist, St. Jude's Children's Hospital, Memphis, Tennessee.

DR. NERENSTONE: Stacy Nerenstone, medical oncology, Hartford Hospital, Hartford, Connecticut.

DR. MILLER: Carole Miller, oncologist at Johns Hopkins, visiting from CBER.

DR. RAGHAVAN: Derek Raghavan, medical oncologist, University of Southern California.

DR. SLEDGE: George Sledge, medical oncologist, Indiana University.

DR. DUTCHER: Janice Dutcher, New York Medical College, Our Lady of Mercy, New York.

DR. SOMERS: Karen Somers, the Executive Secretary to the committee, FDA.

DR. MARGOLIN: Kim Margolin, Medical Oncology and Hematology, City of Hope, Los Angeles, California.

DR. PAPADOPOULOS: Essie Papadopoulos, Memorial Sloan-Kettering Cancer Center, New York, also a visitor from CBER.

DR. SCHILSKY: Rich Schilsky, oncologist, University of Chicago.

DR. ALBAIN: Kathy Albain, medical oncologist, Loyola University, Chicago.

DR. WILLIAMS: Grant Williams, Medical Team Leader, FDA.

DR. HIRSCHFELD: Stephen Hirschfeld, Medical Officer, FDA.

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

MS. BEAMAN: Carolyn Beaman, Sisters Breast Cancer Network, consumer rep to the committee.

DR. DUTCHER: And, our patient representative for this particular topic became ill so will not be here today; and Dr. Justice is here.

All right, we have no announcements for this session so we will proceed with the sponsor's presentation.

**NDA 50-766 Prograf (tacrolimus) capsules, 1 mg and 5 mg and Prograf (tacrolimus) injection 5 mg (for IV infusion only) Fujisawa Healthcare, Inc.**

**Indicated for the prophylaxis of graft-versus-host disease in patients receiving allogenic bone-marrow transplants**

DR. JOHNSON: Madam Chairman, members of the committee, good afternoon.

[Slide]

My name is Jerry Johnson. I am Vice President of

Regulatory Affairs, Quality Assurance and Safety at Fujisawa Healthcare, Inc., the sponsor of the Prograf NDA under this discussion this afternoon.

[Slide]

This afternoon we wish to present a summary of the relevant information relating to a new indication for Prograf. Prograf is the brand name for tacrolimus capsules and injection.

[Slide]

As background, Prograf is currently approved and marketed around the world for a variety of indications related to the prophylaxis of organ rejection in patients receiving organ transplants. In the United States, Prograf was approved for the prophylaxis of organ rejection in patients receiving allogeneic liver transplants in April of 1994, and in patients receiving allogeneic kidney transplants in April of 1997.

[Slide]

The discussion this afternoon will be related to the proposed indication for Prograf of prophylaxis of graft-versus-host disease in patients receiving allogeneic bone marrow transplants.

[Slide]

The IND for development of bone marrow transplant indication was submitted in March of 1992. The end of Phase

II meeting between Fujisawa Healthcare, Inc. and the FDA's Division of Oncology Drug Products to discuss the Phase III development program was held in February of 1993. The protocol for the pivotal U.S. clinical trials program was submitted in April, 1993 and December of 1994. The pre-NDA meeting with the reviewing division occurred in October of 1997, and the NDA was submitted in July of 1998.

For the prophylaxis of graft-versus-host disease Prograf has been granted Orphan Drug status by the FDA. No other drug currently has approval for this indication.

[Slide]

The clinical program for this NDA included two pivotal U.S. clinical trials, a Phase III Japanese clinical trial and several Phase II trials in the United States. The safety database for this NDA includes 464 bone marrow transplant patients receiving Prograf.

[Slide]

In the interest of time, we will omit our presentation of the overview of bone marrow transplantation graft-versus-host disease, and the rationale for use of Prograf in the prophylaxis of this disease. We will be happy to answer any questions regarding this at the end of our presentation.

Dr. William Fitzsimmons will present the efficacy data and conclusions from our Phase III clinical trials. Dr. Fitzsimmons has been involved in the planning and direction

of our bone marrow transplant program since its inception in 1992.

Dr. Donald Buell, Clinical Director for the Bone Marrow Transplant Program at Fujisawa Healthcare, Inc., will then present the safety profile for Prograf in this indication, followed by Dr. Donna Przepiorka, who will discuss her clinical experience with Prograf in bone marrow transplant patients. Dr. Fitzsimmons will then make some concluding statements prior to answering your questions concerning our NDA.

We will now move, for the benefit of the committee, to slide 28 to continue the presentation. Dr. Fitzsimmons?

**Efficacy**

DR. FITZSIMMONS: Madam Chairman, members of the committee, good afternoon.

[Slide]

I would like to present the clinical data which demonstrates the efficacy of tacrolimus for the prophylaxis of graft-versus-host disease after allogeneic bone marrow transplantation.

[Slide]

Fujisawa has performed two Phase III pivotal trials in the United States and a Phase III study in Japan. The first U.S. study, protocol 93-0-004, was performed in patients who were recipients of matched sibling donor marrow transplants.

This was a multicenter trial that included a total of 329 patients at 16 sites.

The second U.S. study, protocol 94-0-018, was performed in recipients of unrelated donor marrow transplants and included a total of 180 patients at 10 investigator sites.

The third Phase III trial, FJ-14/15, was performed in Japan and included a total of 133 patients at 21 investigator sites. This study included both matched sibling and unrelated donor recipients.

[Slide]

The two U.S. Phase III pivotal trials were multicenter, randomized, parallel group, open-label trials which compared an immunosuppressive regimen of tacrolimus in combination with short-course methotrexate to cyclosporine in combination with short-course methotrexate.

[Slide]

The primary endpoint of the matched sibling and unrelated donor studies was the incidence of moderate to severe grade II-IV graft-versus-host disease at 100 days post-transplant. This endpoint was assessed by both the investigators at each clinical site and by an endpoint evaluation committee.

[Slide]

The investigators assessed graft-versus-host disease

utilizing the standardized grading and staging criteria. This diagnosis was based on clinical assessment of the patient. GVHD, as assessed by the investigator, has been a standard used in other clinical trials of this clinical entity. The assessment of the patient is critical in making this diagnosis and dictates subsequent treatment of GVHD.

Even though we previously had agreement with the FDA that these trials would be open-label, utilizing the investigator assessment of GVHD as the primary endpoint, we felt that there may be some added value to attempting to perform a blinded, retrospective evaluation of graft-versus-host disease. This approach to GVHD had not been previously validated.

[Slide]

We formed an endpoint evaluation committee to perform this blinded evaluation. The endpoint evaluation committee evaluated GVHD blinded to the randomized study drug. A consensus diagnosis was determined based on agreement by at least two of the three reviewers. Each committee member reviewed each individual study patient's data to determine the presence or absence of graft-versus-host disease and its grade.

[Slide]

The committee members were provided the following data on each patient, which included patient and donor

demography, clinical and laboratory data, selected adverse events, study drug dosing and blood levels blinded to the randomized drug. Steroid treatment was not provided to the EPEC in order to preserve the blind and reduce bias.

[Slide]

The endpoint evaluation committee was composed of three bone marrow transplantation physicians, Dr. Georgia Vogelsang, from Johns Hopkins University; Dr. Mary Horowitz, who is here today from the Medical College of Wisconsin and the Scientific Director of the IBMTR; and Dr. Nelson Chao, from Duke University. These physicians and their institutions did not participate in the Phase III trials.

[Slide]

Both the matched sibling and unrelated donor studies were designed as equivalence trials. The equivalence of tacrolimus and cyclosporine regimens was defined by the protocol, and determined by the 95 percent confidence interval around the difference in the rate of GVHD at 100 days post transplant. By design, this analysis censored patients for death or relapse.

For the matched sibling study the maximum difference allowable between tacrolimus and cyclosporine was 15 percent, whereas for the unrelated donor study, due to the high rate of GVHD, the maximum allowable difference was 10 percent in order to establish equivalence. The sample size

for each study was calculated based on these criteria of equivalence, with an alpha error of 0.05 and a beta error of 0.2. The rates of acute GVHD in the cyclosporine control arm were assumed to be 30 percent in the matched sibling population and 75 percent in the unrelated donor cyclosporine control group.

[Slide]

This slide illustrates the use of a 95 percent confidence interval in order to establish equivalence. The Y axis represents the difference in the rate of acute GVHD tacrolimus minus cyclosporine. Therefore, if this difference is positive the rate of GVHD in the tacrolimus group would be greater than cyclosporine.

At 100 days post transplant the 95 percent confidence interval around this difference in the rage of GVHD is calculated. With equivalency criteria of 15 percent, if this 95 percent confidence interval falls within the red equivalence area, as shown here, the 2 treatments are determined to be equivalent. Alternatively, if the 95 percent confidence interval crosses the 15 percent bound, as shown here, the rate of GVHD with tacrolimus would be greater than cyclosporine, and the 2 treatments could not be proven to be equivalent.

[Slide]

For both clinical trials an external data safety

monitoring board, chaired by Dr. Thomas Fleming, was utilized. The sponsor, as well as the investigators, remained blinded to the aggregate study results during the conduct of the trial, and prior to data lock and analysis.

[Slide]

Both studies stratified randomization by center. Randomization was also stratified by factors that had been identified in recent analyses to be the strongest predictors of acute GVHD, the primary endpoint. The factors for the matched sibling study were patient age, greater than or equal to 40 or less than 40, and whether the patient was male and receiving a transplant from an alloimmunized female donor. In the unrelated donor study the randomization was stratified by zero or 1 antigen mismatch between the patient and donor. The randomization was performed pre-transplant and patients were randomized to cyclosporine or tacrolimus in a 1:1 allocation ratio.

[Slide]

The dosing regimen of tacrolimus for the Phase III trials was based on the results of our Phase II studies. Cyclosporine dosing was based on the standard practice at participating institutions. The tacrolimus IV dose was 0.03 mg/kg/day and the cyclosporine dose was 3 mg/kg/day, both administered as a continuous IV infusion. Oral tacrolimus or cyclosporine was started at a dose of 4 times the most

recent IV dose.

Therapeutic monitoring was performed and dosing was adjusted to achieve targeted whole blood concentrations in the first 2 months post transplant of 10-30 ng/ml for tacrolimus and 150-450 ng/ml for cyclosporine. Beyond 2 months post transplant for patients who did not experience graft-versus-host disease dosing was tapered and discontinued at 6 months post transplant.

[Slide]

A standard short course methotrexate regimen was administered in conjunction with cyclosporine or tacrolimus at a dose of 15 $mg/m^2$ on day 1 and 10 $mg/m^2$ intravenously on days 3, 6 and 11 post transplant.

[Slide]

The fundamental design characteristics and endpoints of these studies were based on the agreements reached between the sponsor and the FDA at the end of Phase II meetings. Although our knowledge of marrow transplantation has grown since these studies were designed, they reflect the best available data in 1993 and 1994.

[Slide]

Let's begin reviewing the 04 study in matched sibling donor transplants.

[Slide]

Patients were included in the matched sibling study if

they were recipients of a genotypically HLA identical marrow transplant from a sibling for treatment of a hematologic malignancy. Patients 12 years of age and older were eligible for this trial. After discussion with the investigators, pediatric patients less than 12 years old were excluded from the trial due to the known difference in the risk of GVHD between adults and children.

Patients were also excluded if they had previously received a bone marrow transplant, had renal dysfunction as evidenced by a serum creatinine greater than or equal to 3, or were recipients of a marrow graft that had been T-cell depleted.

[Slide]

The patient demography is shown for both treatment groups. There were no differences in the age, gender or race distribution between the two treatment groups, and this demographic profile is typical of an adult HLA matched sibling donor allogeneic marrow transplant in the U.S.

[Slide]

The malignancies for which these patients received marrow transplantation are shown on this slide. The distribution of diagnoses were similar between the two treatment groups, and the two most frequent were chronic myelogenous leukemia and acute myelogenous leukemia.

[Slide]

The protocol specified a number of baseline conditions that would be statistically compared between the two treatment groups to assess for imbalances. If imbalances were found, these factors would be analyzed as covariates. The factors included disease stage, patient and donor sex match and alloimmunization, underlying malignancies, the antineoplastic conditioning regimen, TBI dose, patient age and performance status. These factors were prospectively defined, and were chosen based on their known correlation with both safety and efficacy endpoints.

[Slide]

The only factor that was significantly imbalanced was advanced versus non-advanced malignancy. Although the malignancies were similar between treatment groups, when staged and classified as either advanced or non-advanced there was a significantly greater proportion of advanced stage disease patients in the tacrolimus group, 41 percent as compared to the cyclosporine group, 29 percent.

[Slide]

The antineoplastic conditioning regimen these patients received prior to transplant were similar between the two treatment groups. The largest proportion of patients received busulfan, cyclophosphamide, followed by cyclophosphamide plus total body irradiation.

[Slide]

This slide shows the number of methotrexate doses that patients received in the two treatment groups. By protocol, patients were to receive a total of 4 doses. However, based on tolerability and organ dysfunction some patients had doses omitted. The number of doses of methotrexate were equally distributed between the tacrolimus and cyclosporine groups.

[Slide]

If we now examine the primary efficacy endpoint of grade II-IV, acute GVHD, as assessed by the investigator, there is a statistically significant difference in the Kaplan-Meier time-to-event analysis when evaluating these cumulative incidence curves. At 100 days post transplant the cumulative incidence for GVHD in the cyclosporine group was 44 percent whereas it was 32 percent in the tacrolimus group.

[Slide]

Since disease state was imbalanced between treatment groups, we also analyzed GVHD results in advanced and non-advanced stage disease patients. In both advanced and non-advanced patients the incidence of GVHD was numerically lower in the tacrolimus group as compared to the cyclosporine group.

[Slide]

The cumulative incidence curves for GVHD that were

previously shown censored patients with death or relapse. Therefore, we also performed a post hoc analysis counting GVHD, death or relapse as events. The cumulative incidence curve shown here is the composite endpoint to assess these competing risks in a worst-case scenario. As shown, the incidence is very similar between the 2 treatment groups, 57 percent for tacrolimus and 58 percent for cyclosporine.

[Slide]

The GVHD was also assessed by the blinded endpoint evaluation committee. There was no significant difference in the time to event by the EPEC assessment. At 100 days post transplant the cumulative incidence was 25 percent in the cyclosporine group whereas it was 19 percent in the tacrolimus group.

[Slide]

Examining the rates of acute GVHD, utilizing the protocol-specified criteria, one can see the 95 percent confidence intervals around the difference in the rate of GVHD, as assessed by either the investigator or the endpoint evaluation committee, demonstrate that tacrolimus is at least equivalent to cyclosporine in the matched sibling donor study.

[Slide]

Moving to the 18 unrelated donor Phase II trial, the inclusion/exclusion criteria for the unrelated donor study

were similar to the matched sibling trial. The primary difference is that due to the complex clinical condition of the unrelated transplants it was decided to exclude advanced stage disease patients in order to more clearly assess the GVHD endpoint.

[Slide]

The demographic profile of the patients in this study for age, gender and race was similar between treatment groups. This profile is typical of an adult unrelated donor marrow transplant population in the U.S.

[Slide]

Approximately 17 percent of the overall study population were 1 antigen mismatched between the donor and the patient.

[Slide]

The malignancies for which these patients were transplanted were equally distributed between the tacrolimus and cyclosporine treatment groups. The two most common malignancies were CML followed by AML.

[Slide]

Also, the antineoplastic conditioning regimens which were administered prior to transplant were similar between the treatment groups, and consisted of CY + TBI most commonly and, secondly, BU + CY.

[Slide]

Methotrexate was dosed similarly between the 2 treatment groups, and most patients received the full 4 doses on days 1, 3, 6 and 11 post transplant.

[Slide]

Examining the primary efficacy endpoint of time to acute GVHD, as assessed by the investigators, there is a statistically significant difference between the cyclosporine and tacrolimus groups in this Kaplan-Meier time-to-event analysis shown in these cumulative incidence curves. At 100 days post transplant the cumulative incidence of GVHD was 74 percent in the cyclosporine group whereas it was 56 percent in the tacrolimus group.

[Slide]

The results from the unrelated donor study were also analyzed using a composite endpoint of GVHD--death, relapse or retransplant, in a post hoc analysis of this worst-case scenario. Using this endpoint, there remains a significant difference in the time-to-event analysis. The cumulative incidence at 100 days is 69 percent in the tacrolimus group as compared to 82 percent in the cyclosporine group.

[Slide]

The endpoint evaluation committee in general had lower rates of graft-versus-host disease in both treatment groups. There remained a significant difference in the time-to-event analysis between the two treatments. By the EPEC

evaluation, at 100 days post transplant the cumulative incidence of GVHD was 32 percent in the cyclosporine group whereas it was 20 percent in the tacrolimus group.

[Slide]

In the unrelated donor study, the protocol-specified criteria for equivalence was a difference no greater than 10 percent. Examining these results based on the protocol-specified equivalence criteria, the 95 percent confidence interval around the difference in GVHD between the two treatments clearly met the equivalence criteria by both the investigator and EPEC assessments.

[Slide]

This slide illustrates all GVHD, ranging from grade I through grade IV, as assessed by the investigator in both the matched sibling and unrelated donor studies. Numerically there is a lower overall rate of GVHD if you include grade I, as shown by the lower height of the bars, for tacrolimus compared to cyclosporine in both studies. You can also see that this difference is driven primarily by differences in grade II GVHD, shown in green, and grade IV GVHD, shown in red.

[Slide]

The rate of grade II to IV GVHD is consistently lower in the tacrolimus as compared to the cyclosporine group, and the rate of grade IV, the most severe form of GVHD, was

decreased in the tacrolimus as compared to the cyclosporine groups.

[Slide]

The EPEC diagnosed a lower rate of GVHD than the investigators in both U.S. studies. Without the steroid administration data, the ability of the EPEC to diagnose grade II GVHD that was characterized by transient steroid responsive rashes or diarrhea was diminished. EPEC diagnosed primarily the most severe forms of GVHD, grade III to IV, involving multiple organ systems which are more evident on retrospective data analysis. However, if you examine the relative risk of GVHD there is a consistency between the EPEC and investigator evaluations. There is a greater risk of GVHD associated with cyclosporine, about 1.8 times greater in the unrelated donor study and 1.4 to 1.6 times greater in the matched sibling population.

