FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Oncologic Drugs Advisory Committee

Avastin (bevacizumab) for the Treatment of

Previously Treated Glioblastoma Multiforme

Tuesday, March 31, 2009

8:30 a.m.

Hilton - Washington, D.C.

8727 Colesville Road

Silver Spring, Maryland

M E E T I N G R O S T E R

ONCOLOGIC DRUGS ADVISORY COMMITTEE VOTING MEMBERS:

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Stanford University School of Medicine
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(Roster continued on the next page.)

ROSTER (continued):

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(Roster continued on the next page.)

ROSTER (continued):

RONALD RICHARDSON, M.D.
Consultant, Department of Medical
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Mayo Clinic
200 First Street, SW, Gonda 10
Rochester, Minnesota 55905

WYNDHAM WILSON, M.D. (Acting Chair)
Chief, Lymphoma Therapeutics Section
Metabolism Branch
Center for Cancer Research
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(Roster continued on the next page.)

ROSTER (continued):

INDUSTRY REPRESENTATIVE (NON-VOTING):

GREGORY CURT, M.D.
U.S. Medical Science Lead, Emerging Products
AstraZeneca Oncology
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Garrett Park, Maryland 20896

TEMPORARY VOTING MEMBERS:

PEGGY ALMGREN (Patient Representative)
Mill Valley, California 94941

FREDERICK BARKER, M.D.
Associate Visiting Neurosurgeon
Pappas Center for Neuro-Oncology, Yawkey 9E
Massachusetts General Hospital
Boston, Massachusetts 02114

(Roster continued on the next page.)

ROSTER (continued):

MARK KIERAN, M.D., Ph.D.
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Herman and Joan Suit Professor of
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(Roster continued on the next page.)

ROSTER (continued):

TEMPORARY MEMBER (NON-VOTING):

ERINI MAKARIOU, M.D.
Associate Professor of Radiology
Georgetown University Medical Center
Radiology Department
3800 Reservoir Road, NW
Washington, D.C. 20007

GUEST SPEAKER (NON-VOTING):

VICTOR LEVIN, M.D.
Professor and Bernard W. Biedenharn Chair
for Cancer Research
Department of Neuro-Oncology
The University of Texas M.D. Anderson
Cancer Center
1515 Holcombe Boulevard, Unit 431
Houston, Texas 77030

(Roster continued on the next page.)

ROSTER (continued):

FDA (NON-VOTING):

RICHARD PAZDUR, M.D.
Director, Office of Oncology Drug
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Office of New Drugs (OND), CDER, FDA

PATRICIA KEEGAN, M.D.
Director, Division of Biologic Oncology
Products (DBOP)
OODP, OND, CDER, FDA

LEE PAI-SCHERF, M.D.
Division of Biologic Oncology Products
(DBOP)
OODP, OND, CDER, FDA

(Roster continued on the next page.)

ROSTER (continued):

SANDRA CASAK, M.D.
Staff Fellow/Clinical Reviewer
Division of Biologic Oncology Products
(DBOP)
OODP, OND, CDER, FDA

YUAN LI SHEN, Dr.P.H.
Statistical Reviewer -- Biologic Oncology
Division of Biostatistics 5 (DB5)
Office of Biostatistics (OB)
Office of Translational Science (OTS),
CDER, FDA

A G E N D A

8:30 a.m. Call to Order
Wyndham Wilson, M.D.

Introduction of Committee
Acting Chair, ODAC

Conflict of Interest Statement
Nicole Vesely, Pharm.D.
Designated Federal Official, ODAC

The committee will discuss supplemental biologic license application (sBLA) 125085/169, trade name Avastin (bevacizumab), Genentech, Incorporated, proposed indication, as a single agent, for the treatment of previously treated glioblastoma multiforme.

8:45 a.m. FDA Presentation
Sandra Casak, M.D.

(Agenda continued on the next page.)

AGENDA (continued):

Regulatory History and Product Approvals for GBM
Staff Fellow, Division of Biologic Oncology Products (DBOP)

9:00 a.m. Guest Speaker -- Treatment of
CNS Radiation Necrosis with
Bevacizumab, an Anti-VEGF
Antibody
Victor Levin, M.D., Professor
and Bernard W. Biedenharn Chair
for Cancer Research
Department of Neuro-Oncology
The University of Texas
MD Anderson Cancer Center

9:30 a.m. Sponsor Presentation -- Genentech, Inc.

(Agenda continued on the next page.)

AGENDA (continued):

Introductions

David Schenkein, M.D.
Senior Vice President
Clinical Hematology and Oncology,
Genentech, Inc.

MR Imaging in Glioblastoma

A. Gregory Sorensen, M.D.
MGH-HST Center for Biomarkers in Imaging
A.A. Martinos Center, Massachusetts
General Hospital
Harvard Medical School & Massachusetts
Institute of Technology
Division of Health Sciences and Technology

Study AVF3708g and NCI 06-C-0064E

Julie Hambleton, M.D.
Associate Group Medical Director
Genentech, Inc.

(Agenda continued on the next page.)

AGENDA (continued):

Avastin Study in Context
Michael Prados, M.D.
Charles B. Wilson Professor of
Neurosurgery
Director of Division of Translational Research
University of California San Francisco
Project Leader: North American Brain
Tumor Consortium (NABTC)

Conclusions
David Schenkein, M.D.
Senior Vice President
Clinical Hematology and Oncology
Genentech, Inc.

10:15 a.m. Break

(Agenda continued on the next page.)

AGENDA (continued):

10:30 a.m. FDA Presentation -- sBLA 125085/169
Bevacizumab (Avastin) for Previously Treated Glioblastoma Multiforme
Lee Pai-Scherf, M.D.
Medical Officer, Division of Biologic
Oncology Products (DBOP)
OODP, OND, CDER, FDA
Yuan Li Shen, Dr. P.H.
Statistical Reviewer -- Biologic Oncology
Division of Biostatistics 5 (DB5)
Office of Biostatistics (OB)
Office of Translational Science (OTS)
CDER, FDA

11:15 a.m. Questions to the Presenters

12:00 p.m. Lunch

1:00 p.m. Open Public Hearing

(Agenda continued on the next page.)

AGENDA (continued):

2:00 p.m. Questions to the ODAC and ODAC Discussion

3:00 p.m. Break

3:15 p.m. Questions to the ODAC and ODAC Discussion

4:30 p.m. Adjournment

I N D E X

(Index continued on the next page.)

INDEX (continued):

P R O C E E D I N G S

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

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the Advisory Committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with FDA about these proceedings; however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the Committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

DR. WILSON: I would like to call the meeting to order. Today's agenda involves Genentech's and Roche's supplemental biological license application; trade name, Avastin, proposed indication as a single agent for the treatment of previously treated glioblastoma multiforme.

My name is Wyndham Wilson. I am from NCI and I'm currently acting

chair.

Can I start on the right side and have you each introduce yourself?

DR. CURT: Gregory Curt, Medical Oncologist and Industry Representative.

DR. KIERAN: I'm Mark Kieran from the Dana-Farber Cancer Institute, Pediatric Neuro-Oncologist.

DR. LOEFFLER: Jay Loeffler from the Department of Radiation Oncology at the Massachusetts General Hospital.

MS. ALMGREN: Peggy Almgren, Patient Advocate.

MS. MASON: Virginia Mason, Consumer Rep with the Inflammatory Breast Cancer Research Foundation.

DR. LYMAN: Gary Lyman, Medical Oncologist and Health Outcomes Researcher from Duke University.

DR. VESELY: Nicole Vesely, Designated Federal Official.

DR. RICHARDSON: Ron Richardson, Medical Oncologist, Mayo Clinic, Rochester, Minnesota.

DR. HARRINGTON: Dave Harrington, Statistician, Dana-Farber Cancer Institute.

DR. LINK: Michael Link, Pediatric Oncologist from Stanford.

DR. BARKER: Fred Barker, Neuro Surgeon, Massachusetts General Hospital.

DR. SHEN: Yuan Li Shen, Statistical Reviewer, FDA.

DR. CASAK: Sandra Casak, Pediatric Oncology, FDA.

DR. PAI-SCHERF: Lee Pai-Scherf, Medical Officer, FDA.

DR. KEEGAN: Patricia Keegan, FDA.

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

DR. WILSON: And for the record, Wyndham Wilson, Medical Oncologist, NCI.

DR. VESELY: The Food and Drug Administration is convening today's meeting of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting and nonvoting members of the Committee are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Committee's compliance with Federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C., Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act, is being produced to participants in today's meeting and to the public.

FDA has determined that members and temporary voting and nonvoting members of this Committee are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C., Section 208, Congress has authorized FDA

to grant waivers to special Government employees and regular Federal employees who have potential financial conflicts when it is determined that the Agency's need for particular individual services outweighs his or her potential conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees with potential financial conflicts when necessary to afford the Committee essential expertise.

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

Today's agenda involves Genentech's and Roche's supplemental biologic license application 125085/169, trade name Avastin, bevacizumab, proposed indication as single agent for the treatment of previously treated glioblastoma multiforme. This topic is a particular matter involving specific parties.

Based on the agenda for today's meeting and financial interest reported by the Committee members and temporary voting members, conflict of

interest waivers have been issued in accordance with 18 U.S.C., Section 208(b)(3) to the following participants:

Dr. Mark Kieran for an imputed interest in research involving a competing product, sponsored by the Pediatric Brain Tumor Consortium and the National Institutes of Health. The magnitude of the research contract is zero dollars to $50,000.

Dr. David Harrington for imputed interest in the sponsor. The magnitude is zero dollars to $50,000, and over $300,000 for two subcontracts.

The waivers allow these individuals to participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waiver documents, which are posted on FDA's website at www.fda.gov/ohrms/dockets/default.htm. Copies of the waivers may also be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 6-30 of the Parklawn Building. A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

In the interest of full disclosure, we would like to clarify a professional relationship Dr. Wyndham Wilson, the acting chair, has with Genentech.

Dr. Wilson is the head of the Lymphoma Therapeutic Section of the National Cancer Institute's Metabolic Branch. As part of his official government duties, he attends Genentech's advisory board meetings specifically

to discuss cancer therapies. However, his work with the board has not been related to today's topic.

Specifically, he has never discussed Avastin or its indication as part of his work with Genentech's advisory board. Further, neither Dr. Wilson nor NCI receives any remuneration from Genentech for his services. Dr. Wilson made a full disclosure of these circumstances to FDA, and FDA has advised him that, based on these facts, there is no ethical issue that precludes his participation at the meeting.

Dr. Victor Levin, who is a guest speaker with us today, has acknowledged professional involvements with Genentech and Avastin. In 2008, Dr. Levin was a scientific advisor and member of Genentech's Avastin Glioblastoma Advisory Board. In addition, he is the principal investigator for a National Cancer Institute's sponsored study of Avastin to control brain radiation damage and a co-investigator for Radiation Therapy Oncology Group's sponsored study of Avastin in combination with either irinotecan or temozolomide in recurrent glioblastoma. As a guest speaker, Dr. Levin will not participate in Committee deliberations, nor will he vote.

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

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

FDA encourages all other participants to advise the Committee of any financial relationships that they may have with any firms at issue. Thank you.

DR. WILSON: Let me ask the first speaker, Sandra Casak -- she will be giving an FDA presentation on the regulatory history and product approvals for GBM.

DR. CASAK: Good morning. My name is Sandra Casak and I will present the regulatory background. I will discuss the regulatory requirements for regular and accelerated drug approvals and then review the approval of drugs for brain tumors. The third topic of this presentation will be a summary of the discussion that took place during the January 1999 Temozolomide ODAC Committee, and finally, a summary of the January 2006 Brain Tumor Endpoints Workshop.

The 1962 amendment to the Food, Drug and Cosmetic Act require that new drugs be effective. The law requires substantial evidence of effectiveness derived from adequate and well controlled clinical investigations. In most cases, efficacy is considered equivalent to clinical

benefit.

Currently, FDA's view of what constitutes clinical benefit can be summarized as either prolonging life or improving quality of life. Quality of life is usually indicated by a direct measure of how the patient feels or functions. For regular approval in oncology, the gold standard for evidence of benefit is survival. A surrogate endpoint may support full approval if it is an established surrogate for clinical benefit.

The accelerated approval regulations promulgated in 1992 allow for the use of certain surrogate endpoints for approval of drugs or biological products that are intended to treat serious or life-threatening diseases that either demonstrate an improvement over available therapy or provide therapy where none exist. In this setting, the FDA may grant approval based on an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit.

The drug is approved under the accelerated approval regulations on the condition that the manufacturer conducts clinical studies to verify and describe the actual clinical benefit. If the post-marketing studies fail to demonstrate clinical benefit, or if the applicant has not demonstrated due diligence in conducting the required studies, the drug may be removed from the market under an expedited process. Most accelerated approvals of cancer drugs have been granted on the basis of a demonstrated tumor response rate in a refractory setting, often supported by additional information.

Several endpoints are considered as a study surrogate for clinical benefits. Durable complete responses are acceptable surrogates in acute leukemias where complete response is associated with longer survival, fewer infections and fewer transfusions. A meaningful clinical improvement in PFS has also been accepted as an established surrogate for the treatment of chronic lymphocytic leukemias and renal cell carcinomas. Other response rates are directly attributable to drug effect and FDA has accepted other response rates for accelerated approval in certain refractory tumors where no available therapy exists. In order to support approval, the response rate must be of a significant magnitude. However, as we will discuss today, response rate in the setting of brain tumors is an endpoint with many controversial issues.

Several challenges have limited the development of effective new therapies to treat primary brain tumors, including tumor resistance, drug delivery and bioavailability.

This slide shows all the approved drugs for primary brain tumors. Drug approvals from the '70s were based on tumor response rates. The nitrosoureas, lomustine, and carmustine, both blood-brain barrier crossing alkylating agents, were approved for the treatment of primary and metastatic brain tumors. In the next couple of slides, I will review in more detail the drugs approved under modern standards for approval, carmustine wafer and temozolomide.

Carmustine wafer is an implantable polymer impregnated with

carmustine. The center (phonetic) delivered the drug directly into the surgical cavity created when the brain tumor is resected. The carmustine wafer was approved in 1996 for the treatment of recurrent GBM as an adjunct to surgery on the basis of a randomized, double-blind, placebo controlled trial that showed an improvement in overall survival by 41 percent.

In 2003, Carmustine wafer was granted approval for initial treatment of high-grade, malignant glioma as an adjunct to surgery and radiotherapy. The basis for approval was a randomized, double-blind, placebo controlled trial in 240 patients with newly diagnosed high-grade glioma, undergoing initial resection craniotomy. Median survival increased from 11.6 months with placebo to 13.9 months with the wafer.

Accelerated approval for temozolomide was granted in 1999 on the basis of response rate for refractory anaplastic astrocytoma. The second proposed indication for temozolomide was for the treatment of GBM. The two studies supporting the use of temozolomide for GBM, a Phase II randomized trial of temozolomide versus procarbazine and a single-arm trial of temozolomide as monotherapy, use response rate as the primary endpoint. Based on a six-person response rate, the ODAC vote rejected the approval for this indication by 11 votes and 1 abstinence.

Temozolomide was granted regular approval in 2005 after confirmation of the drug's clinical benefit was observed in an EORTC trial. 573 patients with newly diagnosed GBM were randomized to receive standard, postoperative

radiotherapy or the same radiotherapy with concomitant temozolomide followed by adjuvant temozolomide. The primary endpoint was overall survival. The median survival was increased by two and a half months in the temozolomide arm.

ODAC met in January 1999 to discuss temozolomide approval and endpoints based on imaging for primary brain cancer. When the majority of the ODAC members agreed with the value of PFS and response rate as valued endpoints in the context of gliomas, the interpretation of the MRI scans, particularly in GBM, was a matter of concern. The interpretation of MRI scans is complicated by the delayed effects on edema of radiotherapy and corticosteroids, which are low. Also of concern is the discordance between MRI results and clinical progression and the discordance between investigator's assessments and independent reviewers.

A consensus was achieved in the need of a significant magnitude of effect likely to outweigh the uncertainties associated with MRI scans. The ODAC members agreed that an independent, blinded review of the imaging and supporting data were necessary. Supported data could include reduction of steroid use or improvement in patients' neurological symptoms.

In January 2006, a Brain Tumor Endpoints Workshop was held by the FDA, the American Association for Cancer Research and co-sponsored by the American Society of Clinical Oncology. This workshop was not a formal guidance advice-seeking meeting.

The panel concluded that patient reported outcomes assessments, although useful for the basis of approval for drugs in other therapeutic areas, are not sufficiently developed to be accepted as the primary ground for approval in brain tumors.

On behalf of the North American Brain Consortium, Dr. Ballman presented data from Phase II GBM trials, analyzing the validity of PFS at six months as a predictor of 12 months overall survival. Although strongly correlated, the consortium findings were limited by the fact that all trials belong to a single comparative group or were non-randomized, and none of the therapies tested were successful. However, the panel's consensus was that PFS at six months is an endpoint that should be studied in clinical trials. FDA believes that such time-to-event endpoints can only be validly assessed in randomized trials.

Regarding composite endpoints, the panel agreed on the prematurity of new imaging techniques, such as PET, as useful markers of disease response or progression. Given the uncertainty about whether imaging changes are clinically meaningful in all circumstances, the panel agreed that it could be helpful if photographic evidence of a therapeutic effect could be complimented by the evidence of functional or symptomatic improvement.

As you can see in the slide, the discussion regarding response rates share the same concerns that the January 1999 meeting raised. Besides evaluation, quantification and reproducibility issues discussed before, a new

problem now complicates the MRI-based assessments. Studies must take into account the expected effect of a drug or device on the underlying principles of the imaging techniques being used or, otherwise, they may be misleading. An example of this would be a drug that changes the permeability of the blood-brain barrier and, subsequently, the gadolinium enhancement, like antiangiogenic agents. Once again, the importance of the magnitude of effect obtained and the correlation with supportive measurements was underscored.

Conclusions. Response rate assessments may be complicated by a drug that has an effect on medical imaging. By modern standards, response rate has not been accepted as a surrogate endpoint for accelerated approval in GBM. And as stated at the Brain Tumor Clinical Trial Endpoint Workshop, few effective treatments exist for primary brain tumors. No systemic therapy is approved for recurrent GBM. The literature from the derived historical controlled data is largely undependable. Evaluation of clinical trials is affected by patient and tumor heterogeneity factors shown to have a greater impact than any given therapy on patients' outcome. Survival is the only clearly accepted trial endpoint.

I will now introduce the next speaker, Dr. Victor Levin. Dr. Levin is a professor of neuro-oncology at MD Anderson Cancer Center. The FDA has asked Dr. Levin to present his preliminary clinical research on the radiographic findings following treatment with bevacizumab in patients with radiation necrosis, arising as a complication following therapeutic radiation

for glioma.

Dr. Levin's presentation will illustrate MRI radiographic changes in the brain in patients receiving bevacizumab that do not represent antitumor activity. Distinguishing these effects of bevacizumab from radiographic evidence of reduction in tumor volume is one of the key issues arising from today's application. Thank you.

DR. LEVIN: Well, thank you very much for this opportunity of presenting this information. Some of it has not been presented before since the study is still ongoing.

What I'm going to do is cover a number of areas, and part of it will have to be a discussion of what represents radiation necrosis, what represents radiation toxicity. There are three forms of radiation injury, which have been known for decades. Acute during the radiation usually responds to glucocorticoids. There's an early delayed or subacute, sometimes called subacute radiation change. That's 2 to 3 weeks to 12 weeks after radiation. Some today call it pseudo-progression. It responds also to glucocorticoid therapy.

The late effects are the ones that occur months to years after radiation therapy, and as late as 13 years in our experience. This leads to blatant necrosis and can be a progressive neurologic disease much like the tumor destroying brain in the process. It's associated with increased capillary leakage and destruction of the CNS parenchyma.

When you look at the onset of radiation necrosis, it appears to have a different onset, slightly different, depending if the tumor is an anaplastic glial tumor, astrocytoma, anaplastic astrocytoma, oligo-astrocytoma, or anaplastic oligodendroglioma, or a glioblastoma, abbreviated here as GBM. Early on, most people will see radiation changes in white matter. Later on, depending on dose and time, of course, you can see necrosis. And it can be as much as 55 percent in one of our studies where we pushed radiation and chemotherapy during radiation.

A typical case is seen here. The patient's doing well, and then all of a sudden, eight months after irradiation, the patient presents with the first lesion. Eight weeks later, the lesion grows, and you'll see another lesion near a ventricle, which is common for the condition. And the lesion, which is basically a tumor, but it's radiation necrosis, not a malignancy, gets larger. We've had patients like this literally die of radiation necrosis. So treating radiation necrosis has been a big concern of mine for the last almost four years in my practice -- four decades of my practice.

Let's look at injury. Early injury is not a big problem. The late injury and the imaging issues associated with it are important. For the most part, we can make many of our diagnoses based on the gadolinium T1-weighted image and/or with the gadolinium T2 FLAIR image. We see evidence of leakage, of capillaries to the gadolinium. We see a disproportionate increase in the amount of T2 FLAIR edema. We also see a pattern with contrast that has been

described as soap bubbly or Swiss cheese. So it's more of an observation and a view than it is of a mathematical paradigm at this time.

In the process and in the study of it, we've all been perplexed over the years. We've looked for chemical agents. We've looked for gene abnormalities. Everything has been looked for because it's a progressive problem, and very little has come up. We know that there are events associated with apoptosis, adhesion molecules. But I think more than anything else, the study that I'm going to show you, and our understanding of signaling and protein production in cells that are at risk, would indicate that the production of VEGF is probably really important.

In the nervous system, many states, such as Parkinson's disease, whenever you get neuronal damage, the ascites nearby seem to produce VEGF to protect the neurons. Also, as you know, hypoxic tumor cells will produce VEGF to produce new blood vessels. And I think that this, more than anything, is accounting for some of the capillary leakage and the setting up of this vicious circle of leakage, material coming into the brain, being foreign material, being reacted to, and causing more and more and more damage.

The clinical symptoms from radiation necrosis are basically devastating. Depending on the irradiated site, depending on the extent of the damage, we can have neurocognitive slowing, we can have fatigue, dementia, focal weakness, behavioral problems, hormonal dysfunction, and, yes, death. Spinal cord can lead to growth arrest in children, can lead to cardiac

problems in children, and can lead to myelitis, causing weakness, paresis and pain. It's very, very troublesome and very frustrating for those of us who take care of these patients everyday.

The treatments historically have been very, very poor and almost impossible to document. We all use glucocorticoids, anticoagulants have been tried, hyperbaric oxygen, high-dose vitamins, anti-inflammatory agents. You name it, we've all tried it, and none of it has seemed to work well. Then came along bevacizumab and a small trial that we did, where we were trying to understand how to use the drug. So it wasn't like we were on a protocol; we had access to the drug. Insurance coverage allowed it, and we put patients on a variety of different treatments, trying to understand how to use bevacizumab.

In the process, we came across eight patients whose "tumor" was really more radiation necrosis than it was tumor. So from this group, we picked out the patients, and they had astrocytic tumors; they had glioblastoma; they had an oligodendroglioma; and a couple of them even had biopsies. And from this study, we realized that we could see patterns quite like this, where you have contrast enhancement in sort of a soap bubbly appearance, and after the bevacizumab, it gets better. So this is one of the patients in that study.

Here's a glioblastoma patient, which is a little more difficult because glioblastoma patients, on their own during the growth of their tumor,

will develop necrosis as part of the tumor picture. But here is a case where it was ending up being close to the ventricular system. And, again, it was a more soap bubbly appearance, and with bevacizumab, it responded.

Now, for the sake of learning, there are a lot of criteria that have been and are being constantly upgraded and modified to help clinicians separate out lower grade gliomas, higher grade gliomas, like glioblastoma, and now currently glioblastoma. This is very important as one designs clinical trials.

I darkened these spectroscopy studies a little because the reality is that for the vast majority of cases, we can use conventional, or more conventional, MRI criteria, gadolinium T1, blood flow, which is a measure also of capillary permeability, ADC map. And these are the spectroscopy correlates. And these spectroscopy correlates are not always possible at every institution. And the other problem is that in these lesions, you can go from site to site in the lesion, and one part of it might be blatant tumor and one might be necrosis. So you have to have a very precise understanding of what you're looking at and what it means in relationship to the whole lesion.

These are some of the same cases you've seen, but just look at the left-hand side, and you'll see the dramatic effect that bevacizumab had. What it did is it reduced the T2 FLAIR 60 percent. It reduced the gadolinium enhancement on an average 48 percent. And these were people who were all steroid dependent, and it reduced the dose 8 milligrams.

So this was quite exciting to us. And as a result, we decided there was only one way of finding out how good it really was, and that was to do some kind of a controlled clinical trial. And we were encouraged by CTEP to make it a randomized placebo controlled trial, and that's basically what we did.

So we did a study that had the following criteria. Patients with neurologic symptoms from their radiation necrosis and documented MRI evidence of radiation necrosis would be randomized to either receive the placebo intravenous saline or drug. They would then be followed, and if they had neurologic progression or if their MRI progressed at their first evaluation at six weeks, they could then cross over to the bevacizumab. And that was the design and the intent of the treatment.

The other thing was that given the complexity of dealing with glioblastoma patients and the fact that they did have necrosis, we would not allow them into the study. So we tried to have only the cleanest forms of radiation necrosis, those associated with, say, head and neck cancer, where the temporal lobe might be involved; those associated, say, with angioma; or those associated with a lower grade tumor, where the radiation necrosis is really at a distance.

At the time, we thought that the dexamethasone dosing should be important, and it turns out it's not going to be important in this case. And the patients could be on anticoagulation because many of our patients have to

be as well. They just couldn't have wounds that might break down, surgeries that might be complicated by being on bevacizumab.

You have this in front of you, so I'm not going to go through all the details.

The MRI evaluation turned out to be quite interesting and informative, and we'll see as we go through it. We basically did what can be done in most any facility. We forced coronal, axial and sagittal FLAIRs to get volume measurements. We also wanted to have some measure of permeability or blood flow, and we used a DCE for the dynamic contrast enhancement. And that basically tells us how rapidly things will cross capillaries.

Our endpoints were going to be classic at the time we entered the study. And that is we were going to make bidimensional measurements much like you would for a tumor, and you're going to say the T2 FLAIR is better; contrast is better. And if we had an improvement in T2 FLAIR, we thought that we had a successful study. And we decided a 25 percent reduction was adequate. We were going to treat four times with the bevacizumab, and then we just follow the patients after that. The other thing we did is we did neurological signs and symptoms. We did quality of life measures. We did neurocognitive testing.

The interesting statistics from my perspective was that we assumed that maybe 10 percent of patients would have spontaneous improvement and that the drug would work only about 80 percent of the time. But that gives you a

calculation of a randomized study of 16 patients. As we'll see, the numbers are zero and 1, so we don't really theoretically have to go that far.

The demographics of the patients on study was interesting. And in the process of doing this, when we're doing a lot of head/neck patients, we made a mistake. We had a patient who clinically -- who had improvement in the radiation necrosis, but an orbital lesion got worse, and turned out it was a tumor growing with an associated loculated infection, having nothing to do with the treatment, but we had to drop the patient. Most other patients, we were able to maintain.

Here's a first patient who turns out to be one of the most interesting patients from your perspective, because this is a patient who's going to get randomized to placebo. So here we look at this patient, and the T2 FLAIR volume is 64 squared centimeters, and the contrast enhancement is what you see there. And then the patient goes on to the placebo, and all of a sudden there's a huge increase in the T2 FLAIR because the process is worsening, and the contract is also getting larger.

So we expected to get our patients to six weeks; some did, some didn't. Many patients couldn't make it. They had neurologic progression. We had to break the code usually at three, four weeks. Here's the patient after two treatments with bevacizumab. Dramatic improvement in volume, down to 16, and the contrast also has gone down dramatically. And three weeks after the fourth cycle, it's holding its own in terms of T2 FLAIR, and the contrast is

going down, and this patient never gets worse. And this patient is out about a year now.

So we had a placebo group, and of the placebo group to date -- the study is still open -- there are six patients. And as you can see, a couple of them actually had a reduction in their T2 FLAIR on placebo and they had a variable change in their contrast. All of them had one thing in common, though; their neurologic symptoms got worse and on average they were on six weeks.

Now, we believe that probably 10, 15 percent is within an error of the mathematical volume calculation. When we look at the protocol patients, we see, on average, a 61 percent reduction in the T2 FLAIR -- 59, I guess; 59. Let's go to the median; 59 to 61. About the same thing here with the contrast enhancement. A very dramatic improvement, and it maintains.

Now, we do have side effects. And the problem with treating patients with radiation necrosis and patients who have had tumor is that they're going to have symptoms -- they're going to have conditions that occur that are somewhat related to their disease, possibly related to the treatment.

So in this situation, we had six patients. One had ischemia and worsening visual field. Another had ischemia and hemiplegia. And when I talk about ischemia here, they're basically small vessel strokes. And one patient had pneumonia. We don't worry too much about that. That can happen. And the DVT, or deep-vein thrombosis, also can happen in this patient population just

by chance, and it can be up to 30 percent with some of these high-grade tumors. And we had one patient who developed a superior sagittal sinus thrombosis. You sort of throw up your hands at that because it's such an uncommon occurrence, but then he had a posterior fossa lesion that was irradiated.

So it's hard for us to know, in this small series, how many of these might be treatment related, how many of these are really related to the underlying etiology of the necrosis and the tumor.

So to do a recap, we proposed these endpoints to measure bidirectional distances in the T2 FLAIR. We proposed that there would be a decrease in the T1 contrast and also in the DCE, and we felt that 25 percent reduction would be sufficient.

What we really achieved was something different. One, it turned out it was basically impossible to do hand measurements of the FLAIR changes and contrast, so we ended up having physics people doing quantitative work. We found that none of the placebo patients benefitted. A hundred percent of the treated patients and crossover patients improved. The T2 FLAIR volumes decreased from 23 to 96 percent. The gadolinium enhancement went from 32 to 84 percent. The Chi-squared test was .002, and the study wasn't finished.

We didn't have real good luck with DCE, and I think we'll have to do some work with it. And the problem with it is that you need to have better precision on location for DCE. It can't be just a general measurement

covering the lesion.

All patients had clinical improvement. Glucocorticoid dosing was basically not valuable because many of the patients, since they were deteriorating when we saw them and they knew they were going on study, nobody put them on steroids. So we had very few patients, really, on steroids. You'd only get that if you're treating chronic radiation necrosis without symptoms I think.

We did have some side effects, and some of it we feel comfortable assuming that it's associated with the radiation necrosis, but a larger study would help us determine that.

Our objectives were to see if three-week treatment would work, and it did work. We don't have enough patients to say that the patients showed neurocognitive improvement at this time. That's independent of their neurologic improvement, but my guess is that they will be parallel. But those studies really haven't been completed yet.

The seven and a half milligram per kilogram dose, we used every three weeks was adequate. We even had one patient with the deep-vein thrombosis. We only treated twice, and that patient is still doing fine. And it raises the question to us in our plans and future studies, how little will we have to give to turn off this event.

I think that the conclusion that I draw, and I've been treating these patients for almost 40 years, is this is the first and only treatment I

have ever seen that effectively can treat radiation necrosis. My hope is that we'll put it up front in some of the other situations that produce radiation necrosis, like radiosurgery, and maybe we can nip it in the bud and not produce the extensive necrosis that we see.

My gut feeling is that many of the VEGF-R inhibitors that are coming around today have similar kinds of effects, but I think in the end, they won't work as well because I think turning off the loop of VEGF, causing stimulation, is probably as important or more important than knocking VEGF-R off.

And that's Lake Tahoe. Thank you.

DR. WILSON: Okay. Thank you very much, Dr. Levin.

I'd like to now turn to the sponsor presentation and invite David Schenkein to give introductions.

DR. SCHENKEIN: Good morning. Thank you, Dr. Wilson, Committee members, FDA representatives, and guests. I'm David Schenkein with the Clinical Hematology Oncology Group at Genentech. And we'd like to thank the Food and Drug Administration for the opportunity to present today to the Oncology Drugs Advisory Committee in support of Avastin as a single agent for the treatment of patients with previously treated glioblastoma. We'd also like to thank the members of the Committee for their careful consideration of this topic and the patients who participated in the studies which support this BLA supplement without whom this work would not have been possible.

Our objective today is to obtain accelerated approval of Genentech's supplemental BLA for Avastin, as a single agent for the treatment of patients with previously treated glioblastoma. Following the cloning of vascular endothelial growth factor, VEGF, and discovery of an anti-VEGF antibody, known as Avastin, at Genentech, a broad development program for Avastin was initiated. Avastin is highly specific for the VEGF ligand and has validated the concept of antiangiogenesis in cancer therapy.

It is estimated that over 370,000 patients worldwide have received Avastin since its initial approval. This clinical validation comes from numerous settings. Avastin is currently FDA approved in both first and second-line colorectal cancer, in first-line, non-small cell lung cancer, and recently received accelerated approval in first-line metastatic breast cancer, all in combination with chemotherapy.

Today, our focus is on patients with relapse glioblastoma, who urgently need effective therapies. These patients have a rapidly progressive downward spiral course after diagnosis, and for most patients is universally fatal. There are approximately 10,000 patients afflicted with this disease per year in the United States. Currently, these treatments are largely ineffective and associated with significant morbidity. For patients with relapse disease, the survival is typically measured in weeks, and many patients are not offered additional therapy.

There is strong scientific rationale for exploring the utility of

Avastin in glioblastoma. It is well known that these tumors are highly vascularized and express high levels of VEGF. This figure shows expression profiling for VEGF mRNA in both normal and tumor tissues. You can see the signaling glioblastoma samples, as shown in the red box, is notably stronger than in the other tumor types, with the exception of renal cell carcinoma, another tumor where Avastin has shown promising single-agent activity. In the bottom figure is an in situ hybridization of VEGF in a glioblastoma sample from a patient, and you can see the strong expression of VEGF within the actual tumor.

As shown in this time line, a series of small, investigator-led trials suggested activity of Avastin in patients with relapse glioblastoma. These data led us to design a comprehensive development program to fully assess both the safety and efficacy of Avastin in patients with this disease. This plan included both a Phase II trial in relapse patients and a Phase III randomized trial in newly-diagnosed patients.

Now, as the Phase II study was starting, the FDA informed Genentech that using this study to serve as the basis for approval in glioblastoma was problematic with respect to both the lack of a control arm and the endpoints. We're here today because the results from this Phase II study were sufficiently compelling to warrant the follow-up discussion with the FDA. That discussion resulted in an agreement with the FDA on a path to approval with this trial. We remain committed to our original development plan and

will soon initiate a large, randomized, Phase III, placebo-controlled trial in newly-diagnosed patients with glioblastoma. This confirmatory trial is expected to read out its final results in 2014.

As you well know, the accelerated approval mechanism was designed to speed availability of promising new agents in areas of high, unmet medical need, and as a consequence, require a different bar than for full approval. To satisfy the requirements outlined within the accelerated approval mechanism, we need to demonstrate that the effect observed with Avastin in these patients is reasonably likely to predict clinical benefit.

We do believe that there are two central issues that will dominate today's discussion: to demonstrate that the changes observed on MRI are evidence of clinical activity and that the response rate is substantially higher when compared to historical controls and of sufficient magnitude to support accelerated approval.

We're confident that we have met the criteria for accelerated approval based on the totality of the data within this application. Key elements of this claim include that Avastin led to a high rate of durable responses using conservative and state-of-the-art imaging and review methodology; that all of the secondary and exploratory endpoints point in the same direction as the primary endpoint, including a landmark analysis that suggests that response may predict improved residual overall survival; and that we have data from a second cohort from this study and an independent

study conducted at the National Cancer Institute with very similar supporting data. Finally, we will also show that the response rate and progression-free survival at six months are substantially higher than from historical controls of approved or novel agents in this disease.

Today's agenda is shown on this slide. Given the relative infrequency of applications in this disease, we've asked Dr. Gregory Sorensen from the Radiology Department at Massachusetts General Hospital to spend a few minutes reviewing some issues around imaging in glioblastoma, prior to a full review of the data from this application by Dr. Julie Hambleton from Genentech. Dr. Michael Prados from UCSF will then place this data in the context of the historical controls, and then I will return to conclude the presentation.

Let me mention that Dr. Prados was an investigator in the Genentech Phase II trial of Avastin to be discussed today. In addition, the following experts will be available for questions during the discussion period. I want to thank you for the opportunity to present to you today, and we look forward to your thoughts and questions at the end of the presentation.

Now, I would like to introduce Dr. Gregory Sorensen from the Radiology Department at Massachusetts General.

DR. SORENSEN: Thank you very much, David.

Hello, everyone. My name is Gregory Sorensen. I'm a neuroradiologist at MGH. My remarks today have two parts. First, I'd like to

briefly review how we image brain tumors from a clinical perspective, including how we determine treatment effects in a clinic and how imaging is used in clinical trials to determine treatment responses. Second, I'd like to discuss some of the specific features and challenges of imaging glioblastoma after treatment with anti-VEGF therapies, such as bevacizumab.

A comment method of radiographic tumor assessment is MR imaging before and after the administration of a contrast agent containing gadolinium. The contrast agent leaks out in areas of blood-brain barrier breakdown, and is shown as bright signal on T1-weighted imaging as indicated by the yellow arrow. These areas of blood-brain barrier breakdown are associated with the highest grade tumor and are typically the target for surgery or radiation therapy. Thus, it is not tumor directly, but rather its effect that we visualize.

With MRI, we can acquire images either as two dimensional slices or as a three dimensional volume, which we can rotate around to see the full extent of enhancement. In addition, there are secondary signs of the presence of tumor with mass effect seen as gyral effacement, here highlighted by the pink arrow, compression of the frontal horns of the lateral ventricles are highlighted by the green arrow, and some midline shift here highlighted by the orange arrow. Generally, but not always, imaging findings such as midline shift or compression are associated with marked neurological symptoms.

Tumor can also be detected by the presence of vasogenic edema. This

edema causes a bright signal on T2-weighted MRI as indicated by the yellow arrow here. Again, rotating through the volume can show the full extent of the T-2 abnormality, FLAIR images. And FLAIR is short for fluid attenuated inversion recovery imaging. It's a type of T2-weighted MRI that suppresses the cerebral spinal fluid, the CSF, in order to allow improved discrimination of tumor related abnormalities. FLAIR abnormalities, as highlighted in this glioblastoma patient by the green arrow, are thought to represent a mixture of edema, tumor cell infiltration, and reactive changes. And tumor is known to microscopically extend in most patients even beyond the FLAIR abnormal areas.

So we in neuroradiology are constantly working to find better ways to image brain tumors; however, these remain experimental. At the current time, the state-of-the-art for multicenter trials are post-gadolinium T1-weighted MRI and T2-weighted MRI methods, such as FLAIR. And that is what was done in the Phase II trial that you'll be hearing about. Unfortunately, we have very few effective therapies for glioblastoma. And, typically, even after resection for recurrence, the tumors grow until the patient's demise, as shown here.

This example from my own files shows a set of coronal images taken over a six-month period that demonstrate how a typical recurrent glioblastoma behaves. As you can see, the area of enhancement is enlarging and the effect on the rest of the brain is worsening. In this case, we would say that whatever therapy this patient is undergoing, there's not much biological

effect visible.

Now, the neuro-oncology community is actively performing many clinical trials, and almost all of these use imaging to assess the effectiveness of new therapies against glioblastoma. The Macdonald response criteria are the most commonly used criteria in modern glioblastoma trials, and they're essentially the WHO criteria adapted for brain tumors. From a clinical perspective, we know that boosting steroids can decrease the gadolinium enhancement of a tumor for a few days and after a change in dose. As a result, the Macdonald criteria incorporates steroid dosing information explicitly.

For example, a partial response requires 50 percent reduction in the size of enhancing lesions compared to baseline and stable to decreased steroid dosing. Complete response requires the disappearance of all lesions and no accompanying steroids. All responses are to be confirmed at least four weeks later, something that is frequently not adhered to in academic trials but was in this Genentech study that you'll hear about.

Neurological symptoms are often included in the criteria for objective response, but these can be quite subjective from one neurologist to another neurologist, and sometimes have high variability when included in a clinical trial design. Progressive disease occurs if there is more than a 25 percent increase in the size of the contrast enhancing tumor or if there's any new tumor enhancement evident. In most trials, non-enhancing lesions are not

taken into account; however, with the onset of anti-VEGF therapies this is changing. And the Genentech study explicitly included non-enhancing lesions as part of the criteria for progressive disease.

Finally, these criteria ideally should be applied using a centralized review team, where the team can be isolated from any bias that the local investigator might have due to knowledge about the patient or the treatment.

So now I'd like to turn to the second part of my comments, how do our imaging methods work for the therapy under consideration today, bevacizumab. Well, this is an issue because bevacizumab has some of the same impact on MRI that steroids have; namely, a rapid decrease in gadolinium enhancement, as early as the first day after administering the drug. It seems unlikely that all of this change on day one could be due to an anti-tumor effect and might instead be due to an impact directly on the mechanism of enhancement. How could that be?

Well, you may recall that VEGF, or vascular endothelial growth factor, is also known as VPF, vascular permeability factor. So blocking VEGF means blocking permeability as bevacizumab should do as part of its mechanism of action. Therefore, if we block permeability, we should actually see a decrease in gadolinium enhancement. And so, this is actually evidence of bevacizumab's biological activity.

Still, how do we know that these changes aren't just a steroid like

effect, and how might we modify our response criteria? Well, in some ways, our criteria are already prepared for this, but in other ways we can make modifications. First, steroids have a transient effect, both clinically and radiographically. Steroids do not provide a durable response. By insisting on confirmation a month later of any response, we can be more confident that the changes are clinically meaningful.

Second, a fading of the enhancement might not mean a decrease in the tumor size, so our central readers are trained to measure and include even faint enhancement, not just strong tumor enhancement.

Third, we can look at other images, such as the T2 or the FLAIR images. This is particularly important not just to assess positive response, but also to ensure that there are not unusual modes of progression, such as new lesions that are not enhancing.

Finally, we can look for secondary features, such as changes in mass effect, midline shift, and so on, that can help us feel more confident that the changes we are seeing might truly represent a tumor reducing effect, although we in the field are still working on methods to actually quantify these sort of secondary features.

So the Phase II study of the Genentech design did incorporate these more conservative features into the central radiology review.

So I'd now like to finish by showing you some examples from Genentech's Phase II study that you're going to hear about and which

demonstrate three types of tumor behavior: non-response, response, and then progression based not on increased enhancement, but instead based on an increase in the non-enhancing disease, typically changes in the T2-weighted images, the FLAIR images.

So this example includes MRI scans from a patient who did not respond to bevacizumab. On the top row are the T1-weighted images at baseline and at six weeks, showing the enhancing tumor in the left temporal lobe, which grew substantially over the time course. On the bottom row are the FLAIR images that also indicate tumor growth. So patients in this study whose best overall response was progressive disease had patterns similar to this: steady growth consistent with the history of disease.

This example is one of a durable radiographic response as determined by the independent radiologic review. At baseline, you can see a contrast enhancing mass in the left putamen, highlighted by the yellow arrow, with extensive surrounding changes seen on the FLAIR images. That's in the bottom row. I didn't put an arrow in.

Tumor mass effect is noted by the presence of subtle midline shift, highlighted by the orange arrows, and ventricular compression by the green arrows. Following treatment with bevacizumab, there's a decrease in the tumor size and extent of edema and a decrease in the tumor infiltration seen on the FLAIR images. Improvements in mass effect are also noted by the decrease in midline shift and decrease in ventricular compression.