[Slide]

An additional Phase III multicenter, randomized trial was performed by Fujisawa in Japan. The primary endpoint of the FJ-14/15 study was the incidence of acute grade II to IV GVHD at 100 days post transplant. This trial included patients who received bone marrow transplants for hematologic malignancies from matched sibling, related or other unrelated donors.

[Slide]

A total of 133 patients were studied. There was no significant difference in the age, gender or donor distribution between the 2 treatment groups. The study included 63 matched siblings and 64 unrelated donor recipients.

[Slide]

The cumulative incidence of grade II to IV GVHD as assessed by the investigator was 47 percent in the cyclosporine treated group and 17 percent in the tacrolimus treated group. There is a statistically significant difference in the time-to-event analysis of GVHD.

[Slide]

GVHD data were also analyzed to assess the incidence and severity within the sibling donor and unrelated donor subgroups. There is a numerically lower rate of grade II to IV as well as grade III to IV GVHD in the tacrolimus treated groups for both matched sibling donors as well as for the unrelated donor transplants. The efficacy advantage of tacrolimus seen in the unrelated donor 18 study is replicated in the FJ-14/15 study, which included a substantial proportion of unrelated donors.

[Slide]

A post hoc analysis of the composite endpoint of grade II to IV GVHD, death or relapse, was analyzed for the FJ-14/15 study. There was a significant difference in the

time-to-event analysis of this worst-case scenario. At 100 days post transplant the cumulative incidence is 51 percent in the cyclosporine group and 27 percent in the tacrolimus group.

[Slide]

Summarizing the results from the two adequate, and well-controlled U.S. Phase III pivotal trials and the Japanese Phase III trial on the protocol-specified primary efficacy endpoint of grade II to IV GVHD, you can see that for all three studies, and for both investigator and EPEC evaluations in the U.S. trials tacrolimus has clearly been shown to be at least equivalent to cyclosporine.

The studies included matched sibling donors in the 04, unrelated donors in the 18 and both matched sibling and unrelated donors in the FJ-14/15. These data demonstrate the efficacy of tacrolimus for the prophylaxis of graft-versus-host disease in both recipients of matched sibling donor and unrelated donor allogeneic bone marrow transplants.

I would now like to introduce Dr. Buell to review the safety data of tacrolimus in marrow transplantation.

**Safety**

DR. BUELL: Thank you, Bill.

[Slide]

Madam Chairman, members of the committee, agency

representatives and guests, we will now address the safety information from the Fujisawa comparative trials.

[Slide]

The first topic to be discussed is survival.

[Slide]

As Dr. Fitzsimmons pointed out, there was an unequal allocation of advanced disease group patients in the matched sibling 04 trial. Randomization was not stratified on this variable but, rather, on variables predictive of GVHD. One result was uneven distribution of patients who were transplanted when their underlying malignancy was not in control.

You can see that 68 advanced disease patients were randomized to receive tacrolimus and 48 patients were randomized to receive cyclosporine-based therapy. This difference was statistically significant.

[Slide]

Advanced disease patients include CML patients in blast crisis, leukemia and lymphoma patients with refractory disease and relapse, and patients with multiple myeloma.

[Slide]

The column on the right shows the makeup of the advanced disease population in the 04 study. The makeup of the advanced disease group stands in contrast to that of the non-advanced disease group, shown on the left. AML is the

largest category in the advanced disease groups. The highlighted diseases, ALL, non-Hodgkin's lymphoma, multiple myeloma and CLL, account for 60 percent of advanced disease but only 12 percent of non-advanced disease patients. Even within a single disease, such as non-Hodgkin's lymphoma, there is considerable heterogeneity.

[Slide]

Patients who undergo bone marrow transplantation, when their underlying malignancy is not in control, are a difficult and complex group to manage and evaluate. They tend to have more transplant complications, and have a poorer prognosis for survival.

[Slide]

The classic example is chronic myelogenous leukemia. Patients transplanted in blast crisis have the poorest survival. Note that the survival for the blast phase group is 20-30 percent at 2 years. CML patients transplanted in blast phase are in the 04 advanced disease group.

[Slide]

These are survival curves for acute myelogenous leukemia. The bottom curve represents those patients transplanted with resistant relapse. Note again the poor survival of approximately 20 percent for the lowest curve. Patients transplanted in resistant relapse are in the 04 advanced disease group.

[Slide]

This slide indicates the survival at 2 years for acute lymphoblastic leukemia and intermediate grade non-Hodgkin's lymphoma patients. It contrasts the Kaplan-Meier survivals for patients transplanted in remission versus relapse. For all of these diseases that I have presented the expected 2-year survival for those transplanted in relapse is on the order of 25 percent.

[Slide]

We have 2-year survival data for study 04 and study 18, and six-month survival data for the Japanese randomized study 14/15. The overall survival in the matched sibling 04 study was 47 percent in the tacrolimus group and 57 percent in the cyclosporine group. This was a statistically significant difference. Looking further, it can be seen that survival in the non-advanced groups was identical. The survival difference was restricted to the advanced disease groups where the uneven allocation of patients occurred. This subgroup represents approximately 18 percent of the patients in our Phase III trial. There was no difference in survival in the other 2 comparative trials. In the unrelated donor 18 study the survival at 2 years with tacrolimus was 54 percent and cyclosporine 50 percent. In study 14/15 the six-month survivals were identical.

This unexpected subgroup difference in survival in the

advanced disease group is not consistent with our prior experience in comparing these 2 agents. It comes in the context of an uneven allocation of patients to the 2 study arms in a disease category that is very heterogeneous. These results in these patients can vary very considerably with respect to disease status, duration and intensity of prior therapy, and other factors that could influence post transplant complications and survival.

[Slide]

These are the Kaplan-Meier survival curves for the 04 study, showing the highest survival for cyclosporine-treated patients.

[Slide]

Looking at the non-advance patients, the survival curves are identical.

[Slide]

These are the advanced disease group survival curves. The survival of patients randomized to receive tacrolimus at 25 percent is consistent with the past experience in this group of patients, as I have presented. The cyclosporine group survival at 42 percent is better than one would expect.

[Slide]

We have done a number of exploratory analyses in an attempt to explain the survival advantage of cyclosporine.

We did Cox regression analyses to find potential risk factors for death. We also looked for treatment by factor interactions.

[Slide]

As you can see, we looked at baseline covariates pre-specified in the protocol. We also looked at conditioning regimens and the use of potentially nephrotoxic agents.

[Slide]

Using Cox regression analysis adjusted for treatment, a number of independent predictors of death were revealed. These were stage of disease, age, use of total body irradiation in the transplant regimen, and administration of nephrotoxic agents. The relative risk for advanced disease is 2.39.

[Slide]

We looked to see if there was a study drug treatment interaction with any of these variables. This analysis includes both main effects and a term for the interaction of the main effects in the model. For example, for the first item, disease stage, the model includes treatment, disease stage, and the treatment disease stage interaction.

To interpret interactions due to the lower power associated with this test, a critical p value of 0.15 is often used. By this standard, the treatment disease stage interaction warrants further exploration. There was no

interaction detected for treatment by age, treatment by TBI, or a nephrotoxic agent.

[Slide]

To look further into the discrepancy in advanced disease deaths, we carefully examined causes of death. In order to get a uniform assessment of the underlying cause of death a committee of three investigators reviewed the information related to the patients' deaths. They then reached a consensus on the etiologic cause of death. The committee members were Dr. Wingard, Dr. Nash and Dr. Ratantharathron, the leading enroller in the matched sibling study who is here today.

In the briefing document we have provided the causes of death for both the non-advanced and advanced disease groups. In the 2 non-advanced groups the causes of death were those we expect in a bone marrow transplant population, and were similar between treatment groups.

[Slide]

This slide focuses on deaths due to transplant-related toxicity. These are toxicities associated with the transplant procedure itself, and are often referred to as regimen-related toxicity in the literature. This is a category in which differences between the 2 advanced disease study groups are very apparent.

You can see that the tacrolimus-treated advanced

disease patients have a pattern similar to that of the non-advanced groups--the tacrolimus advanced and the non-advanced groups.

These are toxic deaths we see in patients with malignancy undergoing bone marrow transplantation. The cyclosporine advanced disease group deaths are unusual and are not comparable to the tacrolimus advanced group or even to the non-advanced groups. Note that there were only 2 deaths due to transplant-related toxicity, fewer than expected.

[Slide]

In this slide I have summarized all the causes of death but just for the 2 cyclosporine groups. These numbers emphasize the unusual nature of the cyclosporine advanced disease group. Other than relapse, which should be higher, the cyclosporine advanced disease group has done unusually well compared to the cyclosporine non-advanced disease group.

At this point, it appeared that not only was there a numerical imbalance in advanced disease patients allocated to the 2 study arms but, more importantly, that the advanced disease patients allocated to cyclosporine were somehow a more favorable group, more favorable than one would expect from past experience and more favorable even than the non-advanced cyclosporine patients in the same trial.

[Slide]

The advanced disease group of patients in study 04 was a unique group with no precisely matching historical experience obtainable from the lit. Further, it looked as though the advanced disease cyclosporine patients were quite atypical. At the suggestion of the FDA, made at our pre-NDA meeting, we decided to attempt a matched control study. The purpose was to try to understand the outcome differences apparent in the advanced disease groups.

The International Bone Marrow Transplant Registry is a large registry of data on patients who have undergone bone marrow transplantation. The director is Dr. Mary Horowitz. The registry is located at the Medical College of Wisconsin. After discussion with representatives from the IBMTR, it was determined that it was feasible to attempt a matched controlled study. We provided in study 04 advanced disease patient database and the data group at the IBMTR performed the matched control analysis.

[Slide]

There were over 15,000 patients in the IBMTR database from which the selection process was performed. The final matching was done from 879 IBMTR patients who received matched sibling transplants at a North American center during the time frame of the 04 study; had the same types of malignancies; the same age range; and who had all received a

regimen of cyclosporine plus methotrexate. Matching was based on disease, disease status and age. For the 4 patients for whom more than 2 matches were obtained, 2 were selected at random.

[Slide]

There were 116 advanced disease patients in the 04 study. A 2:1 match was not obtained for 16 patients, 6 tacrolimus and 10 cyclosporine. There were, therefore, 100 study patients and 200 IBMTR patients in the matched control study.

[Slide]

These curves show the survival of the tacrolimus-treated 04 study patients, in yellow, and their IBMTR-matched controls in blue. These curves are very similar, with a 2-year survival of 24-27 percent. You should remember that all of the IBMTR matched controls received cyclosporine plus methotrexate. Both groups show a level of survival that we would expect for advanced disease patients undergoing transplantation.

[Slide]

The study 04 cyclosporine-treated advanced disease patients and their IBMTR-matched controls also have similar survival but these matched patients had a survival of 42-43 percent. This, again, is more favorable than we would expect in an advanced disease group.

[Slide]

Finally, we have plotted the 2 IBMTR control population curves. These groups had both received a standard cyclosporine plus methotrexate regimen. These outcomes are similar to those of the 04 study itself, but they cast out on the survival effect of tacrolimus. These survival patterns from the IBMTR-matched control study suggest that these advanced disease groups had a different survival prognosis that was identified by matching on baseline factors and disease condition.

[Slide]

The IBMTR-matched control study indicated that the cyclosporine advanced patient group appeared to have a more favorable prognosis. The prognostic effect of the advanced disease imbalance is similar to what was seen in the 04 matched sibling study. This prognostic effect appears to be due to a combination of baseline factors which cannot be easily analyzed.

[Slide]

As you have seen in the FDA questions that you will address later this afternoon, the relative risk of death in the advanced disease subgroup is approximately 0.57. In the larger subset of non-advanced disease patients there is no survival disadvantage. The relative risk is 0.96.

Now, we have spent some time addressing this issue of

survival in the advanced disease patient groups of matched sibling study 04 because of the patient imbalance and the differences in survival that we noted, however, this subgroup accounts for only about 18 percent of our Phase III study experience. Looking at all 3 Phase III trials, the risk or hazard ratio for death is essentially 1 for all patients except this advanced disease group, 0.96 for the non-advance, 1.16 for the unrelated donor patients and 0.95 in the Japanese trial.

[Slide]

We will now look at other safety parameters of special interest for bone marrow transplantation and for this class of drugs. Where appropriate, we will examine advanced disease separately.

[Slide]

There is a concern that reduction in graft-versus-host disease might result in a higher relapse rate. In the matched sibling study the relapse rates through 2 years were comparable in the study arms. As expected, the relapse rate was higher in the advanced disease patients, and this was true for both treatment groups.

[Slide]

This is relapse data through 2 years from the unrelated donor study. These are non-advanced disease patients. The relapse rates are comparable.

[Slide]

In the 04 matched sibling study the mean peak serum creatinine value and the number of patients with creatinine values about 2 mg/dl were somewhat higher in the tacrolimus patients. This was due to the advanced disease subgroup.

[Slide]

There was a difference in the incidence of hemodialysis, as shown here, 32 tacrolimus and 16 cyclosporine patients received hemodialysis. These dialysis differences also relate to disease stage. For non-advanced disease patients, 13 in each group received dialysis but 19, or 28 percent, of tacrolimus advanced disease patients received dialysis compared to only 3, or 6 percent, in the cyclosporine advanced disease group.

[Slide]

This is consistent with the transplant-related toxicity findings which indicated that the cyclosporine advanced disease group patients actually did better than the cyclosporine non-advanced disease patients.

[Slide]

In the 18 unrelated donor study the renal parameters were comparable. Dialysis was received by 10 percent of patients in each group.

[Slide]

Hyperglycemia, particularly that which required

insulin use, has been a concern with these agents. In study 04 only 1 patient required insulin at 6 months. The study drugs were often tapered or discontinued by this time.

[Slide]

In the unrelated donor study there was also no difference between groups in the requirement for insulin therapy. At 6 months 7-8 percent of patients were still receiving insulin.

[Slide]

In the matched sibling trial there were no major differences between groups in mean total bilirubin values or mean transaminase values.

[Slide]

And there were no differences in peak bilirubin or the incidence of VOD between the study arms.

[Slide]

In the unrelated donor study the mean total bilirubin and transaminase values were similar for the 2 study group.

[Slide]

In the unrelated donor study 18 the peak bilirubin values and incidence of VOD revealed no between group differences.

[Slide]

We have looked carefully at treatment emergent adverse events. These are the adverse events which have their onset

after the start of study drug administration. There was a high incidence in a number of treatment emergent adverse events. Many of these relate to the rigors of transplantation.

[Slide]

Here we have listed those adverse events in the matched sibling study for which a significant difference in incidence was reported. Those in white are more frequent in tacrolimus patients; those in yellow are more frequent in cyclosporine patients.

As we have noted on our other indications, we tend to see more abdominal pain in tacrolimus groups and more hypertension and hyperlipidemia in cyclosporine-treated patients. For a category such as liver function tests abnormal, we feel it is more clinically relevant to evaluate changes in the laboratory test data rather than rely on laboratory test related adverse event reports. These are lower incidence adverse events for which a significant difference was reported.

[Slide]

In the non-advanced patients we see a number of adverse events whose incidence differences significantly between the study arms. The trend here is toward more events in the cyclosporine patients, with 11/15 being more prominent in that arm.

[Slide]

In the advanced disease patients of study 04, 11 events emerged as having a significant difference in incidence between groups. Some of these adverse events were more frequent in the cyclosporine patients, as you can see in yellow.

[Slide]

In the unrelated donor study the significantly different adverse events are mostly in yellow and due to cyclosporine.

In these last four slides we have looked at the totality of adverse events across these U.S. trials. We have expanded our view beyond those measures such as dialysis and survival that were strongly influenced by early events in the advanced disease subgroup. If anything, these overall adverse event profiles favor tacrolimus .

[Slide]

When we looked at the more severe adverse events, those reported as SWOG grade III or IV, very few significant differences emerged. In the non-advanced groups severe diarrhea was more frequently reported for tacrolimus patients.

[Slide]

In the advanced groups the severe adverse events of lung hemorrhage and hyperventilation were significant for

tacrolimus. This probably reflects the pulmonary transplant-related toxicity differences discussed earlier.

[Slide]

In the unrelated donor study 18 lung edema significantly differed as a grade III or IV adverse event, occurring more frequently in cyclosporine patients.

[Slide]

These outcomes of interest are from the list of toxicities in study 04 that were of concern to the agency, as expressed in their question to the committee. This analysis presents these items separately for the non-advanced and advanced disease groups of the matched sibling study.

It can be seen that these findings are due to differences in the advanced disease patient groups. They are comparable in the non-advanced disease groups. We have already seen that overall differences in the renal parameters were due to the advanced disease patient differences. The same is true of intubation, death and death within 100 days.

[Slide]

The final concern that I will address is engraftment. The incidence and time to neutrophil engraftment was quite similar for the 2 study groups in the matched sibling study.

[Slide]

Also, in the unrelated donor study 18 there was no differential effect on engraftment for these 2 agents.

[Slide]

I have presented the safety data for our Phase III trials, and Dr. Fitzsimmons has presented the efficacy data. I would now like to list our overall conclusions from these Phase III trials.

[Slide]

In three trials tacrolimus was shown to be at least equivalent to cyclosporine for prevention of GVHD. These trials included a substantial number of patients, 392 who received matched sibling and 244 who received unrelated donor transplants. With respect to this first point, we must keep in mind that the investigator assessment is the most proven, reliable measure of GVHD. By the investigator's assessment tacrolimus reduces the incidence of GVHD. Prevention of GVHD by tacrolimus was achieved without any cost in time to engraftment or increase in relapse.

[Slide]

With respect to safety, we have seen that in the unrelated donor and the non-advanced patients from the matched sibling donor study the safety profiles of tacrolimus and cyclosporine were quite comparable, and this represents approximately 80 percent of the U.S. study

populations. However, in the advanced disease groups in study 04 there was a treatment difference in survival and renal parameters.