So these improvements persisted through week 36 of treatment, and then at week 36 of treatment, a small new area of enhancement was noted by the central review team and progressive disease was called. That's in the red arrow.

This patient shows a decreased tumor burden both on the T1-weighted and the FLAIR MRI scans and was deemed a partial response. But again, at week 36, progressive disease was determined, in this case, on the basis of a new, non-enhancing lesion, best seen on the FLAIR images as highlighted by the red arrow on the lower row.

So in summary, our current best clinical practice in multicenter studies is to perform T1-weighted, post-gadolinium MRI and T2-weighted MRI, such as FLAIR imaging. While neither of these show the tumor cells directly, both are used to manage patients, including making decisions about surgery, radiation and other treatments.

We know now that bevacizumab changes the enhancement as part of its biological effect. And this certainly is different than traditional therapies. We believe that the best radiographic approach to dealing with this potential confounder is to consider the duration of the response, the size and not just the degree of enhancement, and to look for secondary benefits such as decreases in mass effect.

Thank you very much for your attention. Our next speaker is Dr. Julie Hambleton, medical director at Genentech.

DR. HAMBLETON: Thank you, Dr. Sorensen.

I will now review the study design and data establishing the efficacy and safety from Genentech's Phase II study, which serves as the basis of our sBLA in patients with previously treated glioblastoma.

Study ABF3708 was a multicenter, randomized, noncomparative trial in 167 patients with histologically confirmed glioblastoma in first or second relapse, all of whom had received prior radiotherapy and temozolomide. The study had two objectives. One, to confirm preliminary results from two single-site Phase II studies assessing Avastin plus irinotecan, and two, to test the efficacy of single agent Avastin in patients with previously treated glioblastoma. No chemotherapy control arm was included due to low activity seen with available options, including irinotecan. We also sought to maintain a moderate sample size in this proof-of-concept Phase II study.

Eighty-five patients were randomized to Avastin, 82 patients were randomized to the combination therapy. Patients receiving Avastin were given the option to receive combination therapy at the time of disease progression. The study was conducted at 11 academic sites in the United States with site monitoring and a hundred percent source document verification of data; co-primary endpoints for objective response and six-month progression-free survival, both of which were determined by independent radiologic review. Clinical and tumor assessments were performed every six weeks.

The preliminary results of the trial were reviewed with the FDA. An

agreement was reached that study AVF3708 could serve as the basis of our sBLA. Only the Avastin arm would be considered for efficacy claims, based on objective response rate. In addition, the FDA requested that Genentech obtain the MRI scans from the second study conducted at the National Cancer Institute and to perform an independent, radiologic review of these scans using the same independent review facility or IRF. For safety information, data from both the Avastin and the combination arm would be reviewed.

In my talk, I will provide an overview of our response and progression criteria and the independent review process. I will then present the efficacy data, starting with our primary objective response and finish with an overview of the safety results.

As Dr. Sorensen discussed, we used the Macdonald criteria as listed here. We defined progression as any new lesion, unequivocal progression of non-index lesions, which included non-enhancing disease or FLAIR, at least 25 percent growth of index lesions, or clear clinical deterioration in the absence of radiographic progression.

Our criteria were more conservative than most previous trials in relapse glioblastoma for the following reasons. One, non-enhancing disease on FLAIR was assessed as non-index lesions and incorporated in the assessment of progression. All responses required confirmation at least four weeks later, and we used a third party radiology facility to perform independent review of all scans.

The independent radiologic review was a standard objective and blinded assessment of radiographic endpoints conducted by trained neuroradiologists who followed a charter that had been reviewed and approved by the FDA. All but one MRI scan in the Avastin arm was reviewed by two neuroradiologists. The radiologists independently determined date of first response, overall best response, namely objective response, stable disease or progressive disease, and the date of progression. A third neuroradiologist adjudicated the best overall response, progression status and date of progression if discrepancies were noted.

Finally, an oncologist at the independent facility reviewed the radiographic results and corticosteroid dosing to confirm that responders met the Macdonald criteria and were confirmed at least four weeks later.

While efficacy from the combination arm of Avastin plus irinotecan would not be considered for labeling claims, these data will be presented side by side to provide support of information. Key baseline characteristics included a median age of 54 years with the majority of patients being in first relapse. Approximately 50 percent of patients were receiving steroids at the time of study entry.

As determined by independent radiologic review, the objective response rate in the Avastin arm was 28.2 percent with one complete response and 23 partial responses observed. Stable disease was noted in 47.1 percent of patients with a disease control rate of 75.3 percent.

This plot illustrates the change in tumor size for all patients enrolled in the trial. Each vertical line represents the largest percent change and by dimensional tumor measurement from baseline in a patient. The yellow lines represent patients who had a confirmed response by IRF. While a small minority of patients progressed quickly, the vast majority of patients receiving Avastin experienced some tumor shrinkage. The horizontal line shown at minus 50 percent indicates the reduction in bi-dimensional measurement required to demonstrate a partial response, which then confirmed confirmation and a follow-up scan and decreased the stable dosing of steroids.

To view response rate by IRF and investigator, this biograph displays the response rate by IRF of 28.2 percent in the Avastin arm and a 41.2 percent as determined by investigator. As seen in other clinical trials using independent radiologic review, objective response rate was lower when determined by the IRF compared with that determined by investigator. The FDA agreed with the IRF on objective responses in 22 of 24 patients in the Avastin arm.

Now, let's look at duration of response. For those patients in the Avastin arm with a response determined by IRF, the median duration of response was 5.6 months, with a range of 1.4 to 11.1 months. The duration of response as determined by investigator was eight months. FDA determined duration of response was 4.2 months, one tumor assessment earlier.

What will be shown here is the time on Avastin therapy and duration

of response for the 24 patients in the Avastin arm who experienced a confirmed response by independent review. Four patients had a duration of response longer than six months, as depicted by the solid white lines. Twelve patients had a duration of response between three and six months, and eight patients had a duration less than three months.

You'll note, most responses occurred at the first or second tumor assessment. The patients also had onset of response at the third or fourth assessment, suggesting the mechanism of response to Avastin is more than impact on vascular permeability alone. Thirteen patients remained on treatment at time of data cut-off and two remained on therapy at least 10 months later at the time of our safety update. The two patient numbers highlighted here in yellow denote those two patients not considered responders by the FDA. One of these patients was on Avastin at the time of data cut-off without evidence of progression by either IRF or investigator.

To lend further support to the objective response endpoint, additional outcomes were assessed. The progression-free survival at six months, an important indicator of tumor stabilization, was 42.6 percent in the Avastin arm by investigator. The PFS-6 rate was similar to that determined by the independent review. The median overall survival of those patients randomized to the Avastin arm was 9.3 months with nearly 38 percent alive for more than one year. All surviving patients in the Avastin arm were followed for more than 16 months.

To address the question of whether the objective responses observed by MRI in this study were likely to predict overall survival, we performed an exploratory analysis of overall survival in responders and non-responders, similar to an analysis presented last year at the Society of Neuro-Oncology meeting. There are two well-known challenges with this type of analysis, survivorship bias and selection bias, which were addressed in the study using standard analysis techniques. Specifically, landmark analysis of residual survival in responders and non-responders beyond 9, 18 and 26 weeks were performed, accounting for possible differences in baseline prognostic characteristics.

These analyses demonstrated a significant association of objective response status and residual survival at 9, 18 and 26 weeks. The hazard ratio at all landmark time points was approximately 0.5 with significant P values. These results indicate that responders were approximately half as likely to die within a given time period compared with non-responders, thus supporting the hypothesis that objective response, based on independent review, was a predictor for survival in this study.

Additional supportive data included the exploratory analysis of neurocognitive function. Three domains were measured by six objective, valid tests of memory, visual motor scanning speed, and executive function. These domains were assessed every six weeks by trained test administrators.

The Reliable Change Index was used to examine change in

neurocognitive function from baseline over time in key patient subsets on the Avastin arm. For the 24 responders, 75 percent were stable or improved in all neurocognitive function tests at the time of IRF documented response. For those 27 patients who were progression free at six months, 70 percent had stable or improved neurocognitive function on all tests at week 24.

When we examined neurocognitive function at the time of investigator determined progressive disease, 69 percent of patients declined on at least one neurocognitive function test. Although these are exploratory analyses, we believe the neurocognitive function data lend additional support to the objective response and progression-free survival endpoints.

For these next two slides, we'll focus on the NCI study. As requested by the FDA, MRIs from a separate Phase II study, conducted by Dr. Fine at the National Cancer Institute, were subjected to the same independent review by the same facility for determination of response rate. All patients were previously treated with radiotherapy and temozolomide and received single-agent Avastin. PFS-6, as determined by investigator, was the primary endpoint of this trial. Objective response rate was secondary. Tumor and clinical assessments were performed every four weeks.

Shown here side by side are the trial results from both the investigator, which includes data published on 48 patients, and an independent review of 56 patients, a total that incorporates data from an additional eight patients. In the single-site study, the response rate was 19.6 percent as

determined by independent review and 35 percent as determined by investigator. Note, an additional three patients had a confirmed response by IRF that was not included in the overall rate because the confirmation scans were done one, two and five days prior to the four-week cut-off. The FDA agreed with all the IRF determined responses in this trial.

Now, we'll review the safety in this study, which is described in more detail in the briefing book. The safety profile in this study was consistent with that seen in other tumor types, and there were no new safety signals identified. Patients included in the safety analyses were those who had received at least one dose of Avastin.

Clinical progression was the cause of death for the vast majority of the 79 patients who had died during treatment and follow up. There were five deaths not related to clinical progression that were attributed to neutropenic infection, pulmonary embolism, complication due to surgery, seizure and clinical deterioration. One patient developed a retroperitoneal hemorrhage more than 30 days after study treatment and expired in the setting of disease progression.

When assessing adverse events that led to Avastin discontinuation, four patients experienced four adverse events of any grade that led to Avastin discontinuation in the Avastin arm. These events were CNS hemorrhage, myocardial infarction, neutropenic infection and adenocarcinoma, an event diagnosed after one dose of Avastin. In the combination arm, 14 patients had

adverse events that led to discontinuation of Avastin and are listed here.

Patients with glioblastoma suffer from considerable morbidity due to their underlying disease and associated treatment related complications. In this trial, adverse events of any grade were reported in the majority of patients treated. Serious adverse events were reported in 26.2 percent of patients in the Avastin arm.

To provide a comprehensive overview of Avastin associated adverse events in this trial, we present the pooled safety data from the Avastin arm, combination arm and post-progression experience. Avastin associated adverse events summarized here are consistent with event rates noted in our product label. Adverse events of special interest in patients with glioblastoma include craniotomy wound-healing complications, CNS hemorrhage, venous thromboembolic events and seizures. The rates of these events were generally within the range reported in the literature in patients with glioblastoma and are consistent with the rates observed in Avastin treated patients in other tumor types.

In closing, study AVF3708 was a well conducted, multicenter trial that demonstrated clinically meaningful activity of Avastin in patients with previously treated glioblastoma. The objective response rate, as determined by independent review, was 28.2 percent with a clinically meaningful median duration of 5.6 months. This activity was supported by the independent review of a second trial conducted at the National Cancer Institute. The activity of

Avastin in this setting was further supported by a PFS-6 of 42.6 percent, a one-year survival of 37.6 percent, stable neurocognitive function in responding patients and data from the combination arm.

Regarding safety, Avastin was generally well tolerated and the safety profile was consistent with that established in other tumor types. Importantly, there were no new safety signals to suggest additional safety concerns regarding Avastin use in patients with previously treated glioblastoma. The totality of these data give us confidence in the activity of Avastin in this disease. Thank you.

I will now introduce Dr. Michael Prados, neuro-oncologist at the University of California, San Francisco, and project leader of the North American Brain Tumor Consortium.

DR. PRADOS: Thank you, Dr. Wilson and members of the Committee. I appreciate and I welcome the opportunity to briefly speak to this panel about recurrent glioblastoma and my thoughts about this specific application.

Since I came to UCSF in 1985, I've spent my entire clinical and academic practice treating patients with this disease, and I'd like to share my perspective both as a clinician and as the project leader of a multi-institutional consortium, the North American Brain Tumor Consortium, that has conducted clinical trials for this patient population over the last 15 years.

I use this slide frequently trying to describe the clinical setting in a typical patient seen everyday in our clinic. This patient has already

been treated wit surgery, radiation and temozolomide, the standard of care. Despite that, there remains a progressively enlarging necrotic, heterogeneously-enhancing mass in the right frontal lobe with edema and pressure effects on that frontal lobe.

A patient like this would typically have seizures and, thus, the need for anticonvulsants; typically would have headaches, requiring the uses of high doses of steroids; would have difficulty with concentration and memory, impacting his activities of daily living and interactions with his family and his friends; and likely a significant loss of independence, with the need for extensive support by his family and caregivers. More importantly, this is a patient who faces early death, typically within four to six months.

Most of the patients I see in this setting are in their mid-fifties, often at the peak of their productive lives with a young, growing family. This clearly is a devastating disease impacting the very identity of patients. It's very difficult emotionally for families and caregivers, as well as for all of us as physicians, trying to sort out what to do next to treat our patients.

Over the years, there's been modest progress, including the use of better imaging with MR, which you've heard about, and more uniform criteria to assess response to treatment. Unfortunately, the result of this journey has given us only two approved drugs to treat glioblastoma, temozolomide and

Gliadel, in the upfront setting, and only Gliadel in the relapse setting. This is despite years of clinical trials effort and testing of multiple new agents, strategies and combinations. "One important milestone has been the agreement of academic neuro-oncologists on the setting of guiding principles to evaluate new agents in the clinic," publishes the Brain Tumor Clinical Trial Endpoints Workshop, which I'll mention in a minute.

So I think this is one of the most compelling and impressive slides that I can show this committee. This is SEER data covering 1973 to 2005, showing the overall survival of all patients with glioblastoma. The median survival is seven months. What this really represents is what's really happening in our communities, including all those patients who don't get to academic centers to participate in clinical trials, particularly those in the relapse setting. Many never reach us, many never are referred, many are just too sick. We publish our results in clinical trials in a very enriched, highly-selected patient population, but the reality of the disease is seen in these survival data. We clearly have to do better. This is definitely an unmet need.

Because I spend most of my time dealing with clinical trials and trial design, I wanted to spend just a minute describing the consensus at the workshop dealing with design of clinical trials and investigating new agents in brain tumors. Several key features were identified, including the need for central pathology review, rigorous response assessments, and I include

clinical and image-based, with a goal to test drugs and strategies that result in a durable, objective response, leading to an increase in progression-free survival at six months. This is a target that has been felt reasonable by the neuro-oncology community and is one of the most common endpoints used in our field. Ideally, this would translate into improved survival in the context of agents that would not lead to excessive toxicity and would enhance quality of life.

So let's look at what we've achieved over the last 20 or so years in this setting. This slide summarizes the collective results of many groups during clinical trials in relapse glioblastoma. Some are older trials, some are more recent, but are all clearly representative of the results using chemotherapy in recurrent disease. The main point of this slide is that the typical response rate is between 4 and 7 percent. The six-month progression-free survival is between 10 and 20 percent. Median survival is about six months, and survival at 12 months is typically around 25 percent.

So let's contrast that with the data in the current study, which shows a substantial improvement in each of these outcome parameters. I think it's important to emphasize that all of the endpoints have improved, not just one or two relative to these trials. Everything points to an agent that seems to be having an important biologic effect. Because I was a project leader of the NABTC, I wanted to spend just a few moments on those trials in particular.

This represents a summary of NABTC trials in a subset of 142

patients who previously had been treated with radiation and temozolomide prior to enrollment in our protocols. This will be a comparable patient subgroup to the current trial under consideration in this application. One can see that the patient population is similar with a few exceptions. We treated more patients in second relapse, which actually didn't change the overall results, as patients in first or second relapse have similar overall outcomes.

We allowed enrollment within four weeks of the end of radiation therapy compared to eight weeks minimum in the Avastin study. And I think this last part is important given the concern of potential pseudo-progression. The NABTC studies would have been much more likely to have those kinds of patients, yet we still had substantially lower response rates, similar to all of the other historical trials discussed previously.

So I've compared our outcomes with the Avastin study, and, again, we see significant improvement in all of the outcome parameters of response rate: median progression-free survival, progression-free survival at six months, median overall survival, and one year survival. It is just very hard for me to believe that these results are due to a steroid effect or just an artifact of imaging. Neither would have been expected to have a durable effect on progression-free survival and overall survival.

So I just have these final thoughts. I think that the data being presented to this committee are very compelling, particularly in the context of recent experience in our oncology clinical trials. It's very rare to see a

drug reduce tumor burden so much and so frequently and in such variable fashion. The progression-free and the overall survival is impressive and it's very encouraging. The academic community is moving forward with new ideas and strategies for this agent, and patients are looking to us to continue to build upon these results.

From my perspective, the data suggest a biologic effect that translates into better outcome and should be made available to patients with recurrent glioblastoma. I appreciate your time and the opportunity to share my thoughts. Thank you.

DR. SCHENKEIN: Thank you, Dr. Prados.

Based on the information you've heard today and based on the totality of the data, we're asking for accelerated approval for Avastin as a single agent for the treatment of patients with previously treated glioblastoma. This approval will provide important labeling guidance to physicians and help ensure the availability of Avastin in a patient population with a serious and life-threatening disease.

We remain committed to conduct further studies to confirm the clinical benefit of Avastin for patients with this disease. Later this year, we will begin a large, randomized, double-blinded, multicenter, global Phase III trial in newly diagnosed patients with glioblastoma. This study will compare standard of care temozolomide and radiation to standard of care with Avastin.

We are completing the special protocol assessment with the FDA, though we've already agreed on the design and the major endpoints from this study. And this study will begin its enrollment around the action date of this application, but will not read out its primary endpoints of overall survival and progression-free survival until 2014.

As I stated earlier, to receive accelerated approval, our data need to demonstrate that the effect of Avastin you have seen from the Genentech Phase II study and the supporting NCI study is reasonable likely to predict clinical benefit. We spent considerable time in providing data and rationale to address two key issues, that the changes observed on MRI are evidence of clinical activity and that the data are of sufficient magnitude in comparison to the historical controls to predict a positive Phase III study.

We have shown that the responses are durable, using stringent and conservative imaging criteria and independent review. The responses to Avastin have a median duration of 5.6 months by independent review and 4.2 months by the FDA analysis. Thirteen patients remained on therapy at the time of data cut-off, which is quite remarkable in these disease settings. Anti-edema drugs like steroids will improve edema for days, but their effect will not last for months, as we have observed in this trial.

All of the secondary and supporting endpoints point in the same direction as the primary endpoint, giving us confidence in the data. And as required by the response criteria, all of the responding patients have had

either a stable or a significant reduction in their steroid dose with a median dose dropping into the physiologic range. The progression-free survival at six months, the one-year survival, the overall survival, and the neurocognitive function data all support the primary endpoint.

The responding patients appear to have a better outcome than patients who do not respond. The landmark analyses suggest that the objective responses seen on MRI may predict residual overall survival for patients. And we know these analyses have their limitations, but the data suggested is more likely than not that our Phase III study will show clinical benefit. We have two lines of supporting trial evidence, one from the second cohort of this study, which evaluated Avastin and irinotecan, and the second from the independent study conducted by Dr. Howard Fine at the National Cancer Institute.

Let's move to the second major issue of whether the patients have had a better outcome than expected from the historical controls.

As shown in this slide, and as already discussed by Dr. Prados, in the relapse setting, the response rate to new or approved agents, as shown in the left graph, is well under 10 percent. Similar to the response rate, the PFS-6 seen with other agents, as shown in the right graph, is in the 10 to 20 percent range. In contrast, the response rate with single agent Avastin is significantly higher, at 28 percent, by independent review and greater than 40 percent by the investigators. The PFS-6 is also significantly higher than the

historical controls, at 42.6 percent by IRF and 43.6 percent by the investigators. We believe it is clear that the activity of Avastin is substantially higher than other available agents.

In summary, we are confident that the activity we have seen in our study and that conducted by the National Cancer Institute, using both the primary and the supporting endpoints, are highly likely to predict clinical benefit for patients with this devastating disease and, therefore, meet the criteria for accelerated approval.

We thank you for your attention today, and we look forward to your thoughts and questions during the discussion period.

DR. WILSON: I would like to thank the sponsor for the presentation. We will now take a short break, and we'll reconvene at 10 past 10. Also, may I please ask the Committee members to recall that there should be no discussion of the meeting topic during the break, either amongst yourselves or any member of the audience. Thank you.

(A recess was taken at 9:54 a.m.)

DR. WILSON: I'd like to ask Dr. Lee Pai to come up and give the FDA presentation on bevacizumab for previously treated GBM.

DR. PAI-SCHERF: Good morning. My name is Lee Pai-Scherf. I'm a medical officer from the Division of Biologic Oncology Products. This morning I will present the FDA review of the bevacizumab application for glioblastoma multiforme. My colleague, Dr. Shen, will present the statistical analysis.

The proposed indication for accelerated approval is Avastin as a single agent, as indicated for the treatment of patients with previously treated glioblastoma. This slide outlines the topics we will cover this morning.

First, I will summarize the regulatory background with current Avastin approvals and background pertaining to this application. Next, I will review the FDA findings for the two studies submitted by Genentech to support this application, studies AVF3708g and NCI 0064E. I will complete the presentation with a summary of our findings and conclusion. And last, I will present our questions to ODAC.

Avastin is currently approved by FDA for using first and second-line metastatic colorectal cancer in combination with 5FU based chemotherapy. Avastin is also approved for using first-line unresectable or metastatic, non-squamous, non-small cell lung cancer in combination with carboplatin and paclitaxel. Approval for both colorectal and lung indications were based on the results of randomized, controlled trials, showing a statistically significant improvement in overall survival for Avastin in combination with chemotherapy when compared with chemotherapy alone. Avastin in combination with paclitaxel received accelerated approval for first-line metastatic breast cancer with endpoint of progression-free survival.

The following slides will address the regulatory background pertaining to this application.

In May 2006, Genentech submitted protocol AVF3708g to the FDA for special protocol assessment. AVF3708g, as you already heard, is a randomized, open-label, multicentered, non-comparative study for patients in first and second relapsed glioblastoma. Eligible patients were randomized to receive bevacizumab alone or bevacizumab plus irinotecan. Patients who progressed on bevacizumab alone were eligible for crossover to bevacizumab plus irinotecan. The proposed efficacy endpoints were six months PFS and objective response rate.

The FDA provided the following comments in a letter on July 19, 2006. The proposed trial as designed is not adequate to support regulatory approval because there's no internal comparison for the primary efficacy endpoint of PFS at six months. The effect of bevacizumab is not isolated in the bevacizumab plus irinotecan combination arm.

The FDA has not accepted a PFS at six months as an endpoint supporting accelerated approval in this disease. Genentech was asked to provide data from controlled clinical trials to support the assertion that effects on PFS at six months is likely to predict an effect on overall survival in support of a request for accelerated approval in an adequately designed trial.

In January 2008, a meeting was held to discuss the preliminary results of AVF3708g and the design of a proposed controlled study. Genentech proposed to submit an sBLA to request accelerated approval for relapsed GBM

based on the results of the AVF3708 study, which showed a significant higher PFS and response rate compared with historical controls. FDA informed Genentech that their proposal was not acceptable, as time-to-event endpoint must be evaluated in randomized, controlled clinical studies, as historically controlled trials do not provide direct evidence of treatment effect.

Further, FDA noted that questions regarding potential surrogate endpoints in GBM are still unanswered, as discussed at the January 2006 workshop on Brain Tumor Clinical Trial Endpoints. However, FDA would consider the results of AVF3708g to support accelerated approval of bevacizumab monotherapy based on evidence of a clinically meaningful and durable objective tumor response. Response would have to be determined by an independent radiologic review.

In addition, Genentech was asked to obtain and submit data from the single-arm, single-center study conducted at NCI by Dr. Howard Fine to support the application. Genentech should propose a confirmatory trial designed to demonstrate clinical benefit. The study should be ongoing and performed with due diligence at the time of regulatory action.

In September 2008, a pre-sBLA meeting was held. Agreement was reached on the content of the submission and the study designed for the confirmatory study.

In November 2008, Genentech submitted a proposal for the Phase III randomized, controlled study designed to demonstrate clinical benefit of

Avastin in patients with GBM. The study was submitted under special protocol assessment. AVF4396g or BO21990 is a Phase III randomized, placebo-controlled study of bevacizumab in combination with radiotherapy and temozolomide for first-line GBM. The study is to be conducted by Roche Worldwide; 920 patients with newly diagnosed will be enrolled. The study has two co-primary endpoints, overall survival and progression-free survival.

A special protocol assessment agreement letter was issued to Genentech on December 29, 2008. The sBLA agreement letter was issued with the understanding that for U.S. regulatory purposes, overall survival will be the primary regulatory efficacy endpoint. sBLA 125085-169 was submitted on November 2008 and is the subject of this ODAC meeting. The supplement is supported by two single-arm studies, AVF3708, sponsored by Genentech, and the NCI study.

I will move on now to the FDA findings. The clinical study design for the study, AVF3708g, has been previously presented and I will not repeat at this time.

Major eligibility criteria are shown on these slides. Adult patients were histologically confirmed. GBM in first or second relapse were eligible. Patients must have received prior standard radiation treatment for GBM and prior temozolomide. Patients must have radiographic evidence with progressive disease following prior therapy with bidimensional measurable disease. If the subject was on corticosteroids, the dose must be stable or

decreasing for five days or more prior to the baseline MRI.

Eligible patients must have KPS more or equal to 70, adequate organ function. Patients with comorbid conditions that preclude use of bevacizumab, such as uncontrolled hypertension, significant peripheral vascular disease, wound-healing complications, and other conditions were not eligible for the study. Patients must have recovered from effects from prior chemotherapy, surgery and radiation therapy. Surgical resection must have been performed more than four weeks prior to study entry, and eight or more weeks must have elapsed since last radiation therapy.

Here, for this last study criterion, the FDA notes that it is well recognized that immediate post-radiotherapy changes in malignant glioma can mimic tumor progression. It is current practice by separate cooperative groups, including NCCTG and EORTC, that patients with progressive lesions within three months after radiotherapy not be entered in clinical trials. The three-month interval between RT and initiation of protocol therapy is to minimize the potential for the MRI changes related to prior radiotherapy being misdiagnosed as progressive disease.

As previously stated, the primary regulatory efficacy endpoint for this application is objective response rate determined by independent review. FDA's primary review focus is on the objective response rate and duration of response for the bevacizumab monotherapy arm. Objective response was assessed by an independent review facility using MRI performed at baseline and every

six weeks until disease progression. Tumor response was determined by using modified WHO response criteria, taking into consideration corticosteroids used. Adverse events were coded by MedDRA and grading based on NCI CTC Version 3.0.

The study was conducted by Genentech at ten U.S. investigation sites. From January 2006 through September 2007, the study enrolled 167 patients, 85 in the bevacizumab alone alarm and 82 in the bevacizumab plus irinotecan arm. The ten investigational centers, the principal investigators and their accrual are shown in this slide. Four centers, UCLA, UCSF, Dana-Farber, Duke University centers, enrolled the majority of the patients.

Patient disposition is shown in this slide. In the bevacizumab monotherapy group, 53 patients progressed after bevacizumab monotherapy. Of those, 44 were crossed over to the treatment with bevacizumab plus irinotecan on progression, three patients were removed from study due to serious adverse events, two patients withdrew consent, 22 patients were receiving bevacizumab, and three patients died.

Patient demographics and baseline characteristics are shown in this slide. In the bevacizumab group, 68 percent of the patients were male. The median age was 54; 91 percent were Caucasian; 45 percent of the patients had KPS 90 to 100 percent. Half of the patients were on corticosteroids at baseline. And as you can see, patients enrolled in the bevacizumab and irinotecan arm have similar characteristics.

Concerning prior therapy, all patients received prior radiotherapy, temozolomide and surgery. The primary surgical resection, 49 percent of the patients underwent partial resection, 42 percent had complete resection, and 8 percent had biopsy only. Eighty-one percent of the patients were enrolled in this study after first relapse.

Patients were enrolled in the study based on the initial diagnosis from the local pathology. An independent central pathology review was performed following accrual of all patients. As shown here, GBM was confirmed in all but two patients. One had anaplastic astrocytoma and one patient's diagnosis could not be confirmed due to missing baseline slides.

Overall, the study was well conducted with a small number of eligibility violations and protocol deviations. Two patients did not meet eligibility criteria and seven patients received bevacizumab dose that differed more than 5 percent from protocol specified dose. Tumor assessment was satisfactory with minimal missing data. One patient had missing tumor assessment by investigator at week 18, and three patients had missing assessment at week 36. All MRI scans, except one scan for one patient in the bevacizumab arm, were available for review by IRF.

Dr. Yuan Li Shen will now present the efficacy findings and the statistical analysis for this trial.

DR. SHEN: Good morning. My name is Yuan Li Shen, statistical reviewer for this application. I'm going to present the efficacy results for

study AVF3708g.

Here is the summary of statistical issues that we have identified. First, this is a single-arm trial; no comparator arm was included. Second, time-to-event endpoint must be evaluated in randomized controlled trials to be interpretable. Historical controlled trials do not provide direct evidence of treatment effect. Third, FDA has not accepted response rate in six-month PFS as endpoint supporting accelerated approval in glioblastoma. Currently, there are no data from controlled clinical trials to support the assertion that treatment effect on response rate and PFS as reasonably likely to predict overall survival.

As Dr. Pai-Scherf stated earlier, for regulatory purposes, the primary efficacy endpoint is an IRF determined objective response rate for the bevacizumab monotherapy arm. The secondary endpoint is duration of response. Objective response is defined as a response of CR or PR, based on modified WHO response criteria, which incorporates corticosteroids used. MRI response must be confirmed at two consecutive assessments greater than or equal to four weeks apart. Complete response requires disappearance of all lesions, determined by MRI.

The corticosteroids used at the time of the MRI scan may not exceed a dose equivalent to 20 milligrams of hydrocortisone per day. Partial response requires a greater than or equal to 50 percent decrease in the sum of the product of the diameters. The corticosteroids dose at the time of the MRI

may not increase from baseline. The baseline corticosteroids used is defined as the maximum does used in the first six weeks from initiation of treatment.

This slide shows Genentech's objective response rate and the duration of the response, based on the IRF assessment. The bevacizumab arm had a response rate of 28 percent, while the bevacizumab plus irinotecan arm had a response rate of 38 percent. The bevacizumab had a median duration of response of 5.6 months, while the bevacizumab plus irinotecan arm had median duration response of 4.3 months. Because the contribution of bevacizumab to the efficacy results cannot be isolated in the bevacizumab plus irinotecan arm, FDA did not perform analysis on this arm. The focus of the analysis was on the bevacizumab monotherapy arm.

Objective responses and duration of responses as determined by study investigator, Genentech and FDA for the bevacizumab are shown on this slide for this application. Genentech was asked to submit all radiographic images from all responders determined by the IRF.

Dr. Erini Makariou, associate professor, neuroradiologist, from Georgetown University Hospital, served as FDA's special government employee for this application. Dr. Makariou reviewed the MRI scans to assess the quality of the images and confirm the objective responses. Objective response rate per FDA's assessment was 25.9 percent. There were no complete responder per FDA's assessment. Median duration of response was 4.2 months. As shown here, objective response rate was reported to be 41 percent by the

investigator, 28 percent by Genentech. Median duration of response was 8.1 months and 5.6 months respectively.

Subgroup analysis of objective response rate by baseline characteristics is shown on this slide. The response rate from most subgroups is very similar to what we observed for the ITT population. However, since some subgroups only had very few patients, such as patients who are 65 years old or older, non-white or a patient who had a second relapse, any interpretation of this subgroup analysis should be made with caution.

Next, I will summarize six month PFS results based on the investigator, Genentech and FDA's assessment. Six month PFS for the bevacizumab treated group was recorded to be 44 percent by the investigator, 43 percent by Genentech, and 36 percent by FDA. FDA's six month PFS finding was different from Genentech due to the use of different cut-off point and different sensory scheme.

I will change the topic now and briefly review post-radiation effect on brain parenchyma. It is noted that all patients enrolled in this study received prior radiotherapy. Some patients were enrolled as early as eight weeks after last radiation treatment. It is well recognized that radiotherapy induced toxicity may mimic recurrent tumor shown as an increase in area of gadolinium uptake on MRI.

As reviewed by Dr. Victor Levin this morning, subacute radiation injury, also known as pseudo-progression, can occur 2 to 12 weeks after

radiation. Late radiation injury or necrosis can occur months to years after treatment. Necrosis leads to increased capillary leakage and destruction of surrounding CNS parenchyma. MRI changes due to radiation injury should not be mistaken for disease progression with this issue in mind.

We looked into the time interval between the end of radiotherapy and baseline MRI in all patients enrolled in the study AVF3708g trial. Of the 84 patients treated in the bevacizumab arm, two patients had missing baseline scan date. Of the remaining 82 patients, 10 percent completed radiotherapy less than three months prior to the baseline MRI; 51 percent completed radiotherapy greater than six months. The remaining 39 percent completed radiotherapy between three to six months.

As an exploratory analysis, we looked into the incidence of responders and non-responders in the bevacizumab treated arm, based on the time interval between the end of radiotherapy and baseline MRI. As shown here, four out of eight patients with time interval between the end of radiotherapy and baseline MRI, less than three months, had objective response; 11 of the 32 patients with a time interval between three to six months had response.

Although, it appeared that there is a small trend of lower responders when the interval is less than six months, due the small sample size and possible confounding factors. Any conclusion based on the data should be made with caution.

Next, I will briefly talk about neurocognitive function test. Neurocognitive function was the exploratory endpoint in this study. Instruments to assess memory, visual motor, scanning speed and executive function are shown on this slide. Tests were performed every six weeks until patients withdrew from study or death.

FDA identified two key issues related to Neurocognitive Function Analysis. First, this is a single-arm study with no comparator arm. Second, the validity and reliability of the instruments have not been demonstrated. FDA agrees with Genentech that any attempt to quantify the results of neurocognitive function should be considered exploratory in nature.

Despite the issues related to the validity of the instruments, in the trial design, FDA attempted to analyze the neurocognitive data for the responders. It is noted that the percentage of patients with missing data for the sixth test at week 24 or earlier ranged from 0 percent to 32 percent. An example of the exploratory analysis is shown on this slide. The plus shows the memory score change from baseline to each subsequent assessment point for the responders. No conclusion can be drawn from this data.

This concludes my presentation on efficacy for study AVF3708g trial. Dr. Pai-Scherf will now present the safety analysis. Thank you.

DR. PAI-SCHERF: I will now summarize the safety findings for AVF3708g. The overall incidence of adverse events is shown in this slide. Almost all patients in the study experienced an adverse event. In the

bevacizumab alone arm, serious AEs were reported in 26 percent of the patients; 46 of the patients experienced a grade 3 or 4 toxicity; 5 percent of the patients discontinued bevacizumab due to an adverse event; and 4 percent of the patients in the bevacizumab arm died due to an AE or other reasons.

The overall incidence of serious AEs and AEs leading to Avastin discontinuation was higher in the bevacizumab plus irinotecan arm. Common adverse events occurring in more than 20 percent of the patients during the planned treatment period are shown in this slide. The most common adverse events, all grades, occurring in patients who received bevacizumab alone were fatigue, 45 percent; headache, 38 percent; hypertension, 30 percent.

Fatigue, nausea, vomiting and abdominal pain occurred at a much higher frequency in the bevacizumab plus irinotecan arm. Side effects are attributed to irinotecan at administration. Epistaxis, a bevacizumab induced adverse event, occurred in approximately 20 percent of the patients in both treatment arms. Serious adverse events occurring with a greater than 2 percent incident on study are shown in this slide. Confusion was the most common serious AE. Other AEs, including deep venous thrombosis, cerebral hemorrhage, diarrhea, pneumonia, hyperglycemia, are also shown here.

This is a rather busy slide, so bear with me as I walk you through. This table includes all bevacizumab induced adverse events from both treatment groups as well as events that occurred during the post-progress crossover phase. Bleeding hemorrhage occurred in 40 percent of the patients, with three

patients having a grade 3 and higher severity. One patient enrolled in the bevacizumab plus irinotecan arm experienced a grade 5 retroperitoneal hemorrhage. Grade 1 to 2 epistaxis was the most common bleeding event, 26 percent. Hypertension occurred in 32 percent of the patients, with 5 percent grade 3 and higher.

Venous thrombotic effect was reported in 8 percent of the patients. The incidence of arterial thromboembolic event, would-healing complications, proteinuria, gastrointestinal perforation, reversible posterior leukoencephalopathy syndrome are also shown in this slide. A neutropenic infection is also a non-bevacizumab induced adverse event.

I show here only the events that occurred in the bevacizumab alone arm; 55 percent of the patients experience infections, or neutropenic infection, with 10 percent grade 3 and higher. Six deaths occurred on study or within 90 days after bevacizumab at the administration. They were not attributed to disease progression; three on the bevacizumab arm and three in the bevacizumab plus irinotecan arm. Causes of that were neutropenia sepsis, pulmonary emboli, complications due to tumor debulking surgery. In the irinotecan plus bev arm, one retroperitoneal hemorrhage, convulsion and clinical deterioration. Review of the case report forms indicated that two deaths were possibly related to bevacizumab, a patient who died of retroperitoneal hemorrhage and a patient on the bevacizumab alone arm who died of neutropenic sepsis.

Next, I'll summarize the FDA findings for the NCI study. NCI 0064E is a Phase II trial of bevacizumab for patients with recurrent high-grade gliomas. This is an open-label, single institution study. Patients with histologically confirmed intracranial malignant glioma and evidence of tumor progression by MRI after radiotherapy were eligible. There was no limit regarding the number of prior systemic chemotherapies.

Eligible patients were entered into two cohorts, high-grade glioma and anaplastic astrocytoma cohort. Treatment consisted of bevacizumab 10 milligrams per kilogram by IV infusion every two weeks on a four-week cycle. Treatment continued until disease progression or significant toxicity.

The protocol study endpoints were PFS at six months, overall response rate and safety. Tumor assessment was performed at baseline and every four weeks until disease progression. The study enrolled patients with high-grade and low-grade glioma, and as per agreement with Genentech, only information for the glioblastoma cohort was to be submitted to support this application.

Patient characteristics are summarized in this slide. From January 2006 through September 2007, 56 patients with high-grade glioma were enrolled. One patient was discontinued from study before receiving treatment. At the time of the data cut-off, 54 patients had discontinued study. All patients had progressed after surgery, radiotherapy and temozolomide; 98 percent of the patients were white, 54 percent male, 75 percent age 41 to 64, and 68 percent

had KPS 90 to 100.

Objective response rate and duration of response information, as determined by independent radiographic review for the 55 patients with GBM, were submitted by Genentech to support this application. This slide shows the objective tumor response as determined by Genentech and the FDA. Objective response rate was 19.6 percent. There were 11 partial responses. Median duration of response was 3.9 months. Dr. Erini Makariou reviewed the MRI scans submitted by Genentech, and Dr. Makariou and the FDA review team agrees with Genentech's findings for this trial.

The incidence of Grade 3-4 bevacizumab-induced adverse events is shown for this study. The most common AE was thrombosis and thromboembolism in seven patients, followed by hypertension, 4 percent. One event each of arterial thromboembolic event, gastrointestinal perforation, and wound-healing complications were reported by the investigator.

Deaths on study. Eight percent of the patients had died at the time of data cut-off date of June 3, 2008 -- 80 percent, sorry -- with 77 percent of the patients dead due to disease progression. One patient died due to pulmonary emboli and CVA, and a second patient had a venous thromboembolic event followed by sudden death.

This slide shows the FDA summary findings. The incidence of bevacizumab-induced adverse events does not appear to be a significant increase in patients with GBM based on these two single-arm studies. As

noted, two deaths in the AVF3708g study were possibly related to bevacizumab treatment. Bevacizumab-induced adverse events of special concern in this population are CNS hemorrhage, wound-healing complications, and venous thromboembolic events. Because these events are also inherent to patients with GBM and associated prior surgery and radiation therapy, the attribution of these AEs to either bevacizumab, or primary disease, or both, cannot be determined with certainty in this single-arm study.

This slide summarizes the efficacy findings for this application. Objective response rate as determined by standard MRI was observed in 25.9 percent and 19.6 percent of the patients in two single-arm studies. Median duration of response were 4.2 months and 3.9 months, respectively. There were no complete responses.

In conclusion, the FDA has two key concerns regarding this application and asks ODAC for advice. First, due to the diffuse and infiltrative nature of GBM histology, anatomical measurement of enhancing tumors on MRI is problematic. Difficulty is even greater for relapse gliomas after surgery and radiation therapy, the target population for this application.

Second, the validity of the objective response as an endpoint to support approval for GBM is further complicated by the questionable relevance of standard MRI response criteria in the setting of VEGF inhibition. Bevacizumab neutralizes VEGF-induced vascular permeability, which stabilizes

the blood-brain barrier, resulting in improvement in edema. This translates into a decreasing gadolinium enhancement on the MRI scan, which should not be taken as anti-tumor effect.

As shown by Dr. Victor Levin this morning, bevacizumab at even smaller doses can reduce radiation necrosis by decreasing capillary leakage. Because radiation necrosis can mimic tumor progression in standard MRI, it is possible that some of the patients enrolled in this study might actually have radiation-induced toxicity that improved with bevacizumab.

In conclusion, it is unclear whether the radiographic improvement accompanied by decreased requirement for steroids reported in this application is a result of an anti-tumor effect of bevacizumab or represents radiographic improvement due to reduction in tumor associated edema, radiation induced necrosis, or both.

We ask ODAC to please discuss the validity of objective response as determined by standard MRI in the setting of VEGF inhibition to support accelerated approval for GBM. Second, is the response seen in this application of sufficient magnitude that is clinically meaningful to serve as a surrogate reasonably likely to predict clinical benefit for the purpose of accelerated approval in refractory GBM? Thank you.

DR. WILSON: Okay. Thank you.

At this time, we'll have questions to the presenters. For the members of the Committee, please do not ask questions until I recognize you.

Let me start the process with a comment and two questions myself.

I think because of the potential mechanism of action of bevacizumab, we are uncertain as to whether or not the radiographic findings, which are very clear and very significant, are adequate surrogates for benefit. So with that in mind, I have two questions for the sponsors.

If, in fact, radiographic responses with bevacizumab reflect benefit, why, then, when we look at the two arms of the Avastin versus the Avastin irinotecan, do we not see an improvement in the response duration or overall survival in the arm that we see the Avastin irinotecan, where the response rate was 38 percent versus the Avastin alone, where the response rate was 28 percent?

DR. SCHENKEIN: Thank you for your question.

Our goal is to demonstrate that the effect of Avastin will improve clinical benefit for patients, ultimately overall survival on our Phase III study. And we are confident from the data that we've shown you today, particularly on the magnitude of the response and the duration of the response among the other supporting endpoints, that we have demonstrated it's reasonably likely that we will be able to predict that benefit.

Now, when we look at the two arms -- this was not a comparative study, and the confidence intervals are clearly overlapping between those two. And so we don't believe that we can make a conclusion at this time that the addition of irinotecan provides any benefit. In addition, we know from

numerous studies, including more recent studies through the Consortium, that irinotecan has minimal single-agent activity in this disease.