[Slide]

Most often when we do a large randomized trial the study groups, and even the subgroups, are comparable but exceptions do occur, and the imbalance in this study has had a major impact on the safety findings. As I have pointed out, several findings draw into question the results in advanced disease patients.

First, the cyclosporine advanced disease patients did unexpectedly better than the cyclosporine non-advanced disease patients, with a lower dialysis rate and less transplant-related mortality.

Second, the matched sibling control study results demonstrated a favorable survival prognosis for the cyclosporine advanced disease patients. We have seen that tacrolimus advanced disease patients had a more typical outcome in that they did less well than the non-advanced disease patients. The resultant contrast in the clinical outcomes in the advanced disease groups is largely responsible for the safety profile differences we have noted today.

At this time, I am pleased to introduce Dr. Donna Przepiorka, Associate Professor of Medicine and Pediatrics,

and Associate Director of Stem Cell Transplantation at the Baylor College of Medicine. Dr. Przepiorka has been an investigator in several of our trials. She has agreed to present the transplant physician's view of the role of tacrolimus as an immunosuppressive agent in bone marrow transplantation. Dr. Przepiorka?

**The Transplant Physician's Perspective**

DR. PRZEPIORKA: Thank you, Dr. Buell. Good afternoon. Thank you for inviting me here to give my perspective on tacrolimus.

[Slide]

I have been caring for transplant patients now for 15 years, and during that time GVH has not only been my research interest but also my primary clinical responsibility. So, for me as for most transplanters, a GVH prophylaxis regimen is not a minor concern.

[Slide]

The impact of acute GVH on transplant outcome is substantial both for the patient and for the medical care delivery team. Treatment requires increased resource utilization and intensity of care. Its therapy further increases the probability of serious and life-threatening infections. GVH is the major morbidity. In addition, two large registry studies have demonstrated a high relative risk of mortality for patients who develop grade III or IV

GVH, and GVH or complications of its treatment remain one of the leading causes of death in this population.

So, before I change the way I handle GVH in my clinical practice I made a critical assessment of any new data, and there are three points I would like to address today in making this assessment.

[Slide]

First, I would like to address the grading of GVH in these clinical trials. This is a figure I made for an upcoming review that summarizes the published reports of the incidence of grades II-IV GVHD using standard prophylaxis regimens.

As you can see, the incidence of GVHD has been 30-50 percent for HLA-matched siblings, and with increasing disparity in histocompatibility it is about 55-90 for the matched unrelated donor transplants. And, these are the results expected using cyclosporine-based immunosuppression.

[Slide]

The EPEC process used by Fujisawa asked three experienced marrow transplant physicians to review data from the patient database. In this figure you see the incidence of GVH determined by the EPEC process for the cyclosporine arms, 23 percent and 30 percent, is much lower than that in the published reports, while the grading by the investigators, 41 percent and 60 percent, is similar to that

in the published reports.

Now, I am in a unique position here, not only since I was an investigator in the Phase III trials but I also served on a data and safety monitoring board for the Phase II trial of tacrolimus, a single-drug prophylaxis, that was published in 1996. So, I am personally familiar with the limitations of the EPEC process.

When I train transplant fellows, I teach them that the diagnosis of GVHD is made at the bedside--the clinical evaluation of the signs is symptoms, the clinical course, the visual assessment of the rash, does the patient look sick. It is this assessment at the bedside that is missing in the EPEC process. Consequently, it is likely that only the most obvious cases of GVH were picked up by the EPEC process.

[Slide]

But in reviewing the data from the Fujisawa studies, what was most interesting to me was that both methods of assessment of the endpoint of GVH provided the same conclusion. Whether using the investigator's grading or the EPEC grading, tacrolimus was at least as effective as cyclosporine for prevention of grades II to IV graft-versus-host disease.

[Slide]

The second point I would like to address is use of

tacrolimus in patients with advanced disease. My personal experience with tacrolimus for GVH prophylaxis comprises over 400 patients, largely with adult HLA matched sibling or matched unrelated donors but with mismatched related donors and others as well. However, less than 10 percent of these patients were transplanted on the Fujisawa studies. Most were treated on our own institutional protocols by completion of the Fujisawa trials and more than 70 percent of our patients had advanced disease.

[Slide]

In 1996, we published our analysis of risk factors for early morbidity and mortality in 85 patients with advanced disease, treated on a prospective study of a new intensified preparative regimen during a period of time when both tacrolimus and cyclosporine immunosuppression were being used.

Our results for the advanced disease patients differ somewhat from the Fujisawa studies. In our population we found that use of tacrolimus was associated with a significant reduction in early mortality.

We also published in 1997 our evaluation of toxicity in over 80 HLA matched blood stem cell transplant recipients, receiving either cyclosporine- or tacrolimus-based immunosuppression, wherein we found that renal toxicity and dialysis were not significantly increased in

the tacrolimus patients.

Clearly, the heterogeneity of the population with advanced disease makes this a difficult group to study. Our experience demonstrated that tacrolimus could be used safely in patients regardless of disease status, and the reduction in GVHD has allowed us to extend allogeneic transplantation to new patient groups such as the elderly and patients with solid tumors.

[Slide]

Finally, I would like to address where I might use tacrolimus in the marrow transplant field. For patients with early disease, where the treatment-related complications rather than a relapse rate are the major cause of death, a reduction in GVH would clearly make for a safer transplant course without the expense of complex marrow processing, and this fact played a role in the decision at M.D. Anderson to abandon the T-cell depletion program for HLA-matched sibs in favor of tacrolimus-based immunosuppression. The other area of interest is with the use of alternative donors where one would want to optimize immunosuppression since the risk of GVHD is so high.

[Slide]

This slide shows increasing numbers of unrelated donor transplants over time, now up to over 1000 each year. Data from the IBMTR indicates that the percentage of allogeneic

transplants from unrelated donors is now running at about 25 percent. The numbers of mismatched related donor transplants, as well as mismatched unrelated cord blood transplants, is also increasing.

We have used tacrolimus for alternative donor transplants with good outcomes. Our results from matched unrelated donors, published in 1996, are similar to those reported in the Fujisawa trials. Moreover, we have been able to reduce the dose of methotrexate used without loss of activity and with added safety.

I first used tacrolimus in 1990 for compassionate treatment of refractory chronic graft-versus-host disease. I was impressed with that initial experience, and happy to participate in the Fujisawa prospective prophylaxis trials, two large controlled trials. Since 1990, I have also been principal investigator at our center for seven other immunosuppressive drugs, and I participated in trials of three different methods of T-cell depletion. Of these, our experience with tacrolimus most favorable, and resulted in tacrolimus becoming the standard of care at our institution. So, I would welcome its addition to the list of drugs available to treat these challenging patients. Thank you. Dr. Fitzsimmons?

DR. FITZSIMMONS: Thank you, Dr. Przepiorka.

[Slide]

Fujisawa has performed several of the largest studies ever conducted investigating the chemoprophylaxis of graft-versus-host disease after allogeneic bone marrow transplantation. These complicated long-term studies were made possible by the efforts of our investigative sites.

We greatly appreciate the efforts of the following investigators, their support staff and colleagues at the 16 sites in the matched sibling donor trial.

[Slide]

And, for the ten investigative sites in the unrelated donor study. Their tireless efforts and diligence have made these studies successful.

[Slide]

You have heard this afternoon the results of three prospective, randomized, comparative trials of cyclosporine and tacrolimus. These data demonstrate that tacrolimus is save and effective for the indication of prophylaxis of graft-versus-host disease after allogeneic bone marrow transplantation.

We will be happy now to entertain any question from the advisory committee members. Thank you.

**Questions from the Committee**

DR. DUTCHER: Thank you for your presentation. Are there questions from the committee for the sponsor? Dr. Papadopoulos?

DR. PAPADOPOULOS: I believe that in the early part of the trial the tacrolimus targeted dose was a bit higher than it was in the later part of the trial. Do you have any data suggesting perhaps that part of the increased toxicity attributable to tacrolimus could have been from higher peak concentrations?

DR. FITZSIMMONS: Yes, we analyzed in the 04 matched sibling study the relationship of blood levels to adverse events, and in particular renal dysfunction, and we did find in the 04 study that renal dysfunction was correlated with higher blood levels, in particular those that exceeded 20 ng/ml.

DR. PAPADOPOULOS: In other words, what I guess what I am driving at is do you think that part of the extra toxicity that was seen, or potential greater toxicity in the tacrolimus arm was due to a learning curve, in other words, that the levels were too high earlier on?

DR. FITZSIMMONS: We do not think that that explains the difference in the survival and serious adverse events in the advanced stage disease group. We analyzed advanced versus non-advanced blood levels and found that they were not different, and there was no relationship of the blood levels to death when we analyzed that.

DR. DUTCHER: Dr. Miller?

DR. MILLER: Can you comment on the incidence of

chronic graft-versus-host disease in the two patient populations?

DR. FITZSIMMONS: Yes, I have some backup slides. If I could have slide 350, please?

[Slide]

The chronic graft-versus-host disease was analyzed through two years in the 04 matched sibling and the unrelated donor study. Of the patients that were at risk, meaning they survived to 100 days without relapse, there were 50/115 and 54/129 who developed chronic GVHD in the 04 matched sibling study. This difference was not significant, however, we did find that of those patients who did develop chronic GVHD there was a significantly higher percentage of extensive disease as compared to limited in the cyclosporine group, 76 percent compared to 54 percent in the tacrolimus group.

[Slide]

We also analyzed these data for the 18 unrelated donor study for overall incidence, and there was no difference in the two treatment groups in two years.

DR. MILLER: Could I also ask you to discussion more about the EPEC group? And, maybe since Dr. Horowitz is here she can comment on her feelings about why that group found a lower incidence of graft-versus-host disease, and how we should use that data for these patients? Some of the

times there is hard data for even mild graft-versus-host disease, such as skin biopsy which should be able to be read independent of whether or not steroids are used. So, especially in a non-blinded trial we tend to, you know, think a blinded reviewer is a good--you know, can also be very helpful. So, I am wondering why there is such a huge discrepancy between the two groups. I agree that the investigators match more carefully with what is reported than the literature, but what is the true incidence of graft-versus-host disease?

DR. FITZSIMMONS: I will let Dr. Horowitz, from the Medical College of Wisconsin, address that question.

DR. HOROWITZ: Certainly, when I was asked to be on the committee I thought it had an admirable goal, which was to try and do a blinded assessment of the GVHD in the two arms of the study. I think it might be helpful to understand what information the EPEC committee had available.

We received a flow sheet for each individual patient that had an array of clinical signs and symptoms, and selected laboratory values, and if a biopsy had been done we had the results of the biopsy although that was blinded to mentions of GVH and gave a microscopic description of the biopsy. However, there was not a prospectively defined requirement for biopsy and not all patients did have

biopsies of their skin or their GI tract when they had manifestations that might be graft-versus-host disease.

And, I think I echo my colleague's sentiments that it is very difficult in that circumstance to diagnose and assess GVHD away from the bedside, and there were two pieces of information that we found the most troublesome to be without, other than a biopsy of every organ that was showing a potential manifestation of GVHD. One was the visual assessment of rash and, the second was the response to specific therapy, particularly corticosteroid therapy. For example, if we had a patient on which the rash box indicated the presence of a rash at week three for four consecutive days and nothing thereafter, we did not know whether that rash resolved spontaneously, in which case it was very unlikely that it was graft-versus-host disease, or responded to a specific therapy. And, I am not surprised that we under-diagnosed graft-versus-host disease. And, the rates that we came up are very different from what one would expect from the literature, and the very similar rates in the HLA identical sibling and the unrelated donor transplant cohort makes this evaluation process highly suspect as a primary tool for evaluating the endpoint of the study.

DR. MILLER: What percentage of the GVHD was actually based on pathologic versus just clinical in the study, and why was it not sort of recommended--since your endpoint is

graft-versus-host disease, why did the sponsor not require skin biopsy for documentation of graft-versus-host disease?

DR. FITZSIMMONS: We didn't require it because at that time we were using the standardized staging and grading criteria that had been published, and were recognized internationally, and in those criteria the biopsy was not a requirement. So, the one thing that all investigators could agree on was that criteria. Then, local practice dictated whether, to augment the differential diagnosis, biopsies were performed. So, we couldn't standardize that across all 16 centers.

DR. DUTCHER: Dr. Papadopoulos?

DR. PAPADOPOULOS: Just as a comment to that question, although in an ideal world I think having pathologic proof for graft-versus-host disease would be ideal, I think in the clinical world, unfortunately, as a transplanter I can tell you that we often have a very, very high clinical suspicion that the disease entity is graft-versus-host disease and cannot get pathologic corroboration with a biopsy. They can often be inconclusive. Pathologists can vary in their experience in reading graft-versus-host disease. So, I think that is just a point for the committee.

DR. DUTCHER: Dr. Margolin?

DR. MARGOLIN: Yes, just a related question to that and then a more substantial question. The really minor

question to that was whether the EPEC also considered what the investigator or treating doctor had done about the steroid therapy--that was excluded? Okay.

The more basic question that I have is about study design. I am just curious, it looked to me as though one of the objectives of this was not to prove that FK506 was less toxic than cyclosporine. So, I am curious to know why the study design was looking for a difference that allowed as much as a 15 percent in the allo or 10 percent in the unrelated high incidence of acute GVH grade II to IV rather than looking for something where the whole 95 percent confidence interval would have to be lower or at no more than zero.

DR. FITZSIMMONS: We knew at that time that cyclosporine plus methotrexate was an effective immunoprophylaxis for graft-versus-host disease, and was actually superior in adult patients to either cyclosporine or methotrexate monotherapy. So, cyclosporine/methotrexate we knew was effective. Therefore, after discussions with the investigators we wanted to design these studies as equivalence to ensure that we didn't raise the risk of graft-versus-host disease into a clinically important difference. Based on the investigators' assessments, we recommended that any difference greater than 15 percent would be clinically meaningful and, therefore, this drug

should not be considered equivalent to cyclosporine.

DR. MARGOLIN: I am sorry, but then how would you actually market or sell the drug? I mean, what would you claim is the benefit of this drug over available therapies?

DR. FITZSIMMONS: Clearly, what we are providing to the transplanters is an approved chemoprophylaxis for graft-versus-host disease that is an alternative to other methods for GVHD prophylaxis that are available now. I think the investigators have been able to glean important clinical advantages. In particular, you can see that GVHD by their assessment is significantly less both in incidence and in severity, and particularly in the unrelated donor and in the grade IV setting. So, as Dr. Przepiorka has described, I think each of the clinicians is able to glean some advantages potentially for a new chemoprophylactic regimen and we are providing that alternative to them.

DR. MARGOLIN: If I might just hog the microphone for a related question then, that is not exactly how it was designed but we will let it go because it is done. Was crossover allowed? This drug was commercially available for another indication, so could either group cross over to the other if acute II to IV GVH did occur?

DR. FITZSIMMONS: Yes, crossover was allowed. If I could have backup slide 328, please?

[Slide]

There were 16 patients in the 04 matched sibling study who crossed over from tacrolimus to cyclosporine, compared to 1 patient in the cyclosporine group. This is because during that time primarily tacrolimus was not available commercially and we didn't have a protocol to allow that crossover.

[Slide]

In the 18 unrelated donor study, when the drug was now commercially available, starting in 1994, you see that crossover from tacrolimus to cyclosporine were 8, whereas from cyclosporine to tacrolimus were 18.

DR. DUTCHER: Dr. Raghavan?

DR. RAGHAVAN: I apologize if you have answered this but I was a little baffled by the fact that you took your own trial and didn't like part of the results so you went back to try to explain it. So, you may have answered this and I was going back through the slides and missed it, but let's go back to the issue of survival.

Now, you were unhappy, and I can understand why, that the survival in the tacrolimus-treated patients with advanced disease was inferior to the other group. I am not sure that it is kosher to go back and try to find subset explanations but you did that.

So, the first thing I want to be a little clear on is the breakdown of cases that made you feel that there was a

non-random variation there. Then, my second part of that question is that I guess you liked the results in study 04 with non-advanced disease and study 18. Did you then do the same breakdown of those subsets to make sure that there weren't imbalances that could have actually accidentally favored the product?

DR. FITZSIMMONS: Yes, to first answer the imbalances in 04, we had prospectively stated in the protocol that we wanted to evaluate the advanced group compared to the non-advanced, as well as a number of other factors, to see if there were any imbalances, of course, with the hope that the study would not be, by chance, imbalanced. When we analyzed that result we found that by chance, since the randomization was not stratified based on disease stage, significantly more patients ended up with advanced disease on tacrolimus. By that, by design in the protocol we said then, we would utilize that factor, any factor that was imbalanced and prospectively identified to analyze the results of the study, and it was very clear then that the survival disadvantage was completely focused in the advanced group and not in the non-advanced group. So that is what drove that analysis.

DR. RAGHAVAN: But, therefore, the obverse of that is if you had non-randomly the patients you don't want in the advanced group that go on tacrolimus, therefore, there must

have been a compensatory imbalance in the others yet your survival was the same. My question, therefore, is, in other words, you might have expected that they should have done better. There should have been a survival benefit, in fact, for the group based on a disease-based survival. So, did you do the same breakdown where there was equivalent survival to make sure that you hadn't, in fact, masked a drop in survival?

DR. FITZSIMMONS: We did look for baseline imbalances in the 18 unrelated donor, the FJ-14/15 as well as in the non-advanced subgroup of the 04 and there wasn't any clear imbalance that we could detect that would explain that.

DR. DUTCHER: Dr. Simon?

DR. SIMON: Was the stage defined in the protocol since it went across several disease types?

DR. FITZSIMMONS: In the protocol it stated advanced versus non-advanced malignancy but it wasn't broken down by definition, but that was provided in the protocol analysis plan which was written prior to any data lock and any unbinding of the data.

DR. DUTCHER: Dr. Schilsky?