So while we cannot absolutely identify the contribution or lack of contribution of irinotecan in this setting, we do believe that the single agent Avastin arm gives us confidence that it is reasonably like to predict clinical benefit ultimately in our Phase III study.

DR. WILSON: No. My question isn't whether or not the irinotecan Avastin arm is better, because I would agree that you can say that. But if, in fact, response rates, you with this agent do track benefit, one might expect at least there is to be some hint that the higher response rate seen in the irinotecan arm, which may have been purely coincidental, would be reflected by at least an equivalent, but, in fact, it's actually got a lower duration of response under the Avastin arm.

DR. SCHENKEIN: Yes. I don't believe we can draw any conclusions, again, because of the non-comparative nature of this study.

DR. WILSON: Okay. And then let me go to my second question, and that goes specifically to the six-month progression-free survival, as well as the overall survival.

Because of the lack of a comparator arm, we need to go back to historical controls. And, the historical control presented is from the NABTC trials, where they showed that the median -- overall survival was 5.9 months and the six-month PFS was 16 percent. When one looks, however, at the line of

therapy, one notes that in the Avastin trial, 81 percent of the patients were enrolled at first relapse, compared to only 42 percent of those in the NABTC trial. Furthermore, the results from your own study shows that if you look at the response rate, according to first or second relapse, it's 29 versus 12.5 percent.

Why, then, is the difference between the historical control data and your data not simply due to lead time bias?

DR. SCHENKEIN: I'm going to begin by addressing that by showing a slide from my concluding deck that shows the bar graphs, if I could get that, please.

Just so I can review again, on the right, the graph that we're referring to is the progression-free survival at six months. And I want to draw your attention to the study all the way on the right, which is a recent study, a Phase III study of an experimental agent, enzastaurin versus lomustine. And this is a study done in the exact same time period as the conduct of the study that you have seen today from single-agent Avastin.

You can see clearly that the PFS-6 -- and I would also show you, the response rate is significantly and substantially higher than the Fine study. When we've looked at the baseline characteristics for the Fine study versus our study, across many different prognostic characteristics, including first versus second, we see they are virtually very, very similar to the study under consideration today. So we're very confident that we can say that the PFS-6

we have seen is substantially higher.

Let me ask Dr. James Reimann from our biostatistics group to elaborate a little bit on this for you.

DR. REIMANN: James Reimann, Genentech Biostatistics.

I'd like to address your question in two ways, with the lomustine data that Dr. Schenkein mentioned, because we did look at a number of characteristics between that study and the study under discussion today.

It is important to look at who is enrolled, their prior treatments, and how they were assessed radiologically, and then also some of the patient characteristics. It's important to note that their study was enrolled in the same time period as our study, so it had current standards of care and used MRI assessments every six weeks. They also incorporated an independent review of tumor assessments, and all patients received prior radiation and chemotherapy as in our study. When you look at patient characteristics, they look very similar with respect to age, sex, Karnofsky performance status, and, importantly, whether the patients are in first and second relapse.

So in this study, with the lomustine experience, they saw an objective response rate of 4 percent, six-month, progression-free survival of 19 percent, and reading it from the Kaplan-Meier curve, one year survival of approximately 25 percent.

With regard to the NABTC study, you are correct that they had more patients from second relapse. And I did correspond with Dr. Lamborn at NABTC

to discuss this. Actually, in their data, the objective response and PFS-6 were similar in the first and second relapse, and we can perform a re-weighted analysis, effectively making the proportion of first and second relapse to match.

So in the re-weighted analysis from NABTC -- now, this is based on patients with prior temozolomide -- they saw an objective response rate of 7 percent and PFS-6 of -- sorry; objective response rates of 7.4 percent and PFS-6 of 7 percent, and overall survival of 24 percent at one year.

DR. WILSON: Okay. Let me go ahead and open it up.

DR. LINK: I just have a question, I'm not sure who I should address it to, related to the follow-on study that's planned and how that will actually confirm the results of this study. In other words, your indication that you're going for here is recurrent glioblastoma, and the study that you will perform will actually be front line -- I mean, I applaud it. I think it's a very important study, but I'm not sure how those results will have any bearing on what you've reported here.

DR. SCHENKEIN: What we believe is that that study will establish, definitively, the clinical benefit of Avastin in glioblastoma, admittedly in the front-line setting. And, again, the primary endpoints, as you've heard today from both us and the FDA, are both overall survival and PFS-6.

I'm sorry --

DR. PAZDUR: Go ahead. I just wanted to say something.

DR. SCHENKEIN: Okay.

We do believe it would be challenging right now to do a randomized study in the refractory, a relapse setting, given the data that's already been in the public domain. And we think it's important to move this as early as we can to make the biggest impact for patients in this disease.

DR. PAZDUR: Just as far as a historical perspective with regards to confirmatory studies in accelerated approval, it is generally the situation -- and I can't even think of one that we didn't do this, where we allowed the confirmatory study to be done in an earlier stage of the disease, an earlier treatment phase of the disease.

The Agency looks at this as a benefit to the patient population, that it moves the therapy along more rapidly to people that are more likely to benefit from it. In addition to that, it's very difficult, once we have an approved drug, to then be enrolling patients on a study to confirm its clinical benefit. So we've really looked at it as a way to move therapy forward in the disease.

DR. HARRINGTON: So just a follow-up question to that, then, given that this agent will be out there in the treatment of refractory diseases.

What if in the earlier stage, the trial, the previously untreated patients, it turns out to be negative, what happens to this indication, then?

DR. PAZDUR: This would have to come back and be discussed here. There are provisions in the accelerated approval regulations that allow for

the indication to be subsequently reviewed and to be removed if confirmatory studies do not demonstrate clinical benefit.

DR. HARRINGTON: And one follow-up question if I might.

One of the key issues I think in putting something out on accelerated approval is to try to get the confirmation as soon as possible, and I applaud the company and FDA for planning a study in previously untreated patients. It looks like a very large study, though, almost a thousand patients, which I would imagine will take you out to that 2,014 time.

Why does that study have to be so big, and why do we have to wait four and a half years for its results to know whether or not we may have made a mistake in this approval?

DR. SCHENKEIN: So, again, the primary endpoint, as we've talked about, is overall survival, and the co-primary is progression-free survival. This will be a global study. And you're right, it is a very large study. It clearly will have interim analyses along the way done by an independent data safety monitoring board. But, again, I'll ask Dr. Reimann to come up from our stats group to walk you through the powering of that study and the reasons for that size.

DR. REIMANN: James Reimann, Genentech Biostatistics.

This study is powered for an overall survival hazard ratio of 0.8, and that would correspond to a 25 percent improvement in overall survival and require 683 events. There is a single interim analysis of efficacy planned in

this study at 72 percent information. That would be 492 events with a possibility of stopping the study earlier at that time. We would expect this analysis to occur between one and one and a half years earlier than the final analysis.

DR. HARRINGTON: What's your anticipated enrollment rate? How many centers will you have participating in this?

DR. REIMANN: The enrollment period is three and a half years.

DR. HARRINGTON: And so, the enrollment rate -- I guess what I'm asking is have you done due diligence to make sure you're going to get as many patients on to this trial as possible, given other constraints that you'll face?

DR. SCHENKEIN: We have. We've done fairly extensive feasibility testing both at Genentech and with Roche because this study will be global. So we've done extensive feasibility analyses, and we're very confident that this study will enroll in a timely fashion around the world.

DR. CURT: I have a question for Dr. Levin. And that is, in the setting of recurrent glioblastoma, how important is FDG-PET in the differential diagnosis between radiation necrosis versus recurrent disease? Do you use it routinely or is MRI sufficiently different to be certain that you're dealing with radiation late effects?

The subtext of the message obviously is that what you may be seeing is actually tumor responses in the patients that you're treating.

DR. LEVIN: We don't use FDG-PET very often, and in the distinction between glioblastoma and radiation, it's usually fairly more straightforward than it is for lower-grade tumors. And we rely, and can rely usually, on MRI in this efficient mode. That's not to say every once in a while you wouldn't do an FDG, but if we did it routinely, we'd be wasting a lot of money.

DR. CURT: Could those differences obviate the FDA's concern about the difference in response rates between early versus late responders in terms of prior radiation therapy?

DR. LEVIN: I don't think so for glioblastoma, but, I mean, you could just as easily do it by stopping treatment. And if the abnormality comes back, then it's tumor; if it doesn't come back, it's radiation.

DR. CURT: Thank you.

DR. WILSON: Dr. Richardson?

DR. RICHARDSON: I actually have a couple of questions, one of which is rather lengthy, but let me get at the shorter one first.

In looking at the FDA analysis on response rate by baseline characteristics, on page 16, it looks as though there are some differences in response rate, based on performance status, with KPS scores of 90 to 100 having a higher response rate, although, granted, the numbers are relatively small.

I'm curious what the differences in performance status may be, looking at the studies that have been cited as kind of historical comparisons

or the enzastaurin's study, when we compare those KPS numbers versus the folks treated in the AVF3708g study.

DR. SCHENKEIN: Thank you. I'll ask Dr. Reimann to address that for you. We do believe that the patients enrolled in this study are very comparable to that in the historical controls that we've used as the basis for comparison.

DR. REIMANN: James Reimann, Genentech Biostatistics.

I'll just address your point in a couple of ways just to review the subset analyses for objective response rate and then look at the characteristics of the lomustine study.

If we could be up the Forrest plots for the subset analysis.

Now, this is a very busy slide, so don't be alarmed. As the FDA reviewer mentioned, there are many subsets -- many of the subsets are very small, and our ability to interpret results within subsets are limited. As you point out in the middle of the graph, when we look at Karnofsky performance status, the response rates were similar in both treatment arms, a fraction higher with the earlier patients.

If we look at the side-by-side graph I showed earlier with the lomustine study versus the Genentech Phase II study, the distribution of Karnofsky 90 to 100 and less than 90, shown at the bottom of this slide, were very similar glioblastoma.

DR. RICHARDSON: Thank you.

DR. SCHENKEIN: And the lomustine study, as we've mentioned earlier, had a -- the lomustine arm in that study had a response rate of 4 percent.

DR. RICHARDSON: Let me ask my second question, then.

I notice that Avastin used in the AVF3708g study is said to be different from the commercially marketed product. And if I recall correctly, and please correct me if I'm wrong, it seems to me that the Avastin product that was used in I believe it's the ECOG prostate cancer study, looking at docetaxel prednisone, plus or minus Avastin, is also different from the commercial product.

I'm curious how these entities differ from the commercial product, and what evidence do you have that they're actually equivalent?

DR. SCHENKEIN: So we have no evidence that the Avastin used in these clinical trials is any different from the commercial Avastin currently in use, other than it comes from a designated investigational lot. We've had discussions with the FDA subsequent to their question about the CMC issue, and I believe that they have been satisfied that we have demonstrated that the material within the clinical trial is essentially same as the commercial.

DR. WILSON: Dr. Lyman?

DR. SCHENKEIN: I believe the FDA wanted to make --

DR. WILSON: I'm sorry.

Pat?

Go ahead.

DR. PAI-SCHERF: Yes, we agreed. During the review process, we requested additional information from Genentech to show product equivalence, and they did provide the data, and we agreed that the product used in this clinical trial is equivalent to the product marketed.

DR. WILSON: Dr. Lyman?

DR. LYMAN: Two questions. One follow-up for Dr. Levin.

Admittedly, a small series you presented, but did any of those patients in subsequent follow up demonstrate a recurrence of their tumor or, in particular, the GBM group of patients? What is his degree of concern around the fact that half of this small series had ischemic or thrombotic events that could have been complications of the antiangiogenic therapy?

DR. LEVIN: So let's deal with the first one. In the trial, the CTEP's trial, the randomized study, there was no patient who entered the study with a diagnosis of glioblastoma. We had one patient who had low-grade glioma, who had very nice radiation response, but subsequently in a different location developed a glioblastoma. But glioblastoma was not included in that study. Typically, in the patient with glioblastoma that we've treated in the past, and sometimes we still treat, it's very obvious that it's a lesion differently located inseparable from the primary disease.

What was the second one? It was on thrombotic?

DR. LYMAN: Yes. I think you reported six of your cases.

DR. LEVIN: Right. Those were -- on was a deep vein -- size

thrombosis, and that patient stabilized, only received two courses of Avastin. And four months later, the radiation change stabilized. The people with VTE, no problem. They just get anticoagulated, and we continue to treat.

A couple of the patients that showed worsening, that was irreversible, that was small vein thrombosis, actually, more typical to the kind that you see with radiation damage. So it's really hard to point at it and say that's an Avastin effect.

Does that answer satisfactorily?

DR. LYMAN: And just one follow-up for the company.

Admittedly, the subgroup analyses were conducted. It's difficult -- and I didn't see any subgroup analysis based on a couple of the exclusion criteria, which included normal organ function -- or abnormal organ function or inclusion based on normal organ function and the absence of any major comorbidity.

Were these also exclusions for the lomustine trial, and does anybody know if the historical series that you have referenced included all comers or also excluded patients with major comorbidities or some abnormality in renal-hepatic function?

DR. SCHENKEIN: We don't have any specific data to show you, although we feel, again, very confident from the discussions we've had that the patients we've entered into this trial, that you've seen today in this application is very representative of what we've seen. Clearly, patients with

comorbidities known to be potential issues with Avastin were excluded from this study, but we don't believe that compromises our ability to look at the substantially higher response rate we've seen and compare that.

DR. BARKER: This is a question for the FDA.

Comparing the results that we've seen presented today for Dr. Fine's trial -- to Dr. Fine's report in the Journal of Clinical Oncology, there are a number of important differences. The FDA says there were 56 patients treated. The report says there were 48 patients enrolled. The FDA says they were enrolled from January 2006 to September 2007. The report says July 2006 to November 2007. Those are not overlapping time periods. The response rate success by the investigators were 35 percent. The FDA, 19 percent.

Are all of these the same patients, and why are there more patients for the FDA than there are for the Journal of Clinical Oncology?

DR. SCHENKEIN: Should I address that? You directed your question to the FDA. We're happy to address that if you'd like, but --

DR. PAI-SCHERF: Since you submitted the data, please go ahead.

DR. SCHENKEIN: Okay. Thank you.

I'll ask Dr. Julie Hambleton from our clinical group to walk you through that.

DR. HAMBLETON: So as mentioned, as requested by the FDA, we were asked to submit the information that Dr. Fine provided. For the trial, the exact enrollment dates, I don't have to share with you in terms of the

differences. They are -- the 48 patients in his manuscript are also 48 patients that we did look at. Additionally, patients enrolled into this trial that had not been analyzed by Dr. Fine and colleagues, and included in that publication, were included in the data provided to Genentech, which we then passed on to the FDA.

DR. SCHENKEIN: If I can just add, we were not involved in the conduct of that study at all, and just were asked to obtain the scans from that study and retrospectively review them, using the same IRF charter and same IRF facilities. We weren't involved at all in the conduct of that study.

DR. BARKER: Can you elaborate a little bit on what the nature of the responses were that the investigators declared that you did not confirm? Were they just the measurements weren't in agreement between the assessments, or the durability was not in agreement, or both?

DR. SCHENKEIN: Is this in the Fine study?

DR. BARKER: Yes.

DR. SCHENKEIN: I don't --

Julie, you want to address that? Do we have data?

I'll ask Dr. Reimann to address that.

DR. REIMANN: James Reimann, Genentech Biostatistics.

One important thing to note in the NCI study, was that confirmation of responses were not required, while in -- since we used the same tumor assessment criteria as in our Phase II study, we were required confirmation

more than four weeks later.

DR. SCHENKEIN: Again, we have very limited data on that study other than obtaining the scans as requested by the FDA to do the retrospective analysis.

DR. WILSON: Let me ask two questions with regard to the radiology.

Just so I know that all of these studies are on the same page, the definition of progression, 25 percent, that was always done from the NadR or the best response.

DR. SCHENKEIN: Yes, that is correct. And that was in the charter that had been reviewed by the FDA.

DR. WILSON: And that's also true for the comparator trials you've given us for historical data?

DR. SCHENKEIN: I believe that's true. I can ask Dr. Prados to come up and walk through some of those details, but I believe that's generally true.

DR. PRADOS: Mike Prados, UCSF. I can speak for the NABTC trials. Number one, we confirmed responses, but we didn't require that for a week. So when a patient was called a response, we reviewed it centrally, but we did not have an independent review. So we did not use the conservative response criteria that was used in this study.

DR. WILSON: And my second question is, one of the issues that we are being asked to look at is how reliable the response is given the nature of

this drug. I understand that it is quite difficult to sort out the differences between changes in water permeability from tumor shrinkage, but there are some indices that can be looked at, such as midline shift and other changes on the scans that are associated with a mass effect.

Were these looked at, and were there, in fact, improvements in mass effect that might be more attributable to an actual tumor response, or is it simply a permeability alteration?

DR. SCHENKEIN: I'll ask Dr. Greg Sorensen to address that for you.

DR. SORENSEN: I'd like a backup slide from Patient 20157, please.

In this study, they did not have any quantitative measure of these improvements, or lack thereof, in secondary responses. However, I would like to point out that with imaging, we can sometimes detect a difference between a permeability difference and actual tumor changes.

This is one of the examples of a patient -- yes, this is it. So this is an example of a patient who did not respond. On the top row, again, are the post-contrast images. On the left, is the baseline scan, and on the top right is the progressive disease-called scan at six weeks.

What I found interesting about this is you can actually see there is a diminishment of the enhancement from the second scan compared to the first. So there is a reduction in enhancement that's visible, but, yet, there was not a shrinkage of the tumor. And so this was appropriately called a non-responder because even though there was a decrease in the permeability, it

didn't actually cause the tumor to shrink. And, in fact, if we remember those waterfall plots that Dr. Hambleton showed, most of the patients had some of this diminishment of enhancement, but they didn't actually have shrinkage. So I think there is a reality to this actual response that 28 percent of the patients had.

DR. SCHENKEIN: I think the other thing I would add, that we do know, although it wasn't part of the response criteria, that a significant number of them who did have shift abnormalities did actually improve during the treatment with Avastin. So we did see improvement in midline shift and ventricular compression in many of these patients.

DR. LOEFFLER: Question for the investigators.

The response rates in a subset analysis -- and, granted, it was a subset analysis with relatively small numbers -- appeared to be inversely related to time of progression. So the best responses were seen in patients who had failed relatively early following Temodar and radiation, which this is an unusual finding in new cancer drug development, that people that have a more malignant phenotype, that failed more rapidly, actually have more response. And I guess it brings up the issue -- or some of these responses, in retrospect -- we'll never know -- effects of treatment related changes on the skin more than tumor effects.

DR. SCHENKEIN: Yes. What we do know is there is certainly evidence, preclinically and some clinical data, that the early progressors,

the patients perhaps with the worst outlook, are ones who tumors are, in fact, producing more VEGF. So it is not entirely surprising that we see a somewhat higher response rate.

We do know if we look at the four patients who are within 12 weeks of entry into the study, those patients either had multiple MRIs or re-biopsies to demonstrate tumor. So confident, again, we've enrolled a population of patients that allows us to compare.

DR. LOEFFLER: Thank you very much.

DR. BARKER: You presented neurocognitive test results. We also heard a little bit about measurements of neurological status in relation to definitions of response.

Were there neurological status measurements that were tracked during your trial?

DR. SCHENKEIN: Yes. One of the secondary endpoints, which we did mention briefly and we can walk you through, was the neurocog instruments that we used. And I'll ask Julie Hambleton --

DR. BARKER: Let me just clarify my question. Not neurocognitive --

DR. SCHENKEIN: Oh, I'm sorry.

DR. BARKER: -- neurological; things like hemiparesis, level of consciousness.

DR. SCHENKEIN: I don't believe we have any of that data captured in a reliable enough fashion that we can make an assessment of whether or not

there was any trend one way or the other. Sorry. I misinterpreted your question.

DR. WILSON: Dr. Kieran?

DR. KIERAN: A couple of questions. The first is radiographics.

In one of the supplemental data, there were the interobserver variability between the different radiologists. Much of this proposal is based on the radiographic changes, and even in the analysis of the first two observers, there was only about a 50 percent agreement, requiring a "break the tie" frequently. I guess I wanted to have some idea of how that impacts our ability to review this data.

DR. SCHENKEIN: Yes. I think there are two important pieces of data to address that question. The first is looking at how often -- and I'm going to address this by asking the question that we asked the radiologists at a patient level, did a patient respond yes or no. And if we look at the concordance between the investigator at the site and the IRF, that was, in fact, over 75 percent, well within what we typically see when we do independent review studies.

Now, if we also then look at Reader 1 and Reader 2, the two readers at the facility, and we ask, again, at the level of did the patient respond yes/no as their best response, the agreement was 73 percent.

The 50 percent between Reader 1 and Reader 2 was not looking at the patient level response yes/no, but, rather, let's look at every scan across

all the patients in this study, which was 308 scans, and ask how often did they agree on the interpretation of every single scan at every single time point. And in that case, the number does drop down to a little over 50 percent.

We think the important number to focus on, and allows us to compare it to other IRFs that have been done, is at the patient level, do they respond yes or no. And we believe that the concordance rate is very much in line, certainly, with what we have seen when we've done independent reviews across a wide range of different tumor types and, in fact, what's been reported across the industry. A little bit over 70 percent is the typical concordance rate. So we're very confident in the data that we've presented to you today.

DR. KIERAN: Thank you.

And then, can I ask another question?

The definition for coming on to this study was at least minimum one centimeter enhancing area.

What happened to patients that had non-enhancing tumor or where the only enhancement was, for example, a necrotic cyst? Were they excluded from this trial?

DR. SCHENKEIN: I'll ask Dr. Hambleton to walk you through that.

DR. HAMBLETON: So just to review briefly, the inclusion criteria, it was as determined by the investigator. We did not do IRF assessment of scans at baseline for study entry. So the investigator was to identify

enhancing disease at baseline, as you described, the one centimeter.

DR. KIERAN: So you had to get on to the trial with enhancing disease --

DR. HAMBLETON: That's correct.

DR. KIERAN: -- but progressive disease could be based on both enhancement and non-enhancement.

DR. HAMBLETON: That's correct.

So the non-enhancing component was used similar to how in oncology trials we use non-index lesions. So the non-enhancing component was assessed to determine progression. So if the patient -- the one example that Dr. Sorensen showed you, where the patient's new lesion was a non-enhancing lesion, that was called progression by the IRF. And if the patient had baseline, non-enhancing disease that was unequivocally progressing, the IRF study team could call that progression as well.

DR. LINK: Just a quick follow-up to Dr. Kieran's question.

So in a non-CNS tumor, the concordance rate in a review panel is in the order of 75 percent. So it's got nothing to do with the difficulties of edema and all that kind of stuff. You see that even in ovarian cancer, something like that.

DR. SCHENKEIN: That's correct. I'll show you a backup slide here.

So there's been a lot of work looking at the role of IRFs versus investigator responses across a wide range of disease. And there have

actually been several interesting panels that have been convened by the Institute of Medicine and workshops that are ongoing between the Institute of Medicine, FDA and industry sponsors to look.

Certainly, this is data that we're showing you here across four of our applications, across a wide range of diseases, as well as two applications from other sponsors. And you can see that the concordance rate between an IRF and an investigator -- this is just looking at overall response rate -- is in that same range. When we look at other time-to-event endpoints, such as progression-free survival, we see a very, very similar concordance type rate.

So we don't believe there's anything unique or different in this application from what we'd expect when we do an independent review of radiological findings.

DR. LINK: And that's fine. And also, how about between radiologists at the review center?

DR. SCHENKEIN: I don't believe we have that data in a table format. But, again, it's our -- discussions with both the center we've used and other centers, that's well within -- again, at the patient level, did the patient respond yes/no, that 73 percent is very much what one would expect in oncology, not specific to GBM.

DR. HARRINGTON: Thank you. A question that's, perhaps, both for the sponsor and Dr. Levin. It's a question about dosing.

The application here is based on 10 milligrams per meter squared. I

believe that the dose that Dr. Levin found was very, very useful in treating the radiation necrosis, was 7.5. More is often, but not always better. And so the question is whether you would expect to see the same beneficial effects on the radiation necrosis at this higher dose or whether that might, in fact, start to cause some things to shut down.

DR. SCHENKEIN: So I can't really comment on the dose that would be appropriate for radiation necrosis because we haven't studied that in any systematic manner. When we set out to design our development program in GBM, our intent was to drive maximal efficacy in this disease that clearly needs effective therapies. And knowing that the blood-brain barrier would be partially disrupted, also decided to err on a dose that would try and get as much Avastin into the brain as possible across that blood-brain barrier.

Now, what we know is that if we look both at our development program for Avastin outside of GBM, both in the Phase II setting and in the Phase III setting, we've seen that in most of the indications, the dose that we've chosen for this application, what we'd call our standard dose of Avastin, of 5 milligrams per kilogram per week, actually looks superior to the lower dose in both Phase II studies and numerically in Phase III studies; and also, that we have not seen any appreciable safety difference between the dose that I just mentioned, the dose in this application, and one dose lower, both in randomized Phase II studies and large randomized Phase III studies done in several different indications.

So we're very confident that we've selected a dose that we consider is the standard dose for Avastin and that has an excellent safety profile. And, again, we were driving to look for maximal efficacy in this indication.

DR. LEVIN: So I really don't have much of an answer, except to say that I come from the less is better school. And since the drug had a half-life of 21 days, and I was going after the entered endothelial type junction, which would have been in the vascular system, I figured that once every three weeks was enough, and I gave a dose that I felt was comfortable, which was 7 and a half.

When I was generating the study, the CTEP critics basically came back and said, why aren't you using 10-15 milligrams per kilogram. But the lower dose worked, and it worked fine. That's all I can say.

DR. WILSON: Dr. Barker?

DR. BARKER: Yes. I had another question about the definition of progression-free survival used in your study and in the historical controls from the NABTC Consortium.

So they both used 25 percent enlargement in enhancing area as declaring progression?

DR. SCHENKEIN: That is correct.

DR. BARKER: And you used T2 FLAIR enlargement also by 25 percent as the definition of -- part of the composite definition of failure?

DR. SCHENKEIN: Within our study.

DR. BARKER: But the Consortium, I would assume, did not include that in their definition.

DR. SCHENKEIN: That is correct. They did not.

DR. BARKER: Thank you.

DR. KIERAN: Have you gone back and looked, to repeat the analyses, for example, by subtracting the few patients that didn't have GBM, by removing the patients that got their treatment before patients -- or I guess the eight patients who got their radiation within the three-month window instead of the -- the two to three-month window instead of greater than three-month window, to compare those numbers with what the FDA presented in their --

DR. SCHENKEIN: We have. We do believe they're very favorable. And I'll ask Dr. Reimann from the stats group to walk you through those sensitivity analyses.

DR. REIMANN: James Reimann, Genentech Biostatistics.

Just to confirm your question, you were asking about the patients who were not confirmed to have GBM histology and then also time from radiotherapy; is that correct?

DR. KIERAN: Correct.

DR. REIMANN: So we performed a number of sensitivity analyses with slightly different study populations, and they're shown on this slide here. There are a lot of numbers, so just focus on the center column in the Avastin arm.

If we look at the bottom row of the table, we see that there were 83 patients in the Avastin arm with confirmed GBM histology with an objective response rate of 28.9 percent. And then to look at the time from radiotherapy, we performed a sensitivity -- actually, a subset analysis on 79 patients in the bottom row of this table, excluding patients within 12 weeks of radiotherapy. And when we would look at those 79 patients, we see an objective response rate of 25.3 percent.

DR. KIERAN: So maybe the follow-up question is, the statistical group at the FDA -- since your numbers have been different all along, in part, because of the definitions of exactly 28-day scan times and so forth, did you go back and remove the patients without GBM? Did you remove the patients if we were going to use the historical comparisons to patients having received radiation therapy a minimum of three months before? Because in your tables, I don't see those comparisons.

DR. SHEN: Yes, we did remove those patients, and then result didn't change too much

DR. KIERAN: Can I ask one more to the FDA?

In looking at the notes that we received, with respect to the meeting, I guess, from July -- sorry; from January 2008, I guess where there was a discussion between Genentech and the FDA with respect to the requirements. And I think these were actually included on the handout from the FDA this morning, on page 2, I think, of Dr. Pai-Scherf's presentation.

It listed three criteria that it wanted Genentech to achieve in kind of meeting the criteria for this accelerated approval. And as I was looking at those three criteria, it seemed to me that -- so these are on Slides 8 and 9; so that the FDA would consider the results of this trial in support of bevacizumab monotherapy with clinically meaningful and durable objective responses; that if they obtained information from Dr. Fine's study that also seemed similar, and that they were willing to do a formal trial.

And I was wondering, does the FDA think that they met those three requirements?

DR. KEEGAN: We believe they complied with what we requested that they provide to us, yes.

DR. KIERAN: So the question today is, really, do we believe that the clinical, meaningful, and durable -- you've got it underlined on your slide. So the question today is, is this clinically meaningful and durable objective response acceptable.

Okay. I wanted to --

DR. WILSON: Well, let me follow up on that. I guess one of the issues is whether or not these radiographic responses are meaningful. And I think this actually begs another question, and that is one that comes from the endpoint, a group that the FDA had, where the PFS six months was considered to be an endpoint of value, but should be looked at further.

My question is, if you take the hypothesis that what we're looking

at is a radiographic -- and I'm being very kind of hard edge here -- a radiographic effect and not a tumor effect, doesn't that also put at risk the PFS six months and does not leave us, really, with having to look at either improvement in quality of life, which we don't have in these studies, or being convinced that there's some survival advantage? And that, of course, then, goes back to the issues as to whether or not the historical controls really reflect a similar group as we're dealing with here.

DR. PAZDUR: I think when we discussed that PFS at a specific time point, that was in the context of a randomized trial, not to be looking at historical data and making inferences from that historical data.

DR. WILSON: So, then, you would say that PFS six months is not an endpoint that we should be putting much value in.

DR. KEEGAN: Correct. We did not really place any emphasis on it because we don't think it can be interpreted in this context.

DR. SCHENKEIN: But we do believe that the other supporting data that goes along with a response rate such as that duration of response, the fact that patients were able to decrease their steroids, and the responders decrease their steroids, into the physiologic range, and the stability on the neurocognitive function, all of that together gives us confidence that this is reasonably likely to predict clinical benefit, ultimately, in our Phase III study.

DR. WILSON: I think that's true, but, again, to your credit, having

such a novel agent here, I think, draws it all in to question. I guess that's what we're dealing with.

DR. RICHARDSON: I confess that, as a medical oncologist, having looked at these articles on MRI scanning, I would say that over time, it appears to me that the whole field of imaging of these brain tumors has become more and more complex. I'm particularly taken by one of the statements that Dr. Levin made earlier today that radionecrosis may be occurring in 24 to 55 percent of patients who are treated with chemotherapy and radiation. And I think that gets at the question of what is the standard of care for these kinds of patients. How many of these patients, in fact, are presumed to have progressive cancer when, in fact, we're dealing with progressive radiation necrosis?

I guess I'd like to ask Dr. Prados about the patient that he described at the beginning of his talk; and that is, did that patient have a biopsy and would that patient, by today's standards, have a biopsy?

DR. SCHENKEIN: So just to clarify, the patient that Dr. Prados showed in his scan was not from the Avastin study. But what I'd like to do is to ask Dr. Cloughesy, if that's okay with you, to walk you through his thoughts on this issue of radiation necrosis in this patient population. I think it's important to note that the radiation dose used in this study was standard radiation, where we know the incidence of radiation necrosis is significantly lower than, perhaps, as seen with more aggressive and higher-

dose radiotherapy.

DR. WILSON: Well, before that, I'd just like to get at this question --

DR. SCHENKEIN: Sure.

DR. WILSON: -- whether or not a patient with that type of an appearance on an MRI scan, by today's standards, would normally have a biopsy.

DR. PRADOS: Mike Prados, again.

Yes, that patient actually underwent a resection and showed tumor progression. So in many cases, in the setting of a polar lesion, where it's accessible for re-resection, we traditionally would do that, and we did with that patient who had tumor progression. I can't say what the exact standard of care is. Our standard of care is to re-resect whenever possible, not only to remove bulk effect and help reduce symptoms, but also reduce tumor burden. It also gives us information about what we're dealing with.

DR. SCHENKEIN: Would you like us to continue to follow up on the radiation necrosis?

DR. RICHARDSON: Please.

DR. SCHENKEIN: Dr. Cloughesy?

DR. CLOUGHESY: I'm Tim Cloughesy from UCLA. I'm an neuro-oncologist. I think that there are a couple of issues that come up with radiation necrosis. One of them is what we expect to see in our patient population.

This is a recent review by Dr. Ruben, who evaluated over 426 patients. And these are patients who had doses -- as you see on the far left-hand side, these are doses that are typically given for glioblastoma, up to 60 gray. And what they found in that setting was about a 4 percent radiation necrosis risk. The radiation necrosis that occurs in that setting is the radiation necrosis that is not an early effect, that some people are calling pseudoprogression, but a later effect that can occur anywhere from many months to many years later.

DR. BARKER: This is a follow-up question for Dr. Prados.

Am I remembering correctly a study from UCSF by Tihan and co-authors from four or five years ago, in which patients who had clinical or radiographic diagnoses of recurrent malignant glioma had biopsies, and their survival was tracked afterward?

DR. SCHENKEIN: Dr. Prados?

DR. PRADOS: There have been a large number of studies, not only ours, who have looked at outcomes after presumed progression, who end up having biopsies or resection and what their fate is. I think the intent of some of these studies was to look at the potential impact of survival when you do a second resection.

I don't know if that's exactly what you're talking about, but those patients --

DR. BARKER: The study I remember was specifically biopsy, and there

was no difference in survival between the patients whose biopsies showed recurrent tumor and those patients who showed radiation damage.

So what I wonder is, if we can't make a clear distinction with MRI, if we can't make a clear distinction with biopsy, if we can't make a clear distinction with PET, shouldn't we just accept the fact that we have to treat these patients, and we have to get them some kind of benefit, even though we don't always know exactly what the path of physiology is that's going on?

DR. PRADOS: Absolutely. Of course, I totally believe that. Anybody who thinks that pseudoprogression somehow translates into a patient who's going to survive is mistaken. That patient is still ultimately going to have progression that results in death. And we don't have confidence in this estimation of pseudoprogression. We've done other studies that have looked at using the Macdonald criteria, and you've done these studies as well, and we have recently.

If you look at early time points after radiation therapy, and you correlate progression using Macdonald criteria, and estimate survival, the patients whose tumors are bigger after radiation therapy, at least in our hands, in upfront studies, live a shorter period of time.

DR. KIERAN: In those biopsy series, what percentage of the patients turned out not to have progressive tumor but actually had what would be consistent with necrosis? Did it fit the 4 percent we just --

DR. PRADOS: And I apologize. I don't have all the numbers in my

head about that particular article. But the majority of patients who end up just having a biopsy in a single site will either have tumor there or necrosis there. But the more samples you take, the more likely you are to see tumor. And at least it's my experience that the overwhelming number of patients that have either a biopsy or a resection at the time of presumed relapse will have tumor cells there, and the fate of that patient is probably dependent on the biology of that tumor. So we're still evolving a story here, but these patients still die of their disease.

DR. KIERAN: I have one last question, I guess more for the FDA.

We talked a lot about whether we can differentiate the effects of this particular drug on altering the blood-brain barrier and contrast or FLAIR T2 signal, and whether that's a direct anti-tumor effect or a symptomatic effect from some of the reaction of the tumor.

I guess one of the questions is, does it matter if you get edema? Because the tumor is causing the edema, and this treats part of the edema. Even if it didn't technically kill a single tumor cell, but by doing so, prevented the tumor cells from moving faster, deeper, or causing those symptoms, would that still be considered a benefit of the drug? Or do we have to prove that it's actually targeting the tumor cell itself, I guess would be a simple way of asking the question.

DR. KEEGAN: You don't have to show the deterrence of tumor cell itself, but the surrogate that we've used in other solid tumor areas has been

anti-tumor activity, tumor reduction. That's the basis for bringing this forward as a surrogate because we believe that reduction in the tumor will be of benefit or could possibly predict a benefit to patients if it's large enough, if it's durable enough.

I don't think we have enough experience to have any idea what other types of radiologic effects really mean in terms of the patients' outcome, but we have a long history of knowing the patients whose tumors reduce in size are likely to do better if that response rate is high enough and durable enough.

DR. KIERAN: I mean, I think this is part of the problem, the age of biologic inhibitors as opposed to cytotoxics, where I don't think it's always going to be clear. We know that many of the biologics also target the stroma, the microenvironment, not just the tumor, and is a way, sometimes, of actually getting at the tumor. So it sounds like, to some extent, that definition is going to have to evolve with the changing.

DR. PAZDUR: I also want to emphasize, even with cytotoxic therapies, what we measure as a response at this trial is probably not all tumor here. What's there is kind of unknown. It's a picture that we're dealing with here with a high degree of uncertainty; is there edema there, is there lymphocytic infiltrate, even in a colon cancer tumor?

So these are rough approximations, and that's why we use the word in accelerated approval "reasonably likely" to predict clinical benefit. Okay? In any tumor, when you're looking at a radiographic imprint, so to speak,

there's going to be some degree of ambiguity here. But given the issue here, the response rate that we're seeing -- and, remember, this response rate has been looked at by several radiologists here, including our own. The 95 percent confidence intervals are pretty much overlapping on all of these readings here, so to get caught up on a specific number is kind of, perhaps, not the way to go, but some consistency in a finding here; does that reasonably likely predict clinical benefit with the ambiguities associated with it?

DR. WILSON: I think that's what we're having to deal with here because the most profound changes we're seeing here are these radiographic changes and the durability of them. And the question is, are they reasonably likely, given the nature of this drug, to translate into a clinical benefit. That's why I keep on going back to the historical data.

But I might ask -- and, again, this doesn't really, perhaps, matter as to what the mechanism is. I think at the end of the day, even if this drug doesn't cause any tumor shrinkage, if it, in fact, improves survival -- because if edema leads to morbidity, lower survival, I think that we would all be quite happy. We don't really care what the mechanism is per se.

With regard to that, one of the points that Howard Fine made in his paper was that a very early radiographic response, which I think we would all agree is probably not due to an anti-tumor effect, was, in fact, correlated with those who did seem to have a longer duration of benefit. And so, I would

like to get the sponsor's thoughts about that, in terms of early changes, which almost, certainly, permeability changes did seem to be associated with the longevity of effect. And the corollary to that is, if, in fact, this drug doesn't have anti-tumor effect, that, in fact, may end up at the end of the day not being reflected in a survival benefit.

DR. SCHENKEIN: So as we showed you earlier in this slide that looked at the duration of response by the individual responders, what we did note is that -- and I'll bring that slide back up for you to see -- is that response needs to be confirmed. And so the white bars represent the confirmed response by IRF. And although many of them do occur early on, as you have mentioned in the first or second assessment, many of these, and even some that are quite durable, are occurring at later time points. While the tumor may be shrinking even earlier, they haven't met the 50 percent bar and then being confirmed. So I don't think we could make a tight correlation here between the onset and the duration. We see a range here.

DR. WILSON: Right. I was just referring to one of the points that was made on the Fine JCL paper.

DR. SCHENKEIN: Right.

DR. BARKER: I have a question for the sponsor.

Did you do any analyses in which you considered a reduction in T2 FLAIR area as response, and considered whether or not there were patient factors that predicted that response, whether or not that response predicted

neurocognitive improvement?

DR. SCHENKEIN: Yes. We have not done that. We've not done any of the response analyses. They were all done by the independent review, using the charter that we had pre-reviewed at the FDA prior to the enrollment, completion. So we have not done any of those type of exploratory analyses.

DR. LOEFFLER: I want to state the obvious for those who take care of patients with brain tumors. But there's a very strong correlation between imaging response and patient's performance, where neurocognitive factors might be an exception to that. So it's not like looking at a response. You don't expect the patient to, at minimum, be stable if not improved, unlike some diseases where you can see dramatic responses radiographically and see no change in the patient's performance.

DR. LINK: So I'd just like to ask a question, a follow-up on Dr. Pazdur's comments about the picture.

So we have a picture, and we're happy to see that there's an improvement in outcome. And one of the stipulations of, I guess, this trial was that we would see a much better than expected 5 or 6 percent response rate to the tumor, which would qualify as being a meaningful response.

As you said, since all the assessments of response are within a couple of standard -- or within the 95 percent confidence intervals of each other, and we're talking in the 20 percent range, is the 20 percent response of the picture, however that was obtained, whether it's killing tumor cells,

whatever it's doing -- does that qualify as a meaningfully better than the 5 percent that we saw in other studies? I guess that's what we're here to ask.

DR. PAZDUR: That's the question. That's why we're here.

DR. LINK: But we're usually talking about tumor response, and now we're calling it sort of response of the picture, I guess, however that was obtained.

DR. PAZDUR: But here again, that's why I did emphasize, even with conventional tumor response, you're not entirely sure is that 100 percent tumor that you're measuring. So there's always that degree of ambiguity. Granted, it may be more larger here with these issues that are surrounding it.

But let me give you also the context of accelerated approval. Remember, we have approved drugs in solid tumors with response rates that have been lower than that, in the range of 15 and 12 percent for accelerated approval. So I want to put that in the context of other accelerated approvals that we've done in various refractory diseases with single-arm trials. But you hit the nail on the head, so to speak. That's why we're here, to discuss that, the whole issue.

DR. LINK: My eyes were glazing over at the palisading effect, or whatever, when I started reading that. It's too many syllables for a pediatrician. So I just wanted to make sure that -- it's better when I talk about a picture and that the picture got better.

DR. SCHENKEIN: Maybe it would be useful -- because there's been a

lot of discussion, again, around anti-tumor versus other potential effects -- to just spend a moment reviewing, actually, some of the preclinical data that we have, that I think would, perhaps, help in looking at this. And I'll ask Dr. Heidi Phillips from our research group to come up and walk you through some of that data that looks at the direct tumor effect.

DR. PHILLIPS: Heidi Phillips, Preclinical Research, Genentech.

One of the advantages we have in our preclinical studies is that we're able to measure tumors in ways that we simply can't do in clinical studies. And because we're able to directly measure tumor in our preclinical studies, we've been able to see very compelling evidence for anti-tumor effect.

So in the earliest series of experiments that were done -- they were performed by my colleague, Dr. Napoleon Ferrara, who had originally discovered the VEGF. And what he and his collaborators did was to grow tumors in the subcutaneous space of immunocompromised mice, and because they were growing there, they were able to measure volumetric changes directly with caliper measurements as the tumors grew in the animals. And at the end of the study, they could dissect out the tumors and weigh them, and subject them to histological analysis.

What these studies showed was, very clearly, that relative to animals that received a controlled antibody, animals that received antibody to anti-VEGF showed reduction in tumor volume and in tumor weight, and then

consistent with the antiangiogenic mechanism of action, showed reduced blood vessel density. So more recently in my lab, we've been conducting experiments using orthotopic graphs of human GBM lines, where we implant the cells directly into the brains of immunocompromised mice.

Now, in order to allow us to have a direct read out of tumor burden, what we've done in these experiments is to engineer our human GBM line to express firefly luciferase, so we would have an optical signal so we could read out tumor burden. And when we put the tumor cells in the tissue culture dish, what we observe is the optical signal, this bioluminescence signal, is directly proportional to the number of cells that are in the tissue culture dish. And when we implant these cells into the brains of immunocompromised mice and monitor them serially, shown on the left-hand side of the slide -- when we monitor them serially, as the tumors grow, we see an increase in the bioluminescence signal, and we see a very nice correspondence between this increase and what we measure volumetrically on T2-weighted MRI. In the plot in the lower left-hand part, you can see a very nice correlation/coefficient between these two measures of tumor burden.