DR. SCHILSKY: I guess I am still somewhat mystified by this definition of advanced versus non-advanced patients because, unless I have missed something, the only thing that you have told us about these two groups of patients is what

their diagnoses are. So, can you tell us something more about the characteristics of the advanced versus non-advanced patients with respect to age, performance status, organ function, other parameters that might perhaps be more important as, you know, providing an explanation for the outcomes than just what the diagnosis was?

DR. FITZSIMMONS: Yes, we did examine that. There were no significant differences, and I don't have a slide to demonstrate them head-to-head in the advanced versus non-advanced based on disease stage--other than disease stage, based on the age, gender, race, Karnofsky score. We looked at all of those factors to compare advanced versus non-advanced and did not find any baseline imbalances between those two.

[Slide]

This shows specifically the advanced stage disease group. It doesn't compare it to non-advanced, but you can see the gender distribution, race, CMB positive or negative in the patient *or* donor, age, baseline serum creatinine and the alloimmunization and patient-donor sex match. When we compared this not only between tacrolimus and cyclosporine but between advanced and non-advanced, we did not find significant differences. They seem to all be driven by what their diagnosis was, and were they in relapse or never in remission primarily.

DR. SCHILSKY: I have one other question that I would perhaps like to address to Dr. Przepiorka as an expert consultant. I would certainly be the first to acknowledge, as Dr. Raghavan did this morning, that I am no expert in transplantation medicine. So, as a non-expert looking at these data, I guess the thing that I would conclude is that cyclosporine looks to be pretty good treatment because it is not inferior to tacrolimus with respect to GVHD prophylaxis and seems like it has a better safety profile. So, as a non-transplanter, if I was asked to choose which of these two drugs I might use in this setting, I would probably pick cyclosporine. So, tell me as a transplanter what am I missing, and what is it that you see in tacrolimus that you think would lead you to choose it rather than cyclosporine.

DR. PRZEPIORKA: First, I would like to emphasize that our experience has been different from the Fujisawa studies and most of our patients have been transplanted on our own institutional protocols. In our hands, we actually learned very early about the upper limit of the target levels for the drugs. So, we stayed away from that upper level very quickly and were able to keep all of our patients at the lower level of what would be now the appropriate level for patients. And, we have not seen those toxicities using tacrolimus in that fashion.

The real important think, however, that really stood

out in our practice was with the unrelated donors. For us, there was truly a clinically visible decrease in graft-versus-host disease and a much easier course for those patients. That was something that we all felt was extremely beneficial. We didn't have patients in the hospital for 60 days or coming back in after that.

DR. DUTCHER: Along those lines, I mean, it would be helpful if we could see some of that actual data. Is that in something you have submitted to FDA or is that not available to review?

DR. PRZEPIORKA: All of that data is published, and I believe it was in the reference section in the NDA, and all that is published.

DR. SANTANA: So, are these primarily children that you treat?

DR. PRZEPIORKA: The published data is all on adults.

DR. DUTCHER: Dr. Margolin?

DR. MARGOLIN: This may open a can of worms, for which there are few answers available here or inadequate answers from the published literature, but I am just curious to know whether Dr. Przepiorka or colleagues from the sponsor have any thoughts about whether the differences in death rates, despite what appears to be a very nice outcome with GVH, may be related in any way to that difference in GVH. Although we don't think of the graft versus malignancy as being

adequate control of advanced disease, I don't think we can ignore it. It was blatantly absent from a slide that talked about the factors that were associated with the poor or favorable outcome where the biggest factor that influenced relative risk of death was actually disease state.

DR. FITZSIMMONS: We assessed that by looking at the composite endpoint, which is the worst-case scenario. In other words, if a patient died that would be counted as an event, as well as if a patient had graft-versus-host disease, that would be counted as an event--sort of the worst-case scenario. What that tells you is GVHD-free survival. What you have seen is that in the 04 matched sibling study that is equivalent, virtually identical rates when you look at GVHD-free survival between the two groups. In the unrelated donor study there is still a significant advantage of tacrolimus over cyclosporine. So, we don't believe that the GVHD advantage that you see in the 04 study or in the 18 is driven by the early deaths in the advanced stage disease group. That composite endpoint sort of takes into account that worst-case scenario.

DR. MILLER: The composite endpoint actually takes away the worst-case scenario because if graft-versus-host disease is good and you are counting it equal to death, if graft-versus-host disease positively influences relapse or death you are losing that in the composite endpoint. From a

statistical standpoint, is that true?

DR. DUTCHER: Why don't you repeat that?

DR. MILLER: If graft-versus-host disease has a positive effect on relapse or death, if you make a composite endpoint being bad--graft-versus-host disease relapse or death, you lose the beneficial effect that graft-versus-host disease may have on relapse or death. You lose your ability in that composite endpoint to evaluate the beneficial effect of graft-versus-host disease on relapse or death, if there is one.

DR. SIMON: Well, I mean, the composite endpoint is--if you want to say, well, there could be a deficit with regard to disease control from the study drug, certainly by using a composite endpoint you would tend not to see that because there as an advantage in terms of controlling graft-versus-host disease.

DR. DUTCHER: Dr. Papadopoulos?

DR. PAPADOPOULOS: Getting back to the advanced patients for a moment, I am sure you must have data demonstrating things like number of previous chemotherapy regimens and what-not. I mean, the group of the advanced patients in the tacrolimus group, many were non-Hodgkin's lymphoma patients and, I believe, CLL, more so than in the cyclosporine group--I don't recall exactly the breakdown between the tacrolimus and cyclosporine, but my point is

that advanced is a somewhat vague term. When you start to look at the number of previous chemotherapy courses, etc., could you see a difference between the advanced group in the cyclosporine group versus the tacrolimus?

DR. FITZSIMMONS: We did not analyze data on the number of previous chemotherapy regimens, and we do have data breaking down the advanced into more specific diseases and whether they were in relapse or in remission. That might help in terms of that explanation, but we don't have data specifically on the exposure to previous chemotherapeutic regimens prior to transplantation.

DR. DUTCHER: Dr. Simon?

DR. SIMON: I think the data is puzzling. If I wanted to take at face value the fact that the study drug has a poorer safety profile for the sibling-matched donors, without getting into the advanced versus non-advanced but just take that study as it was and take it at face value that there was not some imbalance, just that I want to conclude that there is a poorer effect in terms of survival, disease-free survival, for the study drug compared to cyclosporine, can you offer any reasons why that result might not hold for the matched unrelated donors? Why I might see that for matched sibling donors but not matched unrelated donors?

DR. FITZSIMMONS: If there was any potential for

tacrolimus to increase the risk of death overall we would have expected to have seen it in our other two randomized, comparative trials, the 18 unrelated donor and the FJ-14/15. Therefore, the only key differences, particularly between the 18 and the 04, where you can see that it drives this survival differences, again, is the advanced stage disease which was not in the 18 unrelated donor study.

DR. SIMON: Is it not possible that because the incidence of graft-versus-host disease in the unrelated donors might be high enough that controlling that would be of importance but when the severe graft-versus-host disease incidence gets lower, as in the matched sibling donors, control of graft-versus-host disease is not as important as some negative effects that may be the result of the study drug?

DR. FITZSIMMONS: Yes, I think that that is a theoretical possibility, however, we would have expected to see the same cluster of toxicity adverse events, if there were specifically drug induced adverse events, in the unrelated donor population when they were exposed to the same drug in the same doses as what we have seen in the matched sibling, with the underlying difference between the two mainly a higher rate in severity of GVHD in the unrelated donor. We didn't see that.

DR. SIMON: Maybe when you have a high background of

serious illness from the graft-versus-host disease you just don't see that.

DR. FITZSIMMONS: That is possible. I don't think that the high background would eliminate the renal effects of other things that we saw, particularly the renal parameters in the advanced disease 04.

DR. MILLER: I think the IBMTR review of the control group was very interesting. In that review, were they able to pick out any patient characteristics that would help explain that potentially unexplainable--why the cyclosporine group was good?

DR. FITZSIMMONS: We matched specifically on disease and disease stage down to the relapse number and, in addition, the age to within five years. So, what that told us then, because when we matched that specifically we saw that this prognostic imbalance existed, that it must be built somewhere into the combination of age, disease, disease status and relapse number because those were the key factors that were matched. However, there are so many different cells in that analysis, so many different disease, relapse, relapse numbers, never in remission and age ranges, that you can't factor out one particular risk factor. It is a combination probably, as Dr. Buell mentioned, of many different factors simultaneously. When you match identically you can see it, but you can't find just one

individually.

DR. MILLER: Did you include multiple myeloma and CLL independent of whether they were in relapse or remission in that high risk group?

DR. FITZSIMMONS: Correct, multiple myeloma, regardless of that, was included in the advanced stage disease.

DR. MILLER: Why? They are generally poor prognostic and also stratified for older. You have already stratified for older.

DR. FITZSIMMONS: Yes. What we did was we sat down with the investigators and said it is fairly standard to say, okay, the leukemias that are CML blast crisis or that are in relapse are advanced stage. How do you view the others, for instance multiple myeloma? And, they said in their opinion those were advanced stage disease because of their known survival history.

DR. MILLER: But was that determined after the study started or before?

DR. FITZSIMMONS: That was determined after we had started enrollment in the study but before we analyzed or unblinded the data. What we did was--there were 10 patients out of the whole 329 who, using the standard definition, fell out and we couldn't determine where they would go so we said to the investigators, without knowing which treatment

group and the results of the study, where do these 10 fall, advanced or non-advanced? Then, we went with their consensus on those 10.

DR. MILLER: Did they already know the outcome of their patients--not whether they were blinded or not but which patients did badly on the study when they made those prognostic groups?

DR. FITZSIMMONS: No, that was before the long-term follow-up in the study; it was just after enrollment completed.

DR. MILLER: No, but they knew the early mortality data of what happened to their patients in the groups where they may be higher risk classifications. So the investigators, after treating the patients and knowing their outcome, then made that definition of high risk groups.

DR. FITZSIMMONS: No, they didn't make the definition of the high risk group. We had already made the definition. So, 319 of those patients fell into the standard definition. There were 10 who weren't predicted up front in that definition, whom we then just classified not based on outcome. So, they didn't see any aggregate study results. They only knew the few patients that they might have had at their center.

DR. DUTCHER: Dr. Santana?

DR. SANTANA: I have a very practical question. Both

of these drugs require, and I think we heard a little bit about this, experience with clinical monitoring and this issue of targeting at both ends of the curve. If you are too low it may not help immunosuppression; if you are too high you may get into issues of toxicity. So, can you give us a big picture in both subsets of drugs, the number of treatment days within the target, and when you did require adjustments were there differences in the change or the direction for the agents? That is, you required downward adjustment for tacrolimus but for most patients with cyclosporine you would have to give more? Can you give me an idea of what the overall picture was? Including the early learning curve which we all recognize is an issue.

DR. FITZSIMMONS: Yes.

[Slide]

The data that we have that best addresses your question is that we have looked at the tacrolimus and cyclosporine concentrations in whole blood in both studies by time post transplant, shown here on the X axis, and the concentration, here showing tacrolimus in the 04 matched sibling, with the therapeutic range in the first 8 weeks being 10-30.

This plot shows you the median blood levels during that time point, and the 25th and 75th percentile. What you can see is that the median levels were within the 10-30 but

trending downward to 8 weeks and then patients were tapered off through 6 months. And, the 25th and 75th percentiles, as shown here, meaning 75 percent of the patients are above this line in terms of concentration at that time.

What that doesn't tell you is individually how their therapy was manipulated. We had in the protocol specific dosage reduction recommendations based on toxicity and particularly creatinine elevations. We knew from our solid organ experience that there were a number of toxicities for both tacrolimus and cyclosporine, but particularly tacrolimus, that were does and blood level responsive and so we built that prospectively into the protocol.

DR. SANTANA: So, for an individual patient you don't have data to tell me the total treatment days that individual had and how many days he was in the target?

DR. FITZSIMMONS: No, I don't have that data with me.

DR. DUTCHER: Dr. Margolin?

DR. MARGOLIN: I guess we can assume, therefore, that you also don't have data on how patients' blood levels on the two drugs correlated with the day that they were declared as having acute graft-versus-host disease?

DR. FITZSIMMONS: We did analyze the relationship of the blood levels to the risk of graft-versus-host disease.

[Slide]

This plot shows a logistic regression model in which

we analyzed the blood levels in a window, a 7-day window prior to the onset of the event, and the three events that are shown on this slide are, in blue, acute graft-versus-host disease, in red, serum creatinine greater than mg/dl, and in green, creatinine that doubles the baseline. This is in the 18 unrelated donor study.

What you can see is that there is no significant relationship by a logistic regression model of blood levels to risk of acute GVHD in the tacrolimus group of the unrelated donor.

[Slide]

This is that same plot shown for cyclosporine. In the cyclosporine situation what you can see is that the blood levels for graft-versus-host disease, shown in blue, are significantly associated with the risk of GVHD. As you increase cyclosporine blood levels the risk of GVHD drops.

So we did analyze in this type of analysis, both by logistic as well as Cox regression analysis, to better understand the relationship of blood levels of both tacrolimus and cyclosporine to the risk of GVHD as well as renal toxicity in both of our studies.

DR. SANTANA: But maybe the transplanters can tell me. I thought the real risk in which you required the most immunosuppression is in the first four weeks. So, looking at it seven days prior to the onset of GVH just tells me

what happens in that seven-day window but it really doesn't tell me what happened before when it was really brewing, if you want to use that expression.

DR. PAPADOPOULOS: Just to clarify though, the seven-day window was the seven days prior to an individual patient developing graft-versus-host disease.

DR. FITZSIMMONS: That is correct.

DR. PAPADOPOULOS: Not necessarily the first month.

DR. FITZSIMMONS: No, and all of these analyses were run for the first 56 days when they were on full doses of therapy when almost all the GVHD events occurred.

DR. PAPADOPOULOS: I mean, if the serum levels dropped beyond the first 30 days you can certainly precipitate graft-versus-host disease. It doesn't have to be solely within the first 30 days, although that is felt to be rather critical.

Just as another point to this last presentation, would you extrapolate from that data that perhaps we don't have to give as much tacrolimus as we are giving?

DR. FITZSIMMONS: Yes, that is actually why, although the protocol specified that the therapeutic range was 10-30 ng/ml, our recommendation is that the levels be maintained in the 10-20 range because we are not affecting the risk of GVHD based on that analysis but we are increasing the risk of renal dysfunction.

DR. DUTCHER: Thank you very much. I think we will take a short break, and be back here maybe at 3:55.

[Brief recess]

**FDA Presentation**

DR. HIRSCHFELD: Good afternoon, Madam Chairman, committee members, members of the press, sponsor, members of the public and my colleagues at the FDA.

[Slide]

We will try to approach some of the questions that were raised in the previous discussion, and address some of the issues that we faced in trying to examine a number of concerns that we had which are summarized in our questions to the committee. I will try to support the rationale that led us to formulate our questions.

[Slide]

I wish to acknowledge all the members of the review team. We are now to two "Bobs," Temple and Justice. And, the rest of my colleagues.

[Slide]

I wanted to make a statement which was not discussed, because of time, in the rather excellent presentation that the sponsor provided us. Just to note and to set the framework for the study that we will examine that graft-versus-host disease has two very broad clinical forms. The form which is under discussion in this afternoon's

presentation is the acute graft-versus-host disease, and acknowledged but will not be formally discussed is the chronic graft-versus-host disease, and the relationship between acute and chronic graft-versus-host disease is still an area of investigation. But we do know that acute graft-versus-host disease occurs in the majority of patients with bone marrow transplants if they are not treated. As discussed in the literature and mentioned earlier, it can have severe complications and lead to a patient's death.

[Slide]

We analyzed the following studies: A Phase III multicenter, randomized study that was performed in North America with 329 patients, and 165 of them received FK506. I was practicing to say "tacrolimus" and I had trouble getting the emphasis right. So, with the permission of the sponsor, and being consistent with what is in the published literature, I am going to refer to it as FK506. This was in sibling matched donors. The study designation was study 4.

A second study, which was also a Phase III multicenter study, a somewhat smaller study than study 4, and the patient population was different. These were patients who received bone marrow transplants from unrelated donors, and in both cases the indication for bone marrow transplant was a hematologic disorder, primarily malignancies. This is designated as study 18.

Both of these studies received SASS data sets and I gratefully acknowledge the submission of the databases, the SASS data sets.

There was an additional study that was submitted on paper. That was a yet smaller study which was referred to in the sponsor's presentation where 57 patients received FK506.

This study was not analyzed by us for a few reasons. There was heterogeneity in the patient population, that is the diagnoses, the patients, the relationship between the between and the donor, and the types of donors. There was variability in the use of immunosuppressive regimens so it would make interpretation more complex. In addition, there was the absence of independent verification of the results.

[Slide]

The design criteria for the larger of the two pivotal studies, study 4, was to select HLA-identical--and identical when the study was conceived and the technology allowed, was essentially immunologic identity. Now, of course, we know that there are molecular techniques which allow even more precise matching, but HLA-identical sibling bone marrow transplant. And, the protocol, from initial conception and discussions, would have a sample size of 300 patients. Based on the experience at the Fred Hutchinson Cancer Center, which had the largest experience, there was an

estimated incidence of 30 percent moderate to severe grade acute graft-versus-host disease. That was presumed to be replicated in the control arm. The power would be 80 percent and there would be a 15 percent difference in the 95 percent confidence limit for the true difference between FK506 and cyclosporine.

[Slide]

So, what this means is that given that the incidence of acute graft-versus-host disease is greater than 80 percent, one could presume in this patient population, although again the literature is somewhat interesting because there are studies from the mid-'80s where there is a lower incidence, but given that one anticipates greater than 80 percent incidence in untreated patients, and given the fact that graft-versus-host disease untreated could have a negative impact on the patient in terms of quality of life and survival, and given an anticipated incidence of acute graft-versus-host disease of 30 percent, the regimen should demonstrate activity that should have an incidence of acute graft-versus-host disease that is plus/minus 15 percent of the active control. This was, again, I think graphically illustrated in the color slides that the sponsor submitted.