So what we next did, then, was to take cohorts of animals that were bearing these orthotopic graphs and to treat them with either control antibody or antibody to VEGF. And to the line graphs in the lower right-hand part of the slide show you what happens when we monitor these tumors by either bioluminescence, through direct read out of tumor burden, or by T2-weighted

MRI, looking at volumetric measurements. And as you can see, both of these measurements show a very, very similar growth suppression. So this gives us a rather high degree of confidence that what we're looking at in these animal studies is an anti-tumor effect. And as you can see by the Kaplan-Meier curves, this translates into a very nice survival benefit in the animal studies.

DR. WILSON: I would like to ask the FDA one more question.

I think in trying to judge whether or not it is reasonably likely to translate into clinical benefit, obviously, that's very subjective. And so I want to get a sense of the original reason for having accelerated approval. It's my understanding the reason was to make drugs that were promising available rapidly, where they wouldn't otherwise be available. In this case, we're talking about amending a use of this drug, and the drug is out there, available.

Is this something that we should or should be taking into account in terms of where we, for our own sense, draw that bar for reasonably likely?

DR. PAZDUR: No.

DR. WILSON: I like it when it's short and sweet.

Well, we are at noon time. Any other pressing questions?

Well, with that, let me adjourn the meeting. Let's reconvene at five of one. And, again, let me remind the panel to please not discuss among yourselves or with any of the audience. Thank you.

(Whereupon, at 12:01 p.m., a lunch recess was taken.)

AFTERNOON SESSION

DR. WILSON: Okay. We're going to go ahead and get started, so please take your seats, if you might.

Now, for the afternoon session, we're going to begin with the open public hearing.

DR. VESELY: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with the sponsor, its product, and, if known, its direct competitors.

For example, this financial information may include a sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the Agency and this committee in their consideration of the issues before them. That said,

in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy and respect. Therefore, please speak only when recognized by the chair.

Thank you for your cooperation.

DR. WILSON: Our first speaker will be Max Wallace, Chief Executive Officer, Accelerate Brain Cancer Cure.

Let me just say that each speaker will have three minutes, and at the end of three minutes, the microphone will be turned off. Thank you.

MR. WALLACE: Mr. Chairman, members of the Committee, thank you for giving us this opportunity to participate in the process. As you see up there, my name is Max Wallace. I run Accelerate Brain Cancer Cure, which is a national, nonprofit organization designed to do exactly what it says, bring drugs forward to help treat patients with brain cancer.

We're an organization that was borne out of this disease. Our founder, Dan Case, was stricken with glioblastoma seven years ago, and together with his wife, Stacey, his brother, Steve, Steve's wife, Jean, created an organization designed to bring an entrepreneurial approach to bringing drugs forward to try and cure brain cancer. And I think in the end, they were motivated by some of the types of slides that Mike Prados showed you, where no improvement in outcomes, no new drugs. It is a terrible,

remorseless, implacable disease, and few treatments to bring to bear against it. And we set our goal as to finding our way through that process and helping bring things forward. That's why this hearing is so important to us.

I'm lucky to be the first speaker, actually, on this because what I get to do, as a person running an organization, is set the stage for the more important and more powerful stories that are going to follow me. We're going to have a lot of people up here who will talk to you about why this is so personally important to them. I just wanted you to know it's personally important to me and to us as well.

I was pleased with the closing comment by the chair, actually, where we were talking about the purpose of accelerated approval, that the goal is to get this type of drug out to patients so that we can provide help now in an environment where very little is available to help patients at all. And as we look, the criteria that we spent the last part of the meeting talking about was, is it reasonably likely to help patients. And we saw data, and we saw different measurements, different surrogate markers, of efficacy.

But we believe, and I'm here to assert, that we think it will help patients, and we just wanted to voice our strong support. Thank you.

DR. WILSON: Thank you.

Our next speaker will be Harriet Patterson.

MS. PATTERSON: Thank you for having me here today. My name is Harriet Patterson. I'm the director of Patient Services at the National Brain

Tumor Society. After completing my degree in public health, I've been working in this field for the past seven years in Patient Services.

The National Brain Tumor Society invests in innovative research and offers help to brain tumor patients and their caregivers at all stages of their journey. We are funded solely through private donations and receive no public support. We do not endorse any particular treatment or products, and we are not affiliated with any treatment centers. Though we do receive unrestricted educational grants from a variety of pharmaceutical companies, including Genentech, NBTS is only beholden to brain tumor patients, their survivors, and their families.

Through our patient services, we're in touch with over 10,000 patients and families each year, and it is because of them that we're here today. We strongly believe that patients and families have a right to a range of options and choices. NBTS paid for my travel here today because we are committed to advocating for a range of treatment options and patient rights, not to endorse any particular therapy. And there are two main points to my testimony today: to underscore the lack of alternative options for people with a recurrent GBM and to underscore the quality of life that patients experience while on Avastin.

When someone is diagnosed with a glioblastoma, it is a devastating moment. The brain, the very center of who you are, is under siege. And after standard treatment, most glioblastomas recur; sometimes a year later,

sometimes six months, sometimes two months. But at that moment, because there are no approved alternative options, many people are told there's nothing left to do, to go home and get their affairs in order. These are moms and dads with young children, people who are middle age, putting kids through college, people 60 years old about to embark on their retirement adventures.

In the last few years as we've seen more doctors put patients on Avastin, we've heard their stories. People are living longer and with a better quality of life, able to continue working and maybe go on that trip of a lifetime with their families. They're cognitively alert, and they feel better while they're on this medication.

It seems to stave off the more typical downward trajectory that we see in physical and cognitive abilities with this population. People are also able to reduce their steroid doses, and this is very important because as anyone who works with these patients knows, there are a lot of unpleasant symptoms that go along with steroids. So reducing these doses makes a big difference in quality of life.

We know that Avastin is not the silver bullet that's going to cure this disease, or even maybe turn GBM into a chronic condition, but it does represent a marked improvement in quality of life for patients; and it is doing so in a landscape where there has been little hope, where prognoses are grim, and where adding just a few months of life actually is a significant improvement in life expectancy.

Despite some of the issues that people talked about this morning, we believe patients are clamoring for Avastin because it offers legitimate hope and a meaningful extension to their lives where no others exist. Thank you for allowing us to comment.

DR. WILSON: Thank you.

Our next speaker will be Thomas Ward.

MR. WARD: Ladies and gentlemen of the Committee, thank you very much for allowing me the time to speak today regarding the request to approve Avastin for the treatment of brain tumors. My name is Thomas Ward and I represent the Brad Kaminsky Foundation, with headquarters in Pennsylvania and operations in Northern Virginia. Our mission is to fund an ultimately find a cure for brain cancers. At this time, I'm aware of no financial relationship with any of the parties in here.

My personal connection is two-fold. My sister, Ann, a wife and mother of five, a 43-year-old woman, is being treated for Stage IV colon cancer since February of 2008. Avastin has been included in her chemo regime, and today, fortunately with some success.

Next, I would like to read a letter from the Cannata family regarding their mother and wife, Carolyn Cannata, regarding the impact Avastin has had on the quality of her life. From her husband, Robert.

"Dear Committee Members, the purpose of this letter is to urge the FDA for approval of Avastin for treatment of brain tumors. It is my hope and

belief that the remarkable improvement of my wife's quality of life can be realized by other patients and families across America.

In February 2007, Carolyn was diagnosed with glioblastoma multiforme, Stage IV. Surgery removed two large tumors from her frontal lobes, which were interfering with cognitive function and were causing periods of unconsciousness. Following the surgery, we received the devastating prognosis, she had an expectancy of only 14 months.

During the next three months, Carolyn was treated with chemotherapy and radiation, which did not cause remission of the tumors. We were advised to begin a treatment with Avastin, which started in June 2007. Avastin dramatically improved and continues to improve the quality of Carolyn's life. Permit me to share some illustrations.

Prior to Avastin treatment, Carolyn seemed like she was always in a fog. She was not fully aware of her environment, did not interact with others, and took little interest in daily activities. She was entirely dependent upon others for the activities of daily living. Carolyn spent most of her time in front of the TV or napping.

The day following her first Avastin treatment, Carolyn seemed to wake up. In fact, that day, while I was planting flowers in the front yard, Carolyn came out of the house and criticized the way I was arranging the plants. This was shocking to me because just one day early, she was oblivious to anything going on around her.

Since June 2007, Carolyn and I have been able to go on vacations, visit with families, and enjoy the holidays with our families. In December of 2007, Carolyn was involved in all the preparations for the wedding of our daughter, selecting invitations, meeting the caterer, and all other events. It meant a great deal to our daughter that Carolyn was able to share in this experience. Likewise, the wedding, Carolyn and I walked our daughter down the aisle. We danced and celebrated the milestone.

Carolyn certainly has not returned to her pre-tumor level of functioning. She cannot work as a trial attorney nor can she drive or handle the family's finances, and she did require some hospitalization from side effects. Regardless, Avastin has given my family more than we expected from it. While the brain tumor took away my wife's intellect, Avastin gave her back to us."

Thank you.

DR. WILSON: Thank you.

Our next speaker will be Jenny McDevitt.

MS. McDEVITT: Hello. I'm Jenny McDevitt. I am a board member of the Tug McGraw Foundation. Thank you very much for allowing me to speak today. Interestingly, I was hearing your discussions about quality of life, and as you hear a little bit more about my story, you will understand why I am so passionate about Avastin.

I was diagnosed with a malignant brain tumor, with brain cancer,

five and a half years ago, and in that time, I've underwent four craniotomies. I've had endless rounds of chemotherapy, I've had radiation, and anything I could do to possibly make this tumor go away.

Avastin was introduced into my adjuvant therapy in January of 2008, in conjunction with a daily, oral chemotherapy. Unfortunately, I developed severe peripheral neuropathy from the oral chemotherapy and continued on with Avastin alone. For seven months, my tumor did not recur. It was as clear as a whistle on those MRIs, and I was very confident that my brain cancer was gone. It was only after I discontinued the Avastin, that two months later, my tumor recurred. I, once again, am on Avastin in conjunction with some additional chemotherapy, and I'm happy to report that my tumor is not growing, and it is, in fact, going away.

The reason I discussed about the quality of life is I'm holding up these seven marathon medals. Each one of these marathons were completed while I was on some form of chemotherapy treatment for my brain tumor. Interestingly enough, in October of 2008, I crossed the finish line of the Chicago Marathon. Three weeks later, I crossed the finish line of the New York City Marathon, and I ran both of these marathons just three weeks apart on Avastin.

So when you discuss quality of life, I want to let you know that Avastin is continuing to allow me to have a fabulous quality of life. It's allowing me successful survivorship. It's allowing me to help raise my five-

year-old son, who was eight weeks old when I was diagnosed. And I hope that you'll consider allowing Avastin to be introduced into other people and so that they have options, so that looking at me, the face of brain cancer, you know that I'm a success story. Thank you.

DR. WILSON: Thank you.

Our next speaker will be Richard Oropeza.

MR. OROPEZA: Good afternoon. We have received no compensation from anyone, and we thank you for the opportunity to address this committee. My name is Richard Oropeza, Jr. I am a GBM survivor. I live in Williamsburg, Virginia with my wife, Ann.

My journey begins in December 2005. We were living in California, and I had just completed my annual physical with positive results. I was playing golf, walking one to three miles a day, and regularly traveling cross-country for my job. I was pretty much independent and enjoying life with our family and friends, looking forward to our move to Virginia and the birth of our first grandchild.

On February 2006, I was diagnosed with a GBM and my world changed dramatically. This forum and approval of Avastin is so important to me that we moved our normal infusion day from today to yesterday. This is the first time since I started the trial study that we made a schedule change. Everything we do is scheduled around the infusion MRI dates. If it wasn't for Avastin, I wouldn't be here today to address this Committee. I take each day

as it comes; nothing is taken for granted.

MS. LEVY-OROPEZA: I'm Richard's wife, Ann. Five days prior to his diagnosis, Richard was a carefree, happy, fit 57-year-old man, whose biggest care at the time was getting ready to relocate from California to Williamsburg. In five days time, Richard became completely paralyzed on his left side and was ambulanced to the hospital, suffering from excruciating headaches.

The following morning, he had an emergency craniotomy because his neurosurgeon told us his brain had shifted so much that he could die without the surgery. While still in the hospital, Richard's surgeon gave us a prognosis of 9 to 12 months, and that is only if he responded favorably to the standard protocol of Temodar and radiation.

Twenty days after his operation, Richard, who had undergone 14 straight days of intense physical and occupational therapy so he could learn to walk again, boarded a plan for Williamsburg. Within two weeks, we had met his new oncology and radiation team, and started his six weeks of treatment. During this period, he developed a blood clot in his calf and was treated with Coumadin.

Within a few weeks after completing his six weeks of treatment, a follow-up MRI showed new growth. Richard underwent Gamma Knife two weeks later and continued taking Temodar, but within a few weeks, another follow-up MRI showed new growth. In late September '06, Richard underwent a second

craniotomy. Based on the location of his tumor, we were told there was a 50 percent chance he could lose part or all of his eyesight, and, luckily, that was not the case.

Unlike the first surgery, Richard walked into the hospital, but following this surgery, he had to undergo physical therapy to learn to walk again. Following the surgery, Richard's oncologist said she had nothing left in her arsenal for Richard to try, so we asked her to look into options, and within a few weeks, she told us about a Phase II clinical trial that was starting at UVA. We contacted Dr. David Schiff and set up a meeting. Richard met the criteria for entering the trial, and the week after Thanksgiving '06, Richard underwent his first Avastin infusion.

Now, 62 infusions and 22 MRIs later, Richard's tumor has remained stable, no growth.

DR. WILSON: Thank you.

Our next speaker will be Beth Ann Telford.

MR. THOMPSON: Mr. Chairperson and members of this panel, thank you for the opportunity to speak to you today. My name is Steve Thompson, and I'm speaking to you in my capacity as a parent of a 17-year-old that lost her battle with a glioblastoma, and as a friend of Beth Ann Telford, beside me, who is currently fighting a brain tumor with everything she has.

Krista went through three surgeries, temozolomide, radiation twice, with additional temozolomide, and finally, chemotherapy with Avastin. In

February of 2008, my wife, Kathie, and I thought all possibilities to help Krista had been exhausted. We were then presented the option of chemotherapy with Avastin

I'm happy to report to you today that shortly after beginning this therapy, Krista's cognitive functioning returned to its normal levels. Her steroid dose was tapered and finally eliminated. She went back to school and continued her high level of functioning, retaining her honor roll status, as well as pursuit of athletics.

In July 2008, abbreviated results from an MRI showed the following: interval decrease in size of residual right temporal-parietal glioblastoma multiforme. Since 3/26/08, the size and degree of enhancement have diminished. There is reduced mass effect, diminished leftward midline shift, and improving right lateral temporal horn entrapment.

Krista's driving privileges had been suspended prior to Avastin. They were returned as a result of how well it worked. Krista was able to resume her summer job as a lifeguard. Essentially, except for three visits per month to the clinic for therapy, Krista had her life back, and the quality of that life was better during the Avastin phase than any other time during the four years she battled her tumor. For that matter, she continued to attend school until two days before her death, October 24, 2008. I have included a copy of her interim grade report during this period, five A's and one B.

Krista, myself and her mother, Kathie, were on our front porch about a week before she died. Krista reached out, put her hand on mine, and told us how grateful she was to have us as parents and how she never would have made it this far if we hadn't found her great doctors, and, in particular, her last eight months of treatment with Avastin.

Beth Ann, like Krista, and so many other brain tumor patients, can benefit from Avastin, and they need it now because they do not have time on their side. I want to see Beth Ann continue to run triathlons and be able to go to work everyday, and continue together to raise money to fight brain cancer.

I'm asking you, in memory of my daughter, and all of those who continue to fight this disease, accelerated approval of Avastin. It restores quality, lengthens lives of brain cancer patients, and allows them to continue being productive members of society.

Thank you for your time.

DR. WILSON: Thank you.

Our next speaker will be Jennifer Brusstar.

MS. BRUSSTAR: Good afternoon. My name is Jennifer Brusstar. I'm the CEO and president of the Tug McGraw Foundation. I'd just like to say that I've not received any monies on behalf of any organizations or Genentech to appear here today. I apologize. I flew in from California, and I have a frog in my voice since yesterday.

I had written lots of comments. The Tug McGraw Foundation, we started four years ago. My husband was Tug's teammate and Tug was our friend, and he passed away of a GBM on June 4, 2004. There were no options for Tug McGraw. He was given three weeks to live. As you all know, Tug was a man who played the game of baseball like a Little Leaguer.

I look here and I want to hear all the patients' stories and all the people that have come here today. I want to say, Avastin is not -- it's like the game of baseball. My husband being a pitcher would tell you that all games are not won by home runs. And Avastin is kind of the drug that -- it's kind of the RBI, the batted-in drug to get the men, the women, the children, these caregivers, their families, across home plate until a cure can be found.

Quality of life is about options. I'd like to sit here and take the full three minutes, but I'm not going to because of these men and women that are sitting here. And Jenny McDevitt, who Tug McGraw would say would be my closer, is pretty impressive. And I think we should start thinking about running in Avastin. There's a lot of runners on this thing.

But I just want to say in closing that it's sad to hear when Dr. Richardson says that the quality of life element has not been discussed yet. And what is the marker for that? When you've got only two treatments -- as Dr. Prados stated, in 25, 30 years; I don't know the statistics on that -- acceleration needs to happen. And it's not happening quick enough. And five months, your bull pen's empty when you don't have any options here. And if

four months to five months can mean that you can go another inning, it's important that Avastin gets on the market for these men and women, these children and their caregivers.

So I want to appreciate the time that you have given for us to speak today, and I just want to say what Tug McGraw would say to you all, is you've got to believe, to keep on going. And we're going to find a cure. So thank you.

DR. WILSON: Thank you.

Our next speaker will be Gail McWilliams.

MS. McWILLIAMS: I am not being paid by anybody.

My name is Gail McWilliams. On September 14, 2005, I was diagnosed with a brain tumor with a life forecast of nine months to three years. Three and a half years later, I'm still here. My symptoms seemed so benign. I felt a hair on my face. I thought my nose was running, needles and pins down my arm, and then a sensation of heat in my hand. And it just lasted a few minutes, but it happened five times. And I ended up at Jefferson Hospital with a brain tumor, glioblastoma.

The sensations were textbook, Jacksonian seizures. I had the surgery on September 29th. Operative notes and MRI slides were sent to Duke for input, and we proceeded with radiation and chemotherapy at Jeff, after which we went to Duke for a combination of Temodar and Glivec.

A year had passed since I was diagnosed, and we were permitted a

break in treatment. But Christmas of '06, the break was over. I had a seizure and was back at Jeff. I couldn't pronounce words or put together meanings. I had a new, inoperable brain tumor. I was given steroids. I gained 30 pounds. I had a moon face. My head felt squeaky from the fat cells that were going under my skin.

But 2007 was a new year. I was put on a blind, Level 2 clinical study at Duke, and I was only put on Avastin. Every two weeks, I was infused at Duke; plus, blood, urine, and neurological tests were conducted, and every six weeks an MRI. And that was my routine for 2007. And the doctors started to notice shrinkage in my MRIs. And by the end of 2007, when I was off of Avastin, I had two in a row, no growth, no activity. The following May, I had a bone slab removed, but I was still getting cold scans every two months.

March of 2009, I am standing here in front of you 15 months off of Avastin and three and a half years from diagnosis. And I would say, it was a blessing to me. And I just hope you will approve it for others because I feel like the luckiest person on earth.

DR. WILSON: Thank you very much.

Our next speaker is Al Musella.

MR. MUSELLA: Good afternoon. My name is Al Musella, and I'm the president of the Musella Foundation for Brain Tumor Research and Information, Incorporated. Our organization is dedicated to helping families deal with the diagnosis of a brain tumor and speeding up the search for the cure. I have no

direct personal financial interests with Genentech, but my organization has received some small donations, which are detailed in the letter, which I put on a CD, which I gave to the Committee.

Seventeen hundred and two of my members gave me explicit permission to speak for them at this meeting in favor of approval of Avastin. I will give you some more information on them in a minute. Over 1,300 members have submitted letters in support of approval. I put them together into one PDF file on a CD, which I have given to the Committee.

Reminded are some of our members in a patient registry we call the Brain Tumor Virtual Trial. I checked our ongoing results to see how Avastin has fared. We have 31 GBM patients who took Avastin, and our results were better than that reported for Avastin by Rennenberg, et al. in 2007. This data just confirms that Avastin really works in the real world, not just in these clinical trials. I submitted more details to the Committee in a separate handout.

I'd like to read a few excerpts from the letters on the CD, and I encourage the Committee to read all the letters if they're considering voting against approval. The full text of each letter is on the CD. Here's the first letter.

"My name is Katherine. I am 49 and have three children. I also have a GBM and was told I had six months to a year to live. I failed standard therapy, which included Temodar, radiation and Gliadel, all within a year and

a half. I was then put on Avastin, and the next scan was clean. I was on it for a year, and then my doctor decided to take me off of it. I've had clean scans for 14 months now with no sign of tumor. Please approve Avastin. I may need it again. It has given me more precious time with my children."

Here's a second letter.

"My daughter Monica was diagnosed with a low-grade brain tumor, which progressed to a GBM nine years later. She had three surgeries, standard radiation, Gamma Knife, Temodar, high-dose chemo, bone marrow transplant, and several other chemotherapies. But Monica's condition was deteriorating, and her doctors did not think she would survive much longer.