[Slide]

There are a few amendments to the protocol as originally conceived. One was that there was an alteration

in the rating criteria for graft-versus-host disease. The second was that there was an establishment of an independent blinded endpoint evaluation committee in addition to us. Then there was an additional pharmacokinetic study within the primary study.

[Slide]

The primary endpoint was the incidence of moderate to severe, which is defined as grade II to IV, acute graft-versus-host disease within 26 weeks following transplant. There were two secondary endpoints that were defined as disease-free survival at 2 years and the incidence of chronic graft-versus-host disease.

[Slide]

Because it is the central issue to interpreting the data, I will spend a moment discussing the grading of graft-versus-host disease, and how we approached it, and how we thought we could try to confirm the findings that were in the submitted data.

Using the criteria in the amendment to the protocol, which are the same as internationally accepted criteria, each of three organ systems is graded individually--skin, liver and intestine, because both in clinical experience in the laboratory support data in the models of graft-versus-host disease these are the end-organs which manifest graft-versus-host disease in ways that are generally measurable

and most acute.

There is actually a 5-point scale where 0 means it is not apparent, or normal. Then the 4 pathologic grades are outlined here. When each of the 3 organ systems is then assigned a grade or a stage, then there is an overall grade based on a composite of what each of the 3 organ system stages are.

[Slide]

So a grade 1 would involve just skin and have no GI and no liver involvement. Grade 2-4, which is moderate to severe grades, would have any combinations of skin, gastrointestinal or liver involvement.

[Slide]

The sponsor designated an endpoint evaluation committee which, we though, had a number of potentially valuable attributes. They were the following: It is recognized that determining and grading acute graft-versus-host disease is imprecise. It is a judgment. As was mentioned in the discussion earlier, even getting a biopsy doesn't necessarily rule or rule out the diagnosis. If one uses a formal grading scale and a computer algorithm based on the previous grading scales, it turns out that the vast majority of patients will be seen to meet the criteria for having moderate to severe graft-versus-host disease. The sponsor did this in a computer algorithm and we did it too,

and almost cold replicate, or we were in close agreement with the same range that the sponsor reported in their study material on the incidence of acute graft-versus-host disease.

What are the difficulties? They are that the rash could be due to a number of factors. Hepatic function changes could be due to a number of factors, and diarrhea could be due to a number of factors--some infectious; some related to other agents; some complications of other aspects of the therapy; the patients are quite ill. In addition, there were intangible factors that were used on site, and in an unblinded study it is impossible to replicate or verify these.

[Slide]

So, I changed my presentation a little bit to just give you an idea of how we tried to approach this. We took the data that was submitted to us electronically and then set up a method where we could look at each patient individually and try to follow through what the clinical course was. Data always comes in domains. You get all the chemistries together; you get all the events of one type together; you get all the therapies put together, but how do you follow what happens to a patient and make a decision as to their course?

So, we can pick a site, and we will pick one

arbitrarily, the University of Minnesota, we will say. Because these sites were made public, I can now reveal what these sites were. Then we will get a list of patients within that site, and we can pick one of those patients and we can look at what we can see as to the characteristics and the clinical course of that patient.

If you bear with this laptop while it grinds that out, what you will see is a summary first of the general characteristics of the patient and the characteristics of the donor and the recipient, and the cytomegalovirus status. Then we will see when the transplant occurred. Then we will see what doses of the study drug were given; how the doses were adjusted up and down during the course of therapy; when a conversion from intravenous to oral dosing occurred; and then all the adverse events with characteristics.

So, we see here that this is a patient that was a young man. The donor was a male donor. This patient, unfortunately, died from Aspergillosis. But what we will see is that for the graft-versus-host criteria--and we prepared these sheets for the audit team also so they could go out in the field and verify the data--we look at the criteria of the bilirubin; the diarrhea which was divided into three varieties of diarrhea, that is, diarrhea mixed with stool, with urine and what was considered raw diarrhea; the performance status; the rash. By following through and

checking on each date we can see what was happening to the patient. This patient's report is some 25 pages. When we look through we can follow then the results of any biopsies. Here, there were positive biopsies at 2 sites which were indicated on the previous page.

Then, as we just walk through a little further, we will see that the study drug was given here; that there was an adjustment made; that there was some toxicity; there was some further toxicity. It was described, on what date it occurred. The switch over to oral dosing.

As we follow that through we will see that after the oral dosing phase began just a listing of all the adverse events. We only counted, of course, adverse events that occurred after study began. So, these are all days prior to initiation of therapy and transplant. After transplant we can see the events. We can see the frequency. We can see the intensity; if the investigator thought there was some relationship to the study drug; what the therapy was.

By thing sheets like this for every single patient and following chronologically through, we tried to come to some assessment of what was happening to that patient. By using the factors that were described as important for the endpoint evaluation committee, we also could do, as best as possible in a retrospective fashion, a confirmation of the findings of the endpoint committee. We could not verify,

based on any data that was submitted to us, and we had a conversation with the sponsor to see if there was other data that would allow us in some way to verify what the investigators were describing. So, we hope that through this type of careful step-by-step, day-by-day analysis we could in some way get a sense of what was happening to the patient.

[Slide]

The eligibility criteria in the reduced format is that the patient had to have a genotypically identical sibling donor; greater than 12 years. The patient was excluded if the serum creatinine was greater than 3, hypersensitivity and a number of other factors, including a previous transplant or a T-cell depleted marrow.

[Slide]

There was prospective stratification for age and whether there was a relationship in terms of a female donor and a male recipient where the female donor had been alloimmunized or not.

[Slide]

The treatment plan, and there is a slight difference in your handout from the slides because I mentioned corticosteroids and some patients got corticosteroids and some didn't, but it wasn't prescribed in the treatment plan. Methotrexate was to be administered according to a regimen

that is described here and described by the sponsor.

[Slide]

Again, the regimens on study drugs, the two arms are compared and they were parallel regimens with just differences in levels.

[Slide]

The characteristics of the enrolled populations were as described, and they were balanced, with the exception of this category of what was termed advanced disease.

[Slide]

Here is our breakdown of the diagnoses that were submitted. It is the same as was previously described. You can see a broad range. There were patients on both arms who had all diagnoses with the exception of aplastic anemia. There was only one patient who received FK506, otherwise there were somewhat comparable numbers in terms of these diagnoses.

[Slide]

The exposure to medication--if one looks at how many patients were randomized and how many completed 6 months of therapy, more patients on the cyclosporine arm completed the 6 months. More patients on the FK506 arm died within the 6 months. And, there was a difference also in those who discontinued due to an adverse event between the 2 arms.

[Slide]

Of the patients that were able to change to oral medication--the vast majority were able to. Again, in this particular study numerically there was a higher percentage on the cyclosporine arm. The day of changeover was the same on both arms.

[Slide]

To look at the exposure to medication in a slightly different format, those who completed the intended treatment are these numbers you have just seen, and those who died while on the study drug--it was approximately balanced. There were more patients on the FK506 arm who had premature discontinuation for some reason or another. The majority of those had some adverse event or illness that didn't directly result in a patient's death although the patient may have died after withdrawal from either drug. There were a couple of patients who had graft-versus-host disease that didn't result in death. These are withdrawals, not the incidence of graft-versus-host disease. And, there were some other reasons.

[Slide]

Now we get to the efficacy endpoints. We know what happened. What were the results? If we look at the results based on the analysis by the independent committee, which is the only results, again, we could verify being our own retrospective endpoint committee. We find that there was

not a difference between the two study arms that was significant and the 95 percent confidence intervals were within the bounds of the study, and that was looking at patients that died, as censored, for statistical purposes.

[Slide]

We proposed to the sponsor to do a worst-case scenario, and we also did such an analysis and came up with the same result and, in essence, there would be no difference. It would be a tad over the limit that was suggested in the criteria for the protocol under this analysis for looking at non-inferiority.

[Slide]

If we look at the secondary endpoints, and this again is a correction from the handout, just a typo there, for chronic graft-versus-host disease there was no significant difference between the study arms, and for the protocol-defined endpoint of 2-year disease-free survival there was a difference between the study arms and that difference was statistically significant both using unadjusted data or using Kaplan-Meier estimates. This point will be addressed later in the presentation in somewhat more detail.

[Slide]

Looking at grade III or IV adverse events--grade III and IV is determined by using the Southwest Oncology Group rating for common toxicity criteria--we find that there were

some differences between the study arms, and they are noted here. These are similar to the differences that were described by the sponsor.

I would point out that in terms of particularly renal failure and abdominal pain and hyperglycemia there seemed to be differences, and we also notice that there was a much higher incidence of dyspnea here. So, we will just note that there are differences.

[Slide]

Now, these differences had clinical consequences, and the clinical consequences were that in looking at diabetes or having a creatinine greater than 2--this isn't really a clinical consequence but it is a precursor to a clinical consequence, how many patients went on dialysis and there was a higher percentage in the FK506 arm who went on dialysis; a higher percentage who underwent intubation; a higher percentage that died; a higher percentage that had an adverse event that persisted until the death of the patient; a higher percentage that had a death that seemed to be related, in the eyes of the investigator, to the adverse event. The rest of these factors were otherwise balanced between the 2 arms.

[Slide]

When we look at the deaths on the study, if we look at the total number of deaths after 2 years or after 100 days,

there are more patients that died on the FK506 arm; fewer that died in the opinion of the investigators and also, I believe, the evaluation committee that was appointed to look at the deaths retrospectively in terms of graft-versus-host disease, approximately equal in terms of relapse. Then, there were other reasons, other adverse events.

[Slide]

So, the preliminary conclusions that we could come to based on study 4 were that an immunosuppressive regimen, and we must bear in mind that FK506 was part of a regimen; that it was not used in isolation as monotherapy, following sibling-matched bone marrow transplantations in hematologic disorders, primarily malignancies, reduces the incidence of acute graft-versus-host disease compared to historic controls, and is not inferior to a control immunosuppressive regimen with cyclosporine.

[Slide]

There was a higher rate of death attributed to the study drug, of patients requiring dialysis, of patients requiring intubation, of serious adverse events, of adverse events that persisted until the patient's death, and of adverse events associated with the patient's death.

[Slide]

The smaller study, study 18, had a different patient population. It was established to look at a sample size of

170 patients, and the observed incidence of graft-versus-host disease in the published literature for patients who have unrelated donors was anywhere from 52-93 percent, and one can find numbers outside of these bounds if one looks at other sources in the literature, but there was an estimate of 75 percent to be considered as what the natural history would be. It was to have a power of 80 percent, and the upper limit of the confidence interval initially was stated to be 20 percent or 0.2

[Slide]

But there was an amendment which modified the null hypothesis so that the difference between FK506 and cyclosporine was reduced to a 10 percent difference. Then there were some further modifications in the analysis to examine some differences in hypertension, renal function, hepatic function, hyperglycemia at landmarks of 100 days and 180 days rather than 8 weeks and 26 weeks, and some of the centers did some 2-dimensional echocardiography.

[Slide]

The endpoint of the protocol in terms of the primary endpoint was the same, the incidence of moderate to severe grade II to IV acute graft-versus-host disease. In terms of the secondary endpoints, they were somewhat different. There was the incidence of grade III to IV acute graft-versus-host disease, the incidence of chronic graft-versus-

host disease, a further description of whether the chronic graft-versus-host disease was severe or limited at the time on onset, and the incidence of steroid-resistant acute graft-versus-host disease.

[Slide]

Inclusion criteria were somewhat more complex but can be reduced to patients with non-advanced disease who had hematologic disorders, primarily malignancies, who would require bone marrow transplant, and receive that from an unrelated donor, presumably because there was not a sibling-matched donor available. There were some further refinements in terms of the matching criteria using the National Marrow Donor Program, that the patient would have a six-antigen match or a one-antigen mismatch out of one of these three loci, A, B, DR-1. Again, young children were excluded.

I will just clarify a point here, for the agency, for regulatory purposes, a child is defined as 16 years or younger.

[Slide]

The exclusion criteria were now somewhat different than in the previous protocol. Rather than using a serum creatinine level, a creatinine clearance had to be measured and it had to be greater than 60. The Karnofsky performance score had to be greater than 60 percent. There were some

exclusions based on sensitivity to other agents and, again, no T-cell depleted marrows; no previous marrow transplants following conditioning with busulfan or total body irradiation or previous solid organ transplant. Again, another criterion, no uncontrolled infections including any carrier of human immunodeficiency virus.

[Slide]

Prospective stratification was just on one criterion, full antigen match versus one antigen mismatch.

[Slide]

The treatment plan was essentially identical to the previous regimen, and the same for the randomized aspect of it. The enrolled populations were balanced with regard to numbers, race, gender, age, the exposure to lethal radiation and in terms of mismatch.

[Slide]

The diagnosis was of a more limited repertoire than seen previously, and consisted primarily of patients with chronic myelogenous leukemia. There were a few patients with what would have been considered advanced disease in the previous study that did slip through the grading and were enrolled on this study but in general it was a different patient population.

[Slide]

At looking at exposure to medication, more patients on

FK506 completed 6 months than on cyclosporine; less patients died within 6 months, although these differences are not statistically significant; and the number of patients that discontinued due to adverse events was the same.

[Slide]

The changeover to oral medication occurred simultaneously on the two arms, and within essentially the same range and the vast majority of patients were able to convert to oral medication.

[Slide]

The percentage of patients that completed the intended treatment was again balanced between the two arms of the studies. Those that had premature discontinuation was balanced. Those that had an adverse event or illness that didn't result immediately in the patient's death was balanced. Those who had graft-versus-host disease that didn't result in death was a minor imbalance but these are small numbers.

[Slide]

So, what are the results? Again, using the factors that the endpoint committee used, and doing our careful day-by-day analysis, we felt that we could confirm the results that the committee endorsed and that there was no difference between FK506 and cyclosporine in terms of the incidence of acute graft-versus-host disease.

[Slide]

In terms of the secondary endpoints, there were multiple secondary endpoints and we didn't assess the steroid resistant but we looked through the others and I chose two to illustrate here, that there was a slightly higher incidence from our analysis of chronic graft-versus-host disease but there was no statistical difference on the FK506 arm, and survival was identical.

[Slide]

In terms of grade III and grade IV adverse events, again we see that there seems to be some effect on the renal function in the FK506 arm.

[Slide]

In terms of the clinical consequences, we find that there were in this case more patients that died due to graft-versus-host disease with cyclosporine than with FK506. On the other hand, there seemed to be more patients that died due to relapse on FK506 than on cyclosporine. The rest of the factors were approximately balanced although, again looking at small numbers, twice as many patients that died had a death that the investigator thought was related to the drug on FK506 compared to cyclosporine. More patients who had a death that the investigator thought was related to graft-versus-host disease were on the cyclosporine arm than on the FK506 arm.

[Slide]

So, to summarize the deaths on study, again, this is a patient population with unmatched donors, generally a poorer outcome than patients with sibling-matched donors. Nevertheless, the deaths in the first 100 days were relatively modest, 21 percent and overall about 40 percent. Those that were attributed or somehow related to graft-versus-host disease were somewhat more on the cyclosporine arm. Those attributed or thought to be related to relapse disease were higher on the FK506 arm. And, other causes were approximately balanced.

[Slide]

So, preliminary conclusions from study 18 are that an immunosuppressive regimen with FK506 following sibling-matched bone marrow transplant patients with hematologic disorders, primarily malignancies, reduces the incidence of acute graft-versus-host disease compared to historical controls, and is not inferior to a control immunosuppressive regimen containing cyclosporine. There were no significant differences in the toxicity profile per se although there were differences in the patients that died due to graft-versus-host disease versus those that died due to relapsed disease.

[Slide]

So, if we summarize the efficacy results from the two

studies, we can say that an immunosuppressive regimen with FK506 following sibling-matched or unrelated bone marrow transplant in patients with hematologic disorders, primarily malignancies, reduces the incidence of acute graft-versus-host disease compared to historic controls, and is not inferior to the control immunosuppressive regimen with cyclosporine.

I think that is all that one can say because the patient populations were different. So, it is inappropriate to do an integrated summary of efficacy.

[Slide]

However, looking at an integrated summary of safety, we find that there was a balance but there seemed to be somewhat more hyperglycemia, and this is grade III-IV, not total adverse events--an imbalance with regard to FK506 for hyperglycemia and for abdominal pain. Otherwise, there was a balance between the two.

[Slide]

When we look at the clinical consequences, there seemed to be--and this is a type, this should be 40--there seems to be an imbalance in terms of elevated creatinine and an imbalance in terms of patients that went on to dialysis. There is a higher percentage of patients that had an adverse event that persisted until the death of the patient.

[Slide]

Looking at deaths, we find that deaths overall were 48 percent in the patients that received FK506 versus 42 percent for cyclosporine, and that there was an imbalance in deaths--again, small numbers--that occurred in the first 100 days, but of those deaths that occurred in the first 100 days there was an imbalance favoring FK506 in patients that died as a result of what was thought to be graft-versus-host disease. There were more patients numerically that died due to relapse with FK506 and more patients that died with graft-versus-host disease on cyclosporine. Deaths that were related to the study drug were higher--and here is the odds ratio and a p value--in the FK506 population, and deaths that seemed to be related to an adverse event were also higher--and here is the odds ratio and p value--in patients that had been exposed to FK506.

[Slide]

So, I will now pause for a discussion from my colleague, Dr. Gang Chen, who was a collaborator, and he functioned both as the primary reviewer and the team leader for reviewing this application. Dr. Chen?

DR. CHEN: Thank you. Good afternoon. My name is Gang Chen. I am a statistical team leader, FDA.

[Slide]

Dr. George Chee is the Director of the Division of Biometrics I.

[Slide]

I will take a few minutes to discuss the statistical issues on the adjusted survival analyses for study 4. In this NDA submission both survival and disease-free survival were defined in the protocol as safety endpoints. My main focus will be on the sponsor's adjusted analysis for survival and disease-free survival, and the reviewer's conclusions will follow after the discussion.

[Slide]

Before the discussion, I will briefly summarize the sponsor's results. Based on their own adjusted analysis, cyclosporine was significantly better than FK506 in overall survival and disease-free survival if adjusting for disease stage the difference becomes marginally different favoring cyclosporine. For study 18, however, there is no significant difference in either overall survival or disease-free survival.

[Slide]

There are two major statistical issues regarding the adjusted survival analysis. The first issue is what should be adjusted if adjustment is necessary. It is well-known that we need to not only adjust for imbalances but also we need to adjust confounding factors for increased precision of the estimates, and adjust for treatment by covariate interactions if they exist. The second issue is how we

should interpret the results of an adjusted analysis appropriately.

[Slide]

There are three covariates considered in the survival analysis and disease-free survival analysis by the sponsor according to the SASS programming code submitted to us for review. They are age, disease stage and TBI dose. The age was pre-specified in the protocol as a stratification factor. The other two factors, disease stage and the TBI dose, were selected retrospectively.

[Slide]

In these slides I will present the results based on the unadjusted analysis and adjusted analysis. In this figure the numbers on the horizontal axis represent hazard ratios, and the models are on the vertical axis. Those segments with ticks on them stand for confidence intervals of the estimated hazard ratios. Cox regression models were used for the adjusted analysis. The hazard ratio is cyclosporine versus FK506.

The first analysis is unadjusted analysis, and the estimated hazard ratio is about 0.7. Actually, it is slightly over 0.7, with confidence intervals from 0.5 to 0.98, about.

The next analysis is adjusted analysis for disease stage. The estimated hazard ratio is around 0.75, with

confidence interval from 0.5 to 1.03, if I remember correctly.

Similar results can be obtained by using the other combinations of the covariates. By adjusting other combinations of the covariates, for example, adjusting stage and age or adjusting stage, age and the TBI dose, or adjusting age alone, or adjusting TBI dose alone.

We may conclude from this that the results based on the adjusted analysis are very similar to those of the unadjusted analysis. All results demonstrate that survival for FK506 patients were worse although the confidence intervals of some adjusted analyses barely touched the vertical line of the hazard ratio of 1.

Therefore, an appropriate interpretation of the results of the adjusted analyses should be that the results of the adjusted analyses fully support that of the unadjusted analyses.

[Slide]

This slide demonstrates the results based on unadjusted analyses and the adjusted analyses for disease-free survival. A conclusion can be made similarly for disease-free survival. That is, patients treated with FK506 had significantly worse disease-free survival.

[Slide]

These are two survival plots for the two treatment

arms. The top curve is cyclosporine. You can see from this plot that the separation is uniform and statistically significant. This is the estimated hazard ratio, p value.

[Slide]

These are similar plots for disease-free survival. The separation is also significant. The top curve is the cyclosporine.

[Slide]

For study 18 there is no significant difference in either overall survival or disease-free survival. We can see from this figure that the estimated hazard ratios are slightly over 1 for both overall survival and disease-free survival.

[Slide]

Two curves of the disease-free survival plots are very similar, although the FK506 is on the top but it is not significant. The separation is not significant.

[Slide]

In summary, safety conclusions of the trial should be based on the unadjusted analysis, which is a fairly robust giving the results of all adjusted analyses. For sibling donor matched patients, FK506 is not safe compared to cyclosporine because FK506 treatment is associated with a statistically significantly higher risk of death or disease progression.

Thank you.

DR. HIRSCHFELD: Thank you, Dr. Chen.

[Slide]

Now to integrate, FK506 has shown efficacy in two randomized, controlled trials which we were able to verify in combination with other therapy to reduce the incidence of acute graft-versus-host disease compared to historic controls, and in a manner that is at least not inferior to an active control, cyclosporine, in the regimen.

[Slide]

The two comparative clinical studies had different populations, the first consisting of HLA-matched sibling donors and recipient pairs, and the second consisting of unrelated donor and recipient pairs.

It is of concern that FK506 had a higher rate of adverse events, serious adverse events, complications of therapy, and a lower overall and disease-free survival compared to cyclosporine in the larger of the two pivotal studies.

[Slide]

In addition to the risk for death, other significant toxicities were identified, including hyperglycemia, renal toxicity leading to dialysis, and respiratory insufficiency leading to assisted ventilation. These are known toxicities and they are currently mentioned in the approved package

insert.

[Slide]

Why might there be a difference between these two populations? The sponsor submitted one exploratory analysis. Another possibility, and I bring this forth just as a speculation, and the speculation by virtue of having done a fellowship in experimental immunology, published something in the field and, therefore, I know that one can say anything and make it sound plausible--

[Laughter]

--that there may be differences in the biology of sibling-matched and unrelated donors, in particular with regard to cytokine profiles and lymphocyte activations. And, there might be differences, because of these different actions and between FK506 and its molecular targets, in the setting of different cytokine profiles that may appear in different patients. For the cognoscenti, I do have some literature and we could discuss, if need be, why NK and CD28 cell activation and whether there is more TH1 or TH2 activation in the sibling matched context or not, and which agents might be involved. But it is just a speculation.

[Slide]

So to conclude, and it is our mission not only as an FDA reviewer but as an officer in the U.S. Public Health Service to raise questions with regard to public health and

to be skeptical. What this reviewer recommends is that the use of FK506 as part of an immunosuppressive regimen to reduce the incidence of acute graft-versus-host disease in patients who receive bone marrow transplants for hematologic disorders be restricted to the unrelated donor recipient combinations until further information, addressing the serious concerns in sibling donor recipient population, becomes available.

That is the focus of the questions which we wish the committee to address, and I thank you for your attention.

**Questions from the Committee**

DR. DUTCHER: Thank you. We now have some time to ask questions of FDA. Do you have any data on whether patients crossed over at all in this from one agent to another?

DR. HIRSCHFELD: Yes, they did. In essence, we can confirm what the sponsor reported. It was a small minority.

DR. DUTCHER: Dr. Miller?

DR. MILLER: Based on your analysis now, do you feel that it would be better when you are looking at graft-versus-host disease trials to specify blinded? I know this was discussed prior to the initiation of this study, however, in any population when you are looking at a combination of rash, diarrhea, and liver function abnormalities when 98 percent of the patients have had adverse events represented by rash and 20 percent, or

something like that, had diarrhea it is going to be, by definition, subjective, and the only way to actually get around that is blinded.

DR. HIRSCHFELD: You have anticipated the first of our questions. It is an issue we have been grappling with, unless I misunderstood your question.

DR. MILLER: I mean blinded at the bedside, not so much blinded by the reviewers.

DR. HIRSCHFELD: Oh, I see. In terms of the study design--

DR. MILLER: The study design. Because when the study design was discussed it was decided to be open-label. Do you think in retrospect that that is a mistake.

DR. HIRSCHFELD: I can't say it was a mistake because this is new territory for all of us. As the sponsor pointed out, there is no other pharmaceutical that is approved for this indication and this was an exploration, I think, for all concerned.

The literature is difficult to interpret in some cases and highly variable. Certainly, that is a consideration. Is it feasible to have a double-blinded study design in that regard? Potentially, but I think that is a point for discussion, and I think there are pros and cons in terms of implementation and can you really be blinded with regard to administering these agents.

DR. DUTCHER: Dr. Nerenstone?

DR. NERENSTONE: As a non-transplanter, I have just a few questions. One of the things that struck me about the differences in these two patient populations, beside the obvious one of the matched sibling and not matched sibling and extent of disease, which the sponsor has felt was the problem, is that renal function is very different in one group versus the other. In one group it is creatinine clearance greater than 60, in the other it is creatinine of less than 3. Did you look at renal function as an interaction with age and interaction with extent of disease to see if that could explain the variability, or is that something that is not felt worthwhile to do? That is my first question.

My second is that in one of your tables one of the toxicities that you looked at was a creatinine of 2, but patients were allowed on study with a creatinine of 3 or slightly less than 3. Did you really mean a change of creatinine or was that, in fact, a creatinine of 2? If patients weren't allowed on with that creatinine how could you really track that as a toxicity?

DR. HIRSCHFELD: The first question was did we look at renal function, and the answer is, yes, we did. This was one of our first thoughts. We couldn't find a correlation but we were interested to look specifically if there was

some linkage, at least statistically, if we would do an analysis looking at drug levels and also interactions between drug levels and other agents that were taken.

We fairly recently got some more data submitted to us from the sponsor to address some of those issues, and our biopharmaceutic group is looking at that in greater detail using a number of models. So, we will have to stay tuned to see if there is an informative analysis in that regard.

In terms of greater than 2, to my recollection, I don't recall any patient that entered the study with a creatinine between 2 and 3. So, I think that was the rationale for choosing that. Although they could have, they didn't. We could confirm that.

DR. DUTCHER: Dr. Margolin?

DR. MARGOLIN: Yes, I have a couple of questions but I will start with the most pressing one. In what appears to be I think your fifth and maybe fourth to the last slide before the pause, you state in your conclusions in both of these slides that the drug compares favorably with historical controls and is not inferior to the control in the present randomized trials. But you didn't comment--I mean, that was after having gone through a lot of information about how difficult it is, and how difficult it was in this trial to actually define a diagnosis of graft-versus-host. You also did not mention anything about the

sponsor's elegant and probably very expensive comparison of the 2:1 matched controls for all the FK and cyclosporine treated control patients. So, I guess I am still having a problem with what comparison you are making in concluding the activity of this drug.

DR. HIRSCHFELD: Well, I could have been more precise. Historically, meaning untreated since currently I am unaware of people who don't treat. Then there are further categories from the historic because there is an evolution that occurs essentially from when graft-versus-host disease was first recognized. People used monotherapy. They used methotrexate. They used methotrexate and corticosteroid combinations. They used cyclosporine as single agents; cyclosporine and steroid combinations; various types of steroids. So, there is a broad and vast historical literature describing what one may anticipate the incidence of graft-versus-host disease to be.

In terms of the recognition of graft-versus-host disease, I think for that statement whether one takes the endpoint analysis committee or the investigators' analysis, I personally was comfortable with making that linkage just in terms of saying that there is activity for this particular regimen. I don't know if that answers the question.

DR. MARGOLIN: Yes, I think what you are saying is

that the concept is throughout the history of BMT rather than historical, concretely defined as those that were chosen by the sponsor.

DR. HIRSCHFELD: Correct, correct. Yes, I didn't want to limit it to that just that analysis at all. Dr. Temple?

DR. TEMPLE: Well, I just wanted to follow that up. When you compared the analysis by investigator with the analysis by the committee the rate of graft-versus-host disease dropped by almost 50 percent in study 18. Right? So, I thought Dr. Margolin was wondering whether you are still as sure that the true rate is 90 percent since that is presumably based on investigator numbers. How do you really know, how sure are you that you know what the historical rate is? After all, everything depends on that in this study. Or, are you pretty sure it is pretty high but not sure what exactly it is?

DR. HIRSCHFELD: I think that is a fair statement. I couldn't say it more succinctly.

DR. SLEDGE: Getting back to the difference between the EPEC and the investigators, are there significant differences from site to site?

DR. HIRSCHFELD: We actually looked at site effect because that is one of the initial approaches we take to any analysis to see if there are differences from site to site in terms of outcome; in terms of patients that were

recruited; in terms of toxicities that may occur; site to site differences with regard to deaths. And, the only imbalances that we could detect by asking all those questions was the total number of patients. Some transplant centers are busier than others. But I think overall they were well chosen sites and they all seemed to have approximately the same outcomes.

DR. SLEDGE: I mean in terms of what is being called GVHD. Are there major differences, site to site differences?

DR. HIRSCHFELD: Right, we didn't see that either. But that is, again, a good point and we have seen that in previous submissions, not from this sponsor but from other sponsors where there are site to site differences and eliminating one site would change the profile of the analysis.

DR. ALBAIN: Also speaking as a non-transplanter, have you done any of the analyses that the sponsor mentioned regarding blood level correlations in the matched sibling study with adverse events?

DR. HIRSCHFELD: With the data submitted we preliminarily looked at it and came to the conclusion we wanted to see a lot more data. So we made that request to the sponsor and they submitted those data but it was fairly recent and so we haven't completed an analysis.

DR. ALBAIN: Because I thought I heard a comment earlier, perhaps it was from one of the consultants, that when you watch the blood levels very carefully in this type of population--not the unrelated, the matched siblings--that you don't see these adverse events. Perhaps it was the M.D. Anderson consultant that said that.

DR. HIRSCHFELD: I couldn't comment on that. We may be able to in the future.

DR. SIMON: Maybe Dr. Chen will have to answer this. For study 18 with the matched unrelated donors, did you present confidence limits for the difference in the hazard ratio of the two treatments? If you could refresh my memory, what were those confidence limits for study 18?

DR. CHEN: In my presentation I did not present that in text but I presented that in figures. The low limit, as I remember, is from 0.7-something. I have the upper limit and the lower limit in my review but I don't remember the exact figure now. It seems like the estimated hazard ratio is slightly over 1 and the confidence interval covers that 1.

DR. SIMON: How many deaths were there in that study?

DR. CHEN: I am sorry, I don't remember that figure.

DR. HIRSCHFELD: It was about 45 percent, something like that.

DR. SIMON: I guess what I am trying to get at,

because I basically take study 4 at face value, that there is poorer survival with the study drug, and I am trying to see can we conclude from study 18, even though the survival curves look like they are on top of each other and there is not a significant difference, can we rule out a survival deficit corresponding to a hazard of about 0.7, which is what I think you found in study 4?

DR. CHEN: For study 18 the estimated hazard ratio for survival is 1.07. The confidence interval is from 0.67 to 1.7. The p value is 0.8.

DR. SIMON: For study 4 the hazard ratio for survival was about 0.7--

DR. CHEN: 0.71.

DR. SIMON: And the confidence limit range--

DR. CHEN: From 0.5 to 0.98.

DR. SIMON: Okay, so we really can't strongly conclude that study 18 was large enough and definitive enough to be conclusive that there is not really a survival deficit associated with the study drug when used in the context of matched unrelated donors.

DR. CHEN: I think the study was not based on a survival endpoint. It was based on the incidence of GVHD. So, there might not be sufficient power to detect that.

DR. HIRSCHFELD: If I may comment, Dr. Simon, we had the same concern and that is why we at least discussed the

idea that the study which showed the survival difference was the larger of the two studies and the smaller study may, in fact, not have been sufficiently powered.

DR. SCHILSKY: If I understood your presentation correctly, in the sibling donor study you said that the patients in the tacrolimus group had a significantly inferior disease-free survival, as well as overall survival. Is that correct?

DR. HIRSCHFELD: Yes, that is a correct statement.

DR. SCHILSKY: If they had a worse disease-free survival, I am curious to know what your interpretation of that is. Do you think that that could be due to this imbalance in the randomization of the advanced disease patients, or that there was sort of a worse prognostic group, more likely to relapse, or I suppose the alternative interpretation might be that tacrolimus is such a good immunosuppressant that some of the graph versus tumor effect is actually suppressed in patients on that arm and, therefore, there is a higher likelihood of relapse. But how do you interpret the worse disease-free survival in those patients?

[Slide]

DR. HIRSCHFELD: If you can see the data here, most of the differential appears to be early deaths.

DR. SCHILSKY: You don't have to start at the

beginning.

[Laughter]

DR. HIRSCHFELD: I wasn't intending to. In any case, the difference is primarily in the early events. In that particular study, when it comes to relapses there wasn't a difference. There was a difference in relapses in the other study, however. So what the true biology is and what the true effect is still not clear.

I had the impression, and I want to underscore that this is only an impression, that FK506 might be more potent as an immunosuppressant and that it may lower the incidence of graft-versus-host disease but at the expense of some toxicity and also, if one looks at study 18, at the expense of graft versus malignancy effect. But that is just an impression and really I think one would need more data.

DR. DUTCHER: Dr. Margolin?

DR. MARGOLIN: Yes, I am still I guess really bothered by the difficulty in knowing what the contribution of this drug is. I know that sounds negative and I don't mean to. We were fortunate to save time by eliminating what would have been the BMT intro here but that meant that we didn't get to hear the preclinical data about what it is in animal studies, for example, about FK that may look better than cyclosporine. So, I still have to raise the question that without adequate crossover data regarding either safety or

efficacy--and we still haven't heard why patients who did cross over crossed over, and what happened to those patients. And, we have two smallish studies that have somewhat discrepant outcomes, yet we are talking about the possibility of approving the drug for one situation and not the other, which are probably more biologically similar than they are difference, even though we don't really know the immunology that is going.

I am sorry, that is a rambling question but I would like to hear your comments on it, and maybe even some from the sponsor at this point.

DR. HIRSCHFELD: I will share comments. I am not sure how illuminating they will be because, in mulling over the issues, I was facing the same issues.

Certainly, since FK506 was first isolated in Japan there has been, I think, an impressive body of scientific evidence to support its activity as an immunosuppressant. So, I am not concerned about it having activity in that regard, and many types of model systems and looking at in vitro data and looking at clinical data in the organ transplant setting.

The other issue is what is the threshold that we would need to feel comfortable to make a recommendation, and then to whom? In effect, that is why we have come to you because we have questions regarding those issues. I know I didn't

answer your concern, but all I can do is echo the concern. Having looked at the data for the last several months now, I feel convinced that there is activity as an immunosuppressant, but I have concerns and doubts regarding for whom and under what circumstances.

DR. DUTCHER: Dr. Temple?

DR. TEMPLE: Those are all good questions. I just wonder, as a non-immunologist, non-oncologist, not a lot of other things; I have no capacity to talk about receptors--

[Laughter]

--but there are perfectly reasonable explanations for why a drug might have a net adverse effect in one setting and a beneficial effect in the other. If it were providing more benefit to the non-related donors who have a greater risk of graft-versus-host disease, that might overcome its negative effects on creatinine and the fact that it is a greater immunosuppressant so you might have a wash on mortality in that study, but in the more favorable population its illness-making component might overcome it. Unfortunately, that is all speculation too and, to some extent, I think the answer to Dr. Margolin's question is how sure are you that you have an explanation for these disparate findings? If you are clueless about it, then you have to be nervous. I think that is what her question was saying.

DR. MARGOLIN: Thank you.

DR. TEMPLE: So is this just two results, one good and one bad, and you don't know which to pick? Or, is there a rational explanation that puts it all together and really gives you confidence about the other study? I think that was her question.

DR. HIRSCHFELD: Right. Everyone tends to reflect their own biases, their own training, and I was comfortable enough, having read many, many papers about the mechanisms of action of FK506 and binding to its receptor protein and going through all these cascades, and looking at the different populations that I could convince myself that there were differences in the populations. I examined very carefully the explanation about advanced disease as the sponsor has postulated and felt less comfortable with that as an explanation, and if that were the explanation I wouldn't feel comfortable making a recommendation stating that, well, we may have an explanation but who knows the next time what will happen too because the findings could come out leaning even more the other way than leaning in a favorable direction. So, if one puts it in a construct of potential mechanisms which at least in vitro have been described as plausible, then I would feel comfortable in the one setting.

DR. DUTCHER: But, you know, what we are getting are

two fairly good arguments for two totally different reasons for the differences. I think that is what Dr. Temple is bringing out, you know, what are we going to use to judge what makes the most sense in terms of guiding where we are going to use this in patients. Dr. Nerenstone?

DR. NERENSTONE: I think even troubling is Dr. Simon's discussion that the smaller study, which we are saying looks like it is encouraging, is not powered enough to really show that there is not a problem with survival as well. In other words, overall survival was not looked at as an endpoint and, therefore, the study design was not large enough and not powered enough to see that. So, in fact, there could be a problem with that subgroup as well that was not seen because it is too small a study. Dr. Simon, could you comment what size study you would need? Can you do that calculation?

DR. SIMON: No. No, I don't know.

DR. HIRSCHFELD: And, would we know the difference in whatever answer you gave?

[Laughter]

DR. SIMON: Yes, it would have to be bigger. I don't think it would have to be humongous. I think it would be a doable study but I guess my take on it is that for the first group of patients, the matched siblings, there is not really that much justification that I can see for concluding that

the treatment is safe. For the matched unrelated donor study you basically need another study.

DR. TEMPLE: How would you go about deciding whether the results were, in fact, different? You were looking at the confidence intervals, and so on, and obviously it is fairly close to being incompatible with the point estimate but not quite, and certainly not incompatible with the boundaries of the point estimate. What would you do for a formal test, and would that help?

DR. SIMON: I guess you could do it in a couple of ways, but one would be just to size it for being able to detect a deficit in survival of a certain size, maybe of the size that you saw with your point estimate for the matched sibs. I mean, there are ways obviously you could phrase it that would make it impractical to do by trying to detect a very small effect.

I guess all I am saying is that I think there is a spectrum of things you can do but I think right now the data are just inadequate. I mean, we don't biologically understand really why it should be safe in one setting and not in the other, and the fact that we don't understand that and the fact that, to me, it is pretty conclusive that it is not safe with matched sibs leads me to be entirely uncomfortable with concluding that based on the data available that it is safe with matched unrelated donors and

I think we need additional information on that, and another study at least of the size of this study so that they could be put together.

DR. HIRSCHFELD: You will notice that one of our questions addresses that. In looking for replicability, do we have a sufficient pool of information to come to a conclusion or should we request more information.

DR. WILLIAMS: Dr. Simon, you bring up the possibility of pooling studies. It might be okay to do in this case since this study really drew no conclusion. I mean, you are a little reluctant to pool studies sometimes when you are just trying to make a bad result go away--

DR. SIMON: I am talking about another study with matched unrelated donors and pooling the results of that with the current study for matched unrelated donors. I am not talking about for the sibling matched donors.

DR. WILLIAMS: Yes, but you are considering that we would start out from the start of this with an analysis that would plan to pool these data.

DR. SIMON: Right.

DR. TEMPLE: If I understand you, you are not saying that matters a great deal. You want another replication that looks okay.

DR. SIMON: Right.

DR. DUTCHER: Any other comments or questions for FDA?

No? Thank you.

DR. HIRSCHFELD: hank you.

**Committee Discussion and Vote**

DR. DUTCHER: We have to now discuss the questions. The proposed indication is for the prophylaxis of graft-versus-host disease in patients receiving allogeneic bone marrow transplants. The NDA includes data on 329 patients who received sibling matched bone marrow transplants in a Phase III randomized, comparative study and on 180 patients who received unrelated donor transplants in a Phase III randomized, comparative study, for a total of 509 patients; 255 of these patients received Prograf.

Then there is a series of tables that show the efficacy results and including the investigator evaluation and the endpoint evaluation committee evaluation. So, if you would look those over for both the sibling matched and the unrelated donor.

The first question is with respect to the use of the endpoint evaluation committee. The FDA analysis was based upon the evaluation of the independent review committee. Does the committee agree that the most appropriate analyses of GVHD in these studies are those that utilize the results from the independent endpoint evaluation committee, or do they see problems with this kind of an approach? Comments?

DR. PAPADOPOULOS: I have a great deal of difficulty

basing the entire analysis on the endpoint committee, evaluation committee, because I feel that the problems that Dr. Horowitz alluded to are very common in this type of analysis and I would not feel comfortable basing it solely on the EPEC evaluation. I think a great deal of grade II GVHD may have very well been missed, which could have impacted on the differences, and explain the difference between the sponsor and the agency.

DR. DUTCHER: Which didn't really affect the outcome in terms of the other parameters. It only affected the incidence of graft-versus-host disease.

DR. PAPADOPOULOS: But that in essence is the primary endpoint of the study which the FDA asked the sponsor to evaluate in this study.

DR. DUTCHER: Dr. Nerenstone?

DR. NERENSTONE: Again as a non-transplanter, I think I need some guidance. Is grade II disease important? It is treated and it goes away or it doesn't go away, and if it doesn't go away it is going to be picked up by the evaluation team and if it does go away it is not. So, is that important?

DR. PAPADOPOULOS: I think that when you are assessing a drug for its ability to prophylax against graft-versus-host disease anything from grade II to grade IV is significant, which is precisely why it is graded that way as

moderate to severe. I don't think it should be trivialized, although I recognize your point that if it is not treated it will progress. It is not likely to resolve on its own. So I think it is important.

DR. WILLIAMS: Regarding graft-versus-host disease, what are the kind of things that an investigator can see but not record that an endpoint committee couldn't use? I mean, in the future we need data that can be audited, and it seems to me that we ought to be able to find some ways to write down what they see that is they interpreted by an endpoint committee. So what is it? I mean, rash can be written down, a certain percent rash, etc.

DR. PAPADOPOULOS: But I think that one of the issues that Dr. Horowitz raised is very important, and although there was an extremely good reason why the investigators were blinded as to the use of steroids or not, that is a very critical issue in assessing whether somebody has graft-versus-host disease. There are times when patients will have rashes and you can't be absolutely certain that it is GVHD. It could be due to drug effect, etc., etc. And, biopsies are not often conclusive and steroid responsiveness might certainly guide your assessment.

DR. HIRSCHFELD: I would just like to comment on the steroid use. It was difficult to ascertain but there was a table of concomitant medications looking for permutations of

prednisone or dexamethasone. It was only a small minority of patients, if I recall something like 30 patients, 20 percent of the patients who had recorded steroid use. The steroid use was listed for indication "other." There were a number of categories available to record in the case report forms as to what the indication for concomitant medication was and, in this particular case, every time the patients received it, it was always characterized as other and not one of these predetermined categories. We did look at that to see if that would have been helpful and if it would have aided in refining the process of the endpoint committee. Because of the lack of identification as to the reason why it was used and, again, trying to look at the timing, it wasn't clear. But, the only thing that was clear was that it seemed that only 10 percent of the patients got steroids.

DR. DUTCHER: You know, looking at the criteria that are listed, it seems to me that they are pretty quantitative because if grade II GVH is being assessed it includes the GI and the liver toxicity which has specific numbers.

DR. PAPADOPOULOS: Oh, but those numbers can be due to so many other things--

DR. DUTCHER: Correct, but you would code it as GVH if you just had numbers to work from. I mean, you would err on the side of over-diagnosing, it seems to me.

DR. PAPADOPOULOS: Well, that is why the FDA's

original review had greater than 80 percent.

DR. DUTCHER: But that was from the literature.

DR. HIRSCHFELD: No, it was in this study. That is an important point, and the sponsor also had the same kind of algorithmic approach. If you just set up the truly blinded review and say can you tell us whether this patient has graft-versus-host disease, so you write a program and it says if bilirubin is above such-and-such on this day and if there is more percent rash, and you can work it through, many, many patients meet the criteria. Then you have to start teasing out, okay, if this patient has increased bilirubin, or this patient has diarrhea, is it because they also have an infection and are having gastroenteritis; are they also getting antibiotics at that time and the antibiotics could be inducing the diarrhea? And, that is the type of patient-by-patient, day-by-day analysis one has to go through. I don't see another way out of it.

DR. DUTCHER: Dr. Margolin?

DR. MARGOLIN: Well, this is just a total imagination hypothesis--

DR. HIRSCHFELD: Welcome to the club!

DR. MARGOLIN: --but I have to ask either the sponsor's pharmacist or somebody from FDA, if you agree that you cannot blind to things like the assessment of GVH, you can only use a computerized or hand-written data base and

you can't have a consultant go around to all the centers and perform the exams on all of the patients and talk to them, the question is can you blind for the drug in a future Phase III trial? We have done trials with prednisone and other drugs like cyclosporine, etc., etc., and we actually can make a dummy for the prednisone and a dummy bad for the methotrexate, and it is possible to blind sufficiently by the patient, doctor and nurse, the pharmacist, the analytic pharmacologist in order to deal with the levels, etc. But that is the question, as to whether a future study could involve blinding to the drug so that if the errors and the possible introduction of confounding problems to judge the organ consequence of GVH are systematic and, therefore, apply equally to both arms you could still have a meaningful study.

DR. FITZSIMMONS: If I could ask the Chairman if I could address that question from the sponsor?

DR. DUTCHER: Sure.

DR. FITZSIMMONS: Actually, we did very carefully evaluate that possibility and we actually wrote these protocols as double-blind trials in order to do this. What that entails is getting agreement and cooperation and the ability of the other drug manufacturer in order to manufacture capsules that are blinded to the randomized therapy, and then do a double-dummy study. Unfortunately,

after writing the protocol and doing all those negotiations, the other pharmaceutical company refused us to allow us to do that. So, we could not perform the studies double blind even though we attempted to.

I just want to clarify one additional point on the treatment of GVHD, and we do have backup slides. We evaluated the corticosteroid use for treatment of GVHD as well as second-line therapy, and actually it is higher rate than 20 percent. It is very consistent with the investigator grade II to IV GVHD. Most of those patients by protocol in 04 received first-line methylprednisolone, and it is a very similar rate that you see for the overall investigator diagnosis.

DR. DUTCHER: Dr. Temple?

DR. TEMPLE: Getting the other company's drug is a common problem but sometimes people buy it commercially and stick it in a capsule and do a biostudy, and those things can be done.

DR. FITZSIMMONS: Well, I am sure you are familiar with all the bioavailability and pharmacokinetic intricacies of cyclosporine as well as tacrolimus, particularly cyclosporine. It makes that not very feasible to do.

DR. TEMPLE: Really? Even with a quick-release capsule--

DR. FITZSIMMONS: Obviously, cyclosporine has been

available both as a solution as well as a microemulsion with very different pharmacokinetic profiles.

DR. DUTCHER: Dr. Raghavan?

DR. RAGHAVAN: I just wonder if we are agonizing over something that is not tremendously important because, you know, the outcome wasn't really influenced substantially; it was just the incidence bilaterally. I thought that Dr. Horowitz described quite nicely that one of the big problems was the inability to see the patient, look at the rash and so on. That can be fixed with a digital camera or video and making that a requirement of a study to some extent. You will miss the very subtle early changes of GVH but they will declare themselves if they are going to be rip-roaring. For the rest, medication reviewed, looking at whether antibiotics have been prescribed, etc., etc. can help you.

It seems to me that setting this up in such a rigid fashion is not necessarily going to advance the next study a whole lot. You know, where this study seems to have stumbled was on much more fundamental issues that relate to trial design, looking at risk factors for survival, and so on. So, we are kind of looking up at the surface of the thing that probably had the least impact on the decisions that are going to be made, and we are not really talking about the fundamental goofs that relate to stratification of patients and selection of cases as they relate to the

biology of the disease.

DR. DUTCHER: I think for their purposes it relates to how they are going to assess data, what they are going to use for criteria.

DR. RAGHAVAN: Granted, but certainly today we haven't heard anything that suggests really that it makes a huge difference in this sort of randomized trial design. The difference came in the design of things that didn't have to do with the assessment of GVH. That is the only point I am making.

DR. DUTCHER: Dr. Temple?

DR. TEMPLE: It could matter if it was essential in a trial to show superiority to the control. In the present case the hypothesis really doesn't require superiority for graft-versus-host disease. Similarity is good enough. So, it doesn't matter if you lose half your cases. In other trials where showing a difference was critical it could matter if you lose half of them because you can't confirm them.

DR. DUTCHER: Dr. Schilsky?

DR. SCHILSKY: I must say, actually, I tend to agree with Derek's assessment here because it seems to me that it is going to be impossible in a disease as complex as GVHD, in a group of patients as sick as these patients are, to actually know what the real incidence of GVHD is. You see

these patients; they are terribly ill, on lots of medicines. They change from hour to hour and certainly from day to day and, you know, you go to the bedside and you look at them and they have a complaint and you do a diagnostic test; you evaluate what their meds are; you may do an intervention and come back the next day and see if anything is different. You know, you are going to get a different analysis of how the patients are doing from those individuals who are seeing the patients at the bedside than those from those who are just looking at the records.

I suppose to me at least it doesn't seem to be that important which is which so long as we have some confidence that whatever method is chosen is applied equally across all of the elements of the study. But trying to agonize over whether we should use an independent committee or accept the investigator's assessment doesn't seem to me to be very fruitful.

DR. WILLIAMS: I do think it is important in this case because we have biased investigators, biased by the nature that they know what the drug is, and we have no way of verifying what they do. So it is very important to us, and for that reason it is very attractive to have an analysis which is performed by a blinded group.

DR. SCHILSKY: The problem with a blinded group, as far as I can tell is that a blinded group doesn't actually

have the same amount of information available that the investigators have. So, the blinded group may tend to apply the criteria for diagnosis of GVH more stringently based upon more limited information about the patients. So, that is going to lead to a lower incidence. The investigators may apply the criteria less stringently. They may be biased but they have more data available to them.

DR. WILLIAMS: The challenge is for the field to come up with something that can be validated. Look what we do with response. We are not going to accept someone's opinion if we can't in some way verify it.

DR. SCHILSKY: You are dealing with a symptom complex which is comprised of a number of symptoms that have a variety of causes, any one of which may be operative in a patient population that you are dealing with.

DR. SLEDGE: We are talking as much about a syndrome as a diagnosis here, which I think is the big problem.

The question I asked earlier about whether there were site to site differences in terms of what was called GVH was asked for this specific reason. What I heard was that there were no site to site differences. So, you would have to argue that there was a systematic bias across all of the sites, which seems unlikely to me.

DR. HIRSCHFELD: Not necessarily because there sere some sites that had 3 patients and some sites that had 43

patients. There might be biases across sites that couldn't be picked up in that way and still could influence the outcome. The essence of the question is how do we interpret the data, as well as how we can verify it, because the results are different depending on whether one uses the independent committee or the investigator's bedside evaluation. If we subscribe to using one over the other, then we would have a different outcome in terms of what we could endorse.

DR, MILLER: I think that the answer may be that, you know, the independent endpoint evaluation committee is the cleanest, although we may have to accept that it under-represents the true incidence. The other point is that the more information that you collect, such as requiring biopsies that could then be independently reviewed or blindedly reviewed by central blinding--and this has been done in other graft-versus-host disease studies by requiring biopsies as much as you can to try and make the evaluation committee able to collect the data. The other thing that has been used in studies is a blinded investigator at the center where all they do is grade toxicity. This has been used in validated mucositis trials, the idea of a blinded investigator who doesn't know what they are getting at the site. So, I think that is where we may be able to improve.

DR. HIRSCHFELD: Again, we could all speculate on what

the ideal trial would be, or what the true incidence of graft-versus-host disease would be, although I want to emphasize that that is a fuzzy line. The question is which of the available tools that we have provided to us should we use in terms of our analysis?

DR. JUSTICE: We are not really asking the committee to agonize over this. I think we have a sense of the difficulties here.

DR. DUTCHER: I think the idea of an independent evaluator at a site makes a lot of sense.

DR. TEMPLE: Can I tell you what I think I have heard from the discussion? That people who know about this think that the on-site person may have insight that the subsequent review committee might not. There has been suggestion that being able to quantitate what they do better and document what they do would be good, but the greatest credibility would come from somehow blinding everybody to treatment, in which case you wouldn't have to worry about bias. Everybody thinks the subsequent review is reasonably credible but it may miss a lot of cases, which could be important in some studies but probably isn't too important in this one since the conclusions are the same either way.

So, if you think that is what everybody has been saying, we could move on.

[Laughter]

DR. DUTCHER: We agree. Let's look at question number two. There are three tables preceding this that have to do with adverse events, survival, disease-free survival and all patients in advanced disease.

These data demonstrate significant differences in toxicity, survival and disease-free survival that favor cyclosporine over Prograf in patients with matched sibling donors and no significant differences in efficacy.

Does the committee recommend approval of Prograf for the prevention of GVHD in patients receiving matched sibling donor bone marrow transplants for hematologic malignancies?

Discussion? I think we have heard the discussion. Shall we vote? Does the committee recommend approval for matched donor bone marrow transplants?

All those who would vote yes?

[No response]

Zero. All those who would vote no?

[Show of hands]

Thirteen.

The smaller study in 180 patients receiving unrelated donor transplants demonstrated that Prograf was at least as effective as cyclosporine and that there were no significant differences in toxicity. However, replication is generally required for approval of a new drug or a new indication for an approved drug. Although survival and disease-free

survival were worse on the Prograf arm of the larger study, Prograf was at least as effective as cyclosporine in reducing the incidence of graft-versus-host disease.

Do the efficacy results of study 4 replicate those of study 18, or should the sponsor be asked to conduct a confirmatory trial in patients receiving unrelated donor bone marrow transplants?

Discussion. Dr. Miller?

DR. MILLER: For this question, can we use the Japanese study, which had predominantly matched unrelated, as essentially a confirmatory study? That wasn't fully reviewed here but would anybody else consider that a reasonable study to use to compare?

DR. DUTCHER: Well, it wasn't reviewed.

DR. WILLIAMS: We can look into that. I think for now you can vote and we can look into whether or not we think that is one.

DR. JUSTICE: Just to comment though, I don't think it would answer Dr. Simon's question about the survival issue. It is too small.

DR. SIMON: It is not so much the issue of a confirmatory study for efficacy in terms of preventing GVHD; it is a confirmatory study for safety that we need. You can look into the Japanese study but--

DR. WILLIAMS: Besides, the size was much smaller.

DR. SIMON: Yes. I think it was about 50-50 between matched siblings and matched unrelated donors. So, it would be pretty small.

DR. DUTCHER: Dr. Margolin?

DR. MARGOLIN: Just to be fair, since as we said before we really don't understand enough about the biology to explain the differences between the two studies, if we are asking for a confirmatory study in unrelated we might just as well ask the sponsors if they wish to perform a confirmatory study in the related transplant setting as well.

DR. TEMPLE: Maybe at a lower dose.

DR. DUTCHER: And also, one of the concerns that we have all been talking about in the break is the mix of patients, the mix of diagnoses, which may reflect a mix in prior therapy and a mix in baseline end-organ function that may contribute to the excess toxicity, and I don't think we know the answer to that either. So, a more homogeneous group of patients would be helpful.

DR. MILLER: I think 180 patient study is big for a bone marrow transplant study. It is a very large study for bone marrow transplant. The events are higher. So, I wouldn't be surprised that 180 isn't a reasonable sample size where there are so many failures due to death, relapse or toxicity. So, I think it is a good sized study.

DR. SIMON: I don't think it is really an adequate size study. I mean, given that we don't really don't understand why we are getting the safety in one study and not the other, I think we would like to have confidence for showing that there is not a differential in survival. Whereas this may be an impressive size study relative to others that have been done, I just feel that given the great uncertainty as to what is going on here, we need a confirmatory study.

DR. DUTCHER: Miss Beaman?

MS. BEAMAN: I think I heard someone from the FDA allude to the fact that you have received additional data recently and it hasn't been analyzed. Do you think from what you do have, without necessarily revealing what that might be since it hasn't been analyzed, that analyzing that data will perhaps make this picture a little clearer for us?

DR. HIRSCHFELD: I think the answer wouldn't address the fundamental issue. The data is biopharmaceutic data to allow us to look more carefully at interactions and try to relate it to drug dose.

DR. SIMON: The only other thing I would say is I guess in one of the tables Dr. Hirschfeld handed out, even on study 18--I guess he looks at GVHD, 46 percent of all deaths for the study drug, 67 percent of all deaths for the cyclosporine; relapsed, 16 percent of deaths for the study

drug, 0 percent for cyclosporine. So, I just think we just need more data to figure out what is going on.

DR. MILLER: From a transplant point of view that makes sense. You are asking this drug to decrease graft-versus-host disease. You can attack relapse from another standpoint, which is use additional immunotherapy. So we are asking is, is it effective for decreasing graft-versus-host disease in an unrelated patient population, and does it appear to be safe in this patient population, and relapse is a separate issue than toxicity death. There are lots of other ways for getting around that.

DR. SIMON: I am just saying that if we understood the mechanism of the deaths, the relationship between the drugs and the deaths, then I think we would all feel perhaps more comfortable. Given that we don't understand the mechanism, I personally feel that I have to depend somewhat on statistical grounds in terms of what can be concluded about survival differences from study 18. I am saying that given the size of study 18, statistically we really cannot conclude that there is not a similar difference in survival deficit.

DR. PAPADOPOULOS: Let me give a corollary statement to what you are saying. Looking at the clinical data, barring all of the statistical data that has been presented today, I don't fully understand that the number of advanced

patients in study 4 didn't really make a difference with Dr. Chen's analysis. To me, it is really the opposite. It is not so much why was there not a difference even worse for FK506 in the unrelated trial, but why wasn't the advanced patient population significant enough to make it different in the related trial?

DR. SIMON: He compared the study drug to cyclosporine unadjusted, and then he adjusted for it and it made a little bit of difference in the point estimate, not much, and I guess what it must be telling us that their categorization of advanced disease is a little bit screwy.

DR. PAPADOPOULOS: Precisely. Well, that is the problem, and that makes it difficult for me to accept the whole study because I am not sure that what was advanced in the sponsor's mind was the same as what was advanced in the FDA reviewer's mind.

DR. HIRSCHFELD: We used the same coding. We didn't change the categories. However the sponsor defined it is what we used for the analysis. In the smaller study, the 18, advanced patients were excluded.

DR. PAPADOPOULOS: Right.

DR. SIMON: And the other thing is the imbalance in one arm I think was 30 percent and in the other arm it was 40 percent. So it wasn't a huge thing. It was statistically significant but it wasn't a huge imbalance

and, although we are calling it advanced disease, maybe actually in this data the prognostic effect wasn't all that sizeable although it was statistically significant.

DR. DUTCHER: It seems that the issues are that we have a drug that has capabilities of being immunosuppressive in preventing GVHD. The issue is are there patients with sufficiently severe enough risk of dying from graft-versus-host disease that a drug that may be somewhat more toxicity in one setting is clearly worthwhile in another setting, and those are the data that we need to be able to see, that, you know, a little bit of risk-benefit going toward the risk side is worth it in the worst clinical situation, the in the worst transplant setting, and do these data that we have seen give us that information? That is what the question is.

DR. MILLER: As a transplanter, I think in an unrelated transplant setting where, clearly in that high risk patient population, you know, we need better drugs for graft-versus-host disease you are willing to accept more potential risk--

DR. DUTCHER: I don't think we can deny that. The question is do you understand from the data that were presented what is drug, what is disease, and what is GVHD? I mean, do we know enough about this drug to know that in a setting where there is a higher risk of death from graft-

versus-host disease and relapse from other things in fact it does--

DR. MILLER: It makes sense that the more potent immunosuppressive is more active when there is more HLA disparity. So, the clinical findings on the study sort of go along with my way of thinking about unrelated versus allogeneic transplants.

DR. SCHILSKY: But what data have you seen that I haven't seen to suggest that this drug is any better than cyclosporine?

DR. MILLER: I don't think it is any better; it is equivalent to cyclosporine.

DR. SCHILSKY: So, it is equivalent in one setting. It is clearly more toxicity, and in the other setting it might be more toxicity although the toxicity may also be masked by the increased illness in the patient population. So, I come back to the question I asked earlier this afternoon, why would you want to use this drug?

DR. DUTCHER: As opposed to cyclosporine?

DR. SCHILSKY: Right.

MS. BEAMAN: More importantly, why would you want to take it?

[Laughter]

DR. DUTCHER: Well, is there a setting in which you could define it? Dr. Temple?

DR. TEMPLE: It could be, if I understand what people said, that taking one of these drugs probably makes you better off than if you didn't take either one. So, that is why you would want to take one of them, because you are better off, but that then goes to why would you want to take this one.

DR. MARGOLIN: I think the ideal, and I wouldn't propose how to design the study but just from what we do in practical transplantation is you choose the patients who are at most risk for GVH disease, mortality, who have a kind of low risk malignancy and you give them what you perceive as the most active GVH prophylaxis--at our center that is three drugs instead of two--and the ones who are at greater risk for disease relapse who, quote, need a little GV malignancy, if you can define that, you let them have a little more by giving them just two drugs. So, that might be where you might choose FK versus cyclosporine if we had the data.

DR. ALBAIN: I want to come back to the drug level correlation again because it sounds like their data is there waiting to be looked at in more detail. The consultant from Baylor seemed quite strongly in favor of this over cyclosporine based upon--I guess she has left but I guess based upon modulating the drug level. If that data is available to look at here, we haven't seen it yet.

DR. DUTCHER: Well, you also have to keep in mind the

drug is available--

DR. ALBAIN: No, I mean the drug level.

DR. DUTCHER: No, I understand what you are saying. We are not going to see that data today. They may have it.

DR. HIRSCHFELD: It hasn't been analyzed yet. We have consulted it to the biopharmaceutic group and they are busy at work on it right at this moment.

DR. ALBAIN: I was just bringing it up because it seems to me that when you look at that in conjunction with toxicity there may be much less and there may be an advantage over cyclosporine in the unrelated.

DR. DUTCHER: We don't have demonstration of advantage; we have demonstration of similarity in terms of the effectiveness.

DR. ALBAIN: I am talking about the consultant that the sponsor presented, not the data we have before us.

DR. DUTCHER: So, do the efficacy results in study 4 replicate those of study 18, or should the sponsor be asked to conduct a confirmatory trial in patients receiving unrelated donor bone marrow transplants?

DR. ALBAIN: Can you split that question?

DR. DUTCHER: Sure. Do the efficacy results of study 4 replicate those of study 18?

DR. SIMON: By efficacy we mean anti-GVHD?

DR. DUTCHER: Correct, anti-GVHD.

DR. TEMPLE: That is a slightly defective question because, sure, you see an effect on graft-versus-host disease in both studies. We already know that; we don't even need to ask you that. I think the question is the one Rich Simon said, are you confident enough that you are okay in the setting of unrelated donors without another study? That is really what the ultimate question is going to be. This is not critical; sure, it shows the same effect on GVH disease. We know that.

DR. JUSTICE: How about if we modify the first clause and just say are the safety concerns from study 4 sufficient that the sponsor should be asked to conduct a confirmatory trial, which is what Dr. Simon said?

DR. MARGOLIN: Why not just use the term risk-to-benefit ratio because that is really what it is?

DR. DUTCHER: Well, I think the question is do we have sufficient data of risk-benefit ratio for unrelated donors to not require confirmatory data.

DR. TEMPLE: Good question.

DR. HIRSCHFELD: Can you say that again?

DR. DUTCHER: Do we have sufficient data on risk-benefit ratio in matched unrelated BMT to not require a confirmatory trial in that population? I would ask our consultants to please comment.

DR. PAPADOPOULOS: I would not ask for a confirmatory

trial in the unrelated's.

DR. MILLER: I agree. I would ask our previous question about the allogeneic related but not the unrelated.

DR. MARGOLIN: Could I ask Dr. Schilsky a question? If that is the case and it is approvable for unrelated transplants in whom will we give this drug in lieu of cyclosporine?

DR. MILLER: We are currently using it in a trial of what we consider the worst-case offenders, which is the mismatched unrelated or the mismatched sibling transplants, where we are loading up on prophylaxis for graft-versus-host or for infections and we are adding additional immunosuppression to allow--additional anti-tumor to decrease the risk of relapse. So, I think the transplanters as a whole will decide where to use it in the very highest risk patients.

DR. MARGOLIN: Then the question comes up are there patients for whom we would not recommend its use?

DR. DUTCHER: What about molecular matching for matched unrelated? How does that impact on the patient population?

DR. HIRSCHFELD: Just a nuance on it, as I think Dr. Dutcher pointed out, the drug is available both intravenously and orally and what it reduces to a little further in terms of nuance is can a claim be made without

further data?

DR. TEMPLE: That is what the whole discussion is about. That is all we are talking about; we are talking about a claim. The drug is already on the market.

DR. MILLER: Claim and reimbursement for patients who need it.

DR. TEMPLE: Okay, we try very hard not to think about that.

DR. MILLER: Okay.

DR. TEMPLE: Even though it is very important. Can you explain a little further why you reached the conclusion in light of what Rich Simon said before? You must be confident that the result in unrelated is solid enough so you are no longer worried about the other one, or just elaborate a little bit, otherwise we won't know where this comes from.

DR. PAPADOPOULOS: The differences in the results in terms of graft-versus-host disease are, at the very least, equivalent if perhaps not slightly better for the FK506. There are so many variables that go into outcomes, especially in the unrelated trial, that in terms of just looking at this one particular drug can we manage the side effects? I am not really convinced from what I have been shown that these are unmanageable or unacceptable side effects, especially in this patient population. I also was

very surprised to see that there were no relapses. Wasn't it in this category that there were no relapses in the cyclosporine group? Even for cyclosporine that is pretty bizarre. I am not convinced that there is a greater side effect profile that couldn't be managed by adequate levels.

DR. TEMPLE: Okay, but the trial was done in one group and more people died. So, whatever the side effects were, they weren't managed in those people. It is not that usual to find a statistically significant increase in mortality when you compare one drug with another. It doesn't happen every day. You must be comfortable enough that you have a good explanation for why that happened and that it doesn't apply. I am putting words in your mouth--and it somehow doesn't apply to the non-related donors. I take it some thought like that is in there but, you know, you need to help us understand.

DR. MILLER: My feeling, I guess, is that in the unrelated if you are going to see--the study is large enough that if you are going to see severe--the survival is perfectly equivalent--the infectious complications and the VOD are equivalent, early death is equivalent, in that population where there is enough mortality in bone marrow transplants both on cyclosporine as well as the FK506, are very good, very believable and very consistent with what has been published in the best of centers. So, that is why--I

mean, that gives me a comfort level in patients treated with FK506. There have also been several Phase I and Phase II studies looking at this, with similar results. There is one from M.D. Anderson. I think there is one from Seattle also. There is other data in high risk patients that are not randomized data but that are not non-supportive of good survival--

DR. PAPADOPOULOS: At least comparable survival.

DR. MILLER: Comparable survival, and we don't have this hint or this concern about increased mortality. So it is not just this trial but previous data that has been published.

DR. PAPADOPOULOS: You know, not to be argumentative but it looks to me like there is somewhat of a bias and a leap of faith that you are asking this committee to go with you in that you say you are already using FK506 in the highest risk unrelated donor patients, and I don't think that means you just decided after this meeting. This drug was presented to us as an equivalency trial with pretty loose parameters and not as a superiority drug, and it just happened to come out a little bit better. So, that is really just a rhetorical comment based on what you said before.

DR. MARGOLIN: I just want to note that we are not using FK506 at our institution, and we are not using it as a

crossover drug in patients with GVH.

DR. FITZSIMMONS: Madam Chairman, I wonder if I could make just one comment?

DR. DUTCHER: Yes.

DR. FITZSIMMONS: Based on the time restrictions we didn't go into our Phase II studies, but I think an important factor in this deliberation is that we have studied 97 patients treated with tacrolimus with unrelated donor transplants in Phase II.

[Slide]

This slide shows that in the far right-hand column. You can see that we have had very comparable results to our Phase III trial in 97 patients who were exposed to tacrolimus with various adjunctive immunosuppressive regimens, n Phase II.

So, although there was discussion of the small nature of the trial, as was alluded to, this was the largest unrelated donor study and there is also additional data that is available on a large cohort of patients that we didn't present, treated after unrelated donor transplants.

DR. DUTCHER: Thank you. So, the grand total of data would be--what?--about 200 patients for matched unrelated that is reviewable that the FDA could have access to?

DR. FITZSIMMONS: Yes, they have all the data from the 90 patients in the 18 study that were treated with

tacrolimus, 90 with cyclosporine; 97 from the Phase II trials; and you also saw the patients, approximately 35 in each treatment group, that were unrelated donor in the FK-14/15. All that data is included in the NDA.

DR. SIMON: I think it would be pretty difficult in an uncontrolled Phase II study to determine whether you were really having the size of effect that you saw, particularly with unrelated donor transplants, whether you were having a deficit or not.

DR. DUTCHER: Question number three, do we have sufficient data on risk-benefit in matched unrelated transplants to not require a confirmatory trial?

All those who would vote yes?

[Show of hands]

DR. TEMPLE: Let's be clear on that "yes." Make sure everybody know what "yes" means. Yes means you do have enough data; yes means you don't have enough data.

DR. DUTCHER: Yes means you do have enough data.

DR. TEMPLE: Okay.

DR. ALBAIN: Why don't you take out the double negative and make it a straight yes or no?

DR. DUTCHER: Is there enough data--is there sufficient data--

DR. MARGOLIN: To approve the drug.

DR. DUTCHER: Well, that is the fourth question. Is

there sufficient data on risk-benefit ratio in matched unrelated bone marrow transplants to make any decision?

DR. TEMPLE: Well, without a confirmatory study--

DR. DUTCHER: Without a confirmatory study.

DR. TEMPLE: --to reach a conclusion that it works; that risk-benefit is okay.

DR. DUTCHER: Wait a minute, is there sufficient data on risk-benefit analysis in matched unrelated transplants without a confirmatory trial to assess safety and efficacy?

DR. RAGHAVAN: Would it be easier just to ask a much simpler question, is a confirmatory trial required?

DR. DUTCHER: That what was asked and you didn't like it the last time.

DR. TEMPLE: With all the discussion and knowing what it means, that probably would be okay too.

DR. DUTCHER: All right, then should the sponsor be asked--

DR. TEMPLE: This is the opposite of the previous question. Yes now means no.

DR. DUTCHER: Okay, we will go back to the original question three minus the first clause. Should the sponsor be asked to conduct a confirmatory trial in patients receiving unrelated donor bone marrow transplants based on the data we have seen? So we are going to ask the positive, should they conduct a confirmatory trial?

All those who would vote yes?

[Show of hands]

Nine.

All those who would vote no?

[Show of hands]

Four.

Does the committee recommend approval of Prograf for the prevention of GVHD in patients receiving unrelated donor bone marrow transplants for hematologic malignancies?

Discussion? Comments?

[No response]

All those who would vote yes? This is to recommend approval for matched unrelated bone marrow transplants. All those who would vote yes?

[Show of hands]

Four.

All those who would vote no?

[Show of hands]

Nine.

Okay, thank you very much. We are adjourned. We will meet here at eight o'clock tomorrow morning.

[Whereupon, at 6:05 p.m. the proceedings were recessed to be resumed at eight o'clock, Tuesday, January 13, 1999.]

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# *CERTIFICATE*

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

Alice Toigo

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