Within weeks of starting Avastin, she had a remarkable response and was, once again, strong and vibrant. The tumor shrunk significantly, very quickly, on Avastin, and my beautiful daughter's quality of life improved to the point of her becoming fully functioning again. However, since Avastin wasn't approved for brain tumors, we had trouble with her insurance paying for it, and we were forced to stop using it. She died soon afterwards. I don't want this to happen to other families."

And finally, the third letter.

"My daughter Laurie was battling a GBM for 22 months. She failed the standard treatments of surgery, radiation and chemotherapy. We were attempting to put her on Avastin, but her insurance would not pay for it. Before we were able to come up with the money, she passed away. If we would

have been lucky enough to have her insurance pay for it, she could possibly still be alive."

In summary, I would like to ask the Committee members to consider, what would you choose if you were in the situation of having recurrent GBM after failing Temodar? Avastin is the logical drug of choice. It's not perfect, but it's the best of the common alternatives. Your approval will allow brain tumor patients better access to this promising treatment. I would also add that approval may also allow better access to the drug for researchers looking for better ways of using the drug without having ties to the drug company.

Thank you for allowing me to speak on this matter.

DR. WILSON: Thank you.

Our next speaker is Yvonne Stevenson-Schott.

MS. STEVENSON-SCHOTT: Hello. I have no financial relationship with anyone involved in this matter. Thank you for this opportunity. You may question why am I here. You see, I have nothing to gain or lose by your decision today, but I feel strongly and passionately enough about Avastin to be here. My husband, Michael, passed away March 24, 2008. I held him as he took his last breath.

Our journey began in October of '06. It was just a bad headache that took us to the emergency room. The next day, it was a brain tumor, and then a glioblastoma multiforme, Stage IV. I'd never heard of that before.

Unfortunately, today I know a bit too much about it. After the standard treatment of Temodar and radiation, Mike was placed in a clinical trial. It didn't work.

In March of '07, Mike was dying. He was given one month to live. It was brutal watching him fade from me. I took care of him, literally, 24 hours a day. He wasn't able to eat, sleep, walk or use the restroom without help. I needed to assist him with everything. I can remember standing in the shower in my pajamas helping him or helping him literally sit on the toilet by having him slide down my leg. Yes. Can you imagine that?

A second surgery was an option but not recommended. This is when Avastin came into the picture. It really is very simple. Avastin gave Mike his life back. It gave us one more year, a good year, a year of family, friends, travel, and a quality of life that allowed him to really enjoy the simplest things. Mike was gaining weight back, sleeping, and even exercising again.

From what I read, I knew Avastin was the best option for him. I was told it was expensive and not FDA approved. That didn't matter. We paid for it. Yes, it was very costly. My husband was a successful executive, and he could afford it. He was one of the lucky ones.

That is really why I'm here today. Everyone should have the chance, the chance to live one more year. It was a beautiful year. After the first month, I could see changes. Avastin gave us hope. Avastin gave us time.

Mike began to swim again. I will never forget that day in June of '07. I thought I was watching a miracle, but I was watching my husband swim, sometimes up to 30 laps a day.

I am not a doctor. I am not a scientist. I was just a wife, a wife that would have done anything to save her husband. No one will ever know how difficult and painful it is watching the one you love suffer unless you have lived it, and I did. Avastin gave me the chance, the chance to dance with my husband again.

Life is precious, time is critical. Neither should be wasted. Your endorsement today is monumental and will give those fighting for their lives more hope for a better tomorrow. Thank you.

DR. WILSON: Thank you.

Our next speaker is Lindsay Zortman.

MS. ZORTMAN: My name is Lindsay Zortman, and my son Armstrong was diagnosed on November 20th. His tumor is the size of his entire left hemisphere, and he's had three total resections, and the tumor has regrown totally, in less than 21 days. My husband has returned home from overseas, fighting for this country, to take care of my son.

Avastin is his only hope. He's tried Temodar. He's had surgeries, and there's nothing that worked for him. My son has lost the use of his right side, his speech, his walking. He's in horrible pain. His quality of life is not reduced; it's nonexistent. So when we talk about clinical benefits and a

PFS of six months, that's important to me.

This is my son, Armstrong. Thank you.

DR. WILSON: Our last speaker is Ann Levy-Oropeza

MS. LEVY-OROPEZA: 2006 was a very difficult year. I wish there had been time to take a caregiver 101 course, but GBM doesn't afford you the luxury of time. Almost everyone we spoke to said that when the tumor comes back, it does so with a vengeance, not leaving you much time. Instead of being able to really enjoy the move into our new home, we were busy finding an attorney to make sure all our legal paperworks were in order in the event of Richard's death. I visited a nearby hospice facility to learn what options were available.

We were fortunate that our son-in-law and daughter had relocated to Williamsburg at the same time. Our youngest son, who lives in D.C., drove down almost every weekend for over a year, providing love and support. Our granddaughter, Zoey, born one month after our arrival in Williamsburg, proved to be great therapy Richard and provided everyone a much needed distraction.

GBM brought about changes in Richard. Due to being completely paralyzed going into the first surgery, Richard had balance and coordination issues. Richard, who is a degreed engineer, at the time of his diagnosis was a program manager, overseeing the Navy's latest defense ship, had to stop working for almost a year due to the effects of treatments. When he did go back to work on a part-time basis, although he could still do his job, it left

him both mentally and physically drained. So after a year of part-time work, in March of '08, Richard retired after 39 years of service to the Navy.

From a caregiver's perspective, the first nine months living with Richard was like riding a rollercoaster. Between the effects of the steroids and his chemo and radiation, Richard was oftentimes moody. He said things out of frustration that were hurtful, but you had to remind yourself it was the cancer and the treatments that were causing him to be that way.

Richard was an extremely independent person who had traveled rather extensively during his career. For the two years prior to his diagnosis, he spent 70 percent of his time on the East Coast, so imagine all of a sudden you couldn't drive, take a shower without help, and had to rely on others when that was supposed to be your job.

At times, I felt like all we could do was hope, but when each MRI was telling you the treatments were failing, it was hard to hang on to that hope. After Richard's second craniotomy in September '06, when his oncologist said she had run out of options, we were devastated, to say the least. And then we met Dr. David Schiff at UVA, and our hopes were allowed to be cautiously raised, hearing about Avastin and what it might do for GBM.

I did not begin to start breathing easier until about four months into the trial, when after three MRIs, Richard's tumor, which had previously proved too powerful for Temodar, radiation and Gamma Knife, continued to remain stable. The side effects Richard has experienced taking Avastin are

increased hypertension, stiffness in his joints, fatigue, nausea, headaches, and his voice has become hoarse. But he takes additional meds, which have lessened these side effects. During the course of this trial, we have met others who are not here today, but if they or their loved ones could be, they would tell you how much they appreciated that extra time Avastin gave them and their families.

Avastin gave us back our hope, and we are here today to ask you to approve this drug, so Richard and others who are currently suffering with GBM, and the thousands yet to be diagnosed, can experience that same hope for one more day. We'd like to take this opportunity to thank Dr. Schiff and his team at UVA, as well as Genentech and all the other drug companies who continue to work tirelessly to make a difference in the lives of cancer patients. Thanks for giving us hope.

DR. WILSON: Thank you very much.

I'd like to thank all of the speakers for taking the time and coming to speak to us.

(Applause)

DR. WILSON: All right. So now we're going to move on to the questions to the ODAC and to the discussion, the first question, number 1, which is for discussion purposes.

GBM are morphologically, heterogenous tumors with varying amounts of necrosis and edema. Due to the diffusely infiltrative nature of the tumor and

the presence of surrounding edema, measurement of enhancing lesions on MRI is problematical. This difficulty is even greater for relapse gliomas after prior surgery and radiation therapy, the target population for this application.

In addition, bevacizumab neutralizes VEGF-induced vascular permeability, stabilizes the blood-brain barrier, decreasing extravasation of fluid into the brain parenchyma, and results in reduced edema and decreased corticosteroid requirements. It is unclear whether the radiographic improvement, accompanied by a decrease requirement for steroids reported in this application, is the result of an anti-tumor effective bevacizumab or represents radiographic improvement due to reduction in tumor-associated edema and radiation induced necrosis, or both.

For these two reasons, the value of using objective response, determined by standard MRI, as surrogate endpoint for survival in GBM is unclear.

The discussion question is to discuss the validity of objective responses as determined by standard MRI in the setting of VEGF inhibition to support accelerated approval of bevacizumab for GBM.

Let me open up the floor for discussion.

Well, then, let me see if I can't start this.

I guess the discussion points that we touched upon in the morning session really were with regard to whether or not we can rely upon the

radiographic changes as a surrogate for a reasonable likelihood of this having clinical benefit. And I guess the two points that I would bring out is, number one, even if there isn't tumor reduction per se, the reduction in the edema, could that in and of itself result in clinical benefit or not? And secondly, do people feel that we really need hard endpoints, such as overall survival or PFS six months in a randomized study?

Yes? Dr. Curt?

DR. CURT: (Microphone off) -- clinical effects could be significant. But I would rely more on the glioblastoma experts here.

DR. WILSON: Well, then, could I ask both the neuro-oncologists as well as the neurosurgeons to comment on that? I think we all recognize, having dealt with brain tumors, that steroids can certainly reduce symptoms. And so, I think the point that Dr. Curt is making is certainly very relevant.

DR. KIERAN: Okay. I guess I'll start.

I think the question is unanswerable in the sense of I think only further study can give us a definitive answer. But the questions that you asked at the end of the morning session, with respect to, I guess, the burden of proof, I think are addressable here. We've heard not just from the patients and families, but also from a variety of secondary surrogate points, use of steroids, a variety of substatistical analyses -- that maybe each individually don't speak to themselves -- do raise an issue that there seems to be a sense that there is something going on here.

As Dr. Harrington asked in the morning session, if the goal of the follow-up study is to confirm in a more standardized, statistically validated method the utility of this drug, we'll know this answer for sure. But as this committee and many people have pointed out, this is a patient population that doesn't have a lot of options and appears to have something that is benefit. And I would say that everything I have seen, both in the material that was provided to us previously, as well as what we've seen here today, nothing makes me think that if this were my father, my grandfather, that I wouldn't want to do the same thing.

DR. BARKER: I think those of us who deal with this more or less on a daily basis, in patients who have seen enough patients treated with this drug, can say for sure that the drug is having an effect. That effect is not necessarily the effect that we used to expect from these drugs. It may be more in certain ways and it may be less in certain ways.

I think it does largely have an effect like what steroids do. It seems to have much less toxicity than steroids do, and the effect seems to be beyond what steroids can do in the doses that can be clinically delivered. It's a stronger effect on edema, and I think that does correlate, although we haven't seen numbers to prove it, with a benefit in terms of symptoms, in terms of objective signs such as weakness of an arm or leg, and in terms of cognitive function. I think it's unfortunate that we seem to be unable to capture that in numbers or in graphs, but I think it really does happen not

universally to patients treated with this agent, but very commonly.

I think it would be nice if we knew ahead of time who was going to drive that benefit and who was not. Whether or not that's going to lead to longer survival, my suspicion would be that it may. But I think if the objective is both longer life and better life, I think clinical experience strongly suggests that many patients have a better life because of the agent. Whether that life is going to be longer it's obviously going to have to await Phase III trial.

DR. LINK: I have a concern that if we raise the second part of this question about the validity of objective response, if we don't -- if we hear all of the concerns of the neuroradiologists and what they're actually measuring, one is setting up the proposition that the only way we can do a trial of response is to actually do a biopsy before we administer the drug, and then a biopsy afterwards, which you can do that in leukemia. It's a little more difficult to see that in a glioblastoma situation. And, then, we've also heard from our neuro-oncology/neurosurgeons that it's not clear that the biopsy is actually representative anyway, because depending on how many biopsies you do, you may or may not find tumor cells.

So I think that a more strategic question is, if we accept that -- or if we can't accept what we can learn from neuroimaging, then I don't see how we're going to ever be able to do a response-based Phase II trial. We'll have to look at survival as the only endpoint with all its problems.

DR. WILSON: Well, I think what is particularly different about this drug is that it has very profound effects on the vascular permeability. But I think at the end of the day, what we really need to be judging is whether or not in the totality of the data we have seen, do we think there is a reasonable likelihood, irrespective of the mechanism through which this drug works, that it is having either a significant prolongation of survival or, equally critical I would say to many people, a significant improvement of quality of life. To me, that's the real issue here, do we feel the data suggests that.

Let me ask the members of the Committee what their thoughts are, given the totality of the data.

DR. BARKER: I would say that the responses that we have seen are, if not unprecedented, at least extremely unusual to see from prior agents. I think that the drug clearly has a unique effect -- perhaps not unique with reference to other members of the same class. But drugs that do this do something different than cytotoxic drugs do. The fact that response measures that were developed solely with cytotoxic drugs in mind don't capture the entire effect of this drug doesn't really bother me that much. I think it's pretty good. I would say it convinces me.

DR. WILSON: One of the issues is we really -- I think that we sort of typically want to look at tumor measurements, but I think we have the setting here where the microenvironment -- and I use that more in a global way

-- is really being impacted. And I think that, again, it is different than what we typically see, but there does appear -- in the totality of evidence, that there appears to be having biological, if not physical, impacts on the patients in a positive way. I think that it is more a matter of the burden of proof at the current time.

DR. HARRINGTON: So we really only have surrogates for everything here, including the quality of life, because we have very good data on the possible reduction in swelling, et cetera. My own sense is that we have the best possible surrogates we could have in the context of this trial, which was not designed initially as a registration trial. And we don't have evidence from either the Agency or the company that potentially valuable measurements were overlooked here or not taken in the right way.

I think that, for me, the value of these surrogates increases as the risk profile of the agent decreases. And so, if we were looking at an agent that had significant side effects, and we were substantially uncertain about what the benefits were, then the lack of perfect interpretability of the surrogates becomes problematic. In this instance, I haven't seen any data yet to suggest there's any evidence at all that this is worse, worse in any way, worse either in a side effect profile, given the side effects of the sequelae, of the glioblastoma itself, or worse, certainly in terms of survival.

I think we do see a lot of balancing around in survival. And I think the question that Dr. Wilson raised to start the morning session about

the apparent lack of a survival extension in the group that got the irinotecan plus Avastin probably suggests that the measurement of the survival benefit here is subject to a lot of uncertainty. And the randomized trial may not show up as nearly as great as it is here, but I'm fairly convinced that it's not worse than we've seen in the past.

DR. WILSON: So any other thoughts, discussion, on this?

DR. RICHARDSON: I'm not sure what we're seeing on the MRI scans. I think as we look at these changes in these scans over time, I think many of these become more and more confusing, and our level of uncertainty seems to grow. I'm not sure any of it really matters, however, because I think the reduction in steroids is a very meaningful improvement for a lot of the folks who are on bevacizumab.

Clearly, the patients who take high doses of steroids have a reduced quality of life from that. I think it would be great if we could somehow separate out what is truly an anti-tumor effect from whatever is going on at the vascular permeability level. My own gut feeling is that the anti-tumor effect is probably quite small. Hopefully, the Phase III study will sort this out. I'm not confident that that's going to answer the question, though.

I think that it would be better if we had a survival endpoint to be looking at here. With the data at hand, though, I think there does seem to be a favorable effect of this compound. And I think whether it's going to be worth the economic impact I think is a different question.

DR. WILSON: Dr. Lyman?

DR. LYMAN: Yes. I think, as is often the case, Question 1 is not as problematic for us as the ultimate question, or Question 2. I think we're not going to resolve, until there are further advances in imaging, the issue of how much of this effect is tumor or peri-tumoral in nature. I think we can all be a bit reassured that these are all potentially favorable effects in terms of symptoms, signs, and we'll see long term whether the net effect is an improvement in survival.

I think we're also bothered by a number of things, not just the uncertainty around that, and the uncertainty around the fact that the higher response rate in the other arm of the trial, actually, if anything, had a lower median progression-free survival associated with it. And, in fact, most of the studies of bevacizumab in other tumor types, it's been the combination therapy that has been where the greatest benefit has been, and we don't see that in this context.

I think bothered by the lack of concurrent control. We all know the problems of patient eligibility selection criteria, exclusion of sicker patients, and comparability of this population with any of the historical control data I think is problematic as well. And I think another problem -- David may have mentioned this earlier -- is what will the Agency do if that large prospective randomized trial, which I think we have to laud the company and the Agency for pushing as quickly as possible -- for earlier stage of

disease, what if that is in fact a negative study, and where do we go in terms of access and approval in this setting? It's a little bit of the cart before the horse in a sense.

But on the other hand, I think if the Agency does approve for recurrent disease, it's going to be difficult to do further prospective comparative trials in the advance disease setting because of the general availability, and most patients will have been exposed prior to going on to a trial where they might get randomized to no bevacizumab.

So these are all problems, not to mention, again, the crossover design. Of course, we can't really address survival issues in the context of this trial. And given the imaging problems, progression-free survival or time to event, it has this considerable uncertainty with it. But with all that, and that benefit, I think I share what others have said. Putting it in context of just about everybody else's experience, both anecdotal and in series, reporting the literature, we seem to be seeing something that's considerably different. And I think the problem of not approving it or not recommending approval may outweigh many of these uncertainties, and they are many, about the quality of the data that's before us.

DR. WILSON: Let me pose a question for the FDA.

If the randomized study does not show any improvement in survival, would the FDA, as they have in the past, recognize significant improvement in quality of life for other measures as an indication for approval?

DR. PAZDUR: It doesn't necessarily have to be a -- it has to be the demonstration of clinical benefit, which could either be an improvement in survival and improvement in disease related symptoms, something that's tangible to the patient. However, that would have to be met with statistical persuasiveness. It just couldn't be an ad hoc finding that one obtains.

Granted, here again, one would hope that if the drug does get approved, that one would be seeing additional trials, and this wouldn't be the last time we hear about this drug in brain tumors. I think everybody in the neuro-oncology community would like to see further development of this drug. So I don't think we have to take a look at this trial, this Phase III trial, as the last and ultimate trial that will ever be done with this drug.

DR. LYMAN: Just one additional comment. I think, again, probably shared by others, if we do feel that there's, despite the uncertainty, some net benefit being impacted on patients in this setting, given the testimonies that we've heard and the availability of the agent, I am also a bit concerned about a two-class system in a sense, that is patients who can afford the drug and so forth, getting access to it.

So the question to the Agency would be -- of course, we assume that reimbursement will be tied to label and approval, but if the ultimate decision was not to approve at this point but to await, say, the Phase III trial, patients are going to still continue to get it, probably both in and outside of trials. But those that can't get at it, if we feel there really is

something going on here that's beneficial, we create a real dilemma for you folks and for clinicians.

DR. PAZDUR: Gary, don't go there, okay? The issue is does this drug demonstrate safety and efficacy. We should not -- and I'm going to emphasize this to everybody on the committee because several inferences have been made in discussions here about cost of drugs. This should bear -- there should be no bearing in any decision about the cost of this drug. The decision should be solely based on a risk/benefit decision and the demonstration of safety and efficacy.

DR. WILSON: Dr. Curt?

DR. CURT: And Dr. Pazdur just answered the question. But I was going to make the point that the ODAC does not consider the economic impact of its decisions, just the science and the clinical relevance.

DR. WILSON: If there is not a survival difference, my question to the Agency and to the sponsor is, what is the power of the current study to detect differences in quality of life, and is that power adequate to see the types of improvement that the Agency would like to see that they might consider approving the drug on?

DR. KEEGAN: I just want to make a point that, although, as Dr. Pazdur says, we'll look at all the information, it does represent something of a problem, if a study fails on its co-primary endpoints, to start looking at lots of other endpoints. And we have not discussed using this trial as a

basis for establishing quality of life benefits, which would be a somewhat complicated undertaking. I mean, it really needs to be considered up front before the study gets started. A number of exploratory analyses is not going to really be satisfactory.

DR. PAZDUR: If the Committee, however, feels that there should be additional trials looking at quality of life, that would meet criteria that assesses quality of life in an accurate fashion, please tell us about your concerns about this and the need for additional trials other than the one trial that has been proposed.

DR. WILSON: I think the point that I'm getting at is that I think the totality of the evidence would suggest that there is some clinical benefit here. But if you were to say, well, what is the likelihood there will be a survival benefit here, I have to say that I have a much lower index on that. And so, that's why I bring up these other issues because if we are, in fact, looking at there being the likelihood of clinical benefit and many of us think that's primarily going to be in quality of life, -- and, again, we obviously don't have a crystal ball here -- one would hope that a confirmatory trial would end in a prospective manner, have that built in. And that's really the issue I was raising here.

DR. PAZDUR: Remember, the co-primary endpoint also is progression-free survival, so that could be interpreted as a positive trial based on that.

The other point that hasn't been discussed here that I'd like to

bring up, remember, this is the fourth or fifth approval for this drug. We're not talking about a new molecular entity here, and we have other diseases to draw upon of demonstration of this drug's activity in colorectal carcinoma, in lung cancer, and in breast cancer, albeit, the third one is under accelerated approval. But we have a drug here that has demonstrated activity in a wide variety of diseases.

DR. LYMAN: I would just add to that, in addition to further efficacy data, I think we really need more safety data, particularly in this population where we have a 26 percent serious adverse event rate, essentially the same as the purported response rate. And we are dealing with a tumor that already has accessed thromboembolic complications, bleeding risks, and we're adding an agent that appears to contribute even in other tumor settings. So I think those events, and wound perforation, all these things, we need better data, longer-term data, in this specific population.

DR. HARRINGTON: So perhaps not to belabor this point, but I want to go back to Dr. Wilson's question because I don't think we quite have heard the answer yet. So let me try to rephrase it.

I think his question was, in the plan's trial, the randomized trial that's about to start, is it sufficiently powered, does it have an analysis plan for symptom relief or quality of life? And if it doesn't in a patient population where those are clearly very important endpoints, why doesn't it?

DR. SCHENKEIN: So in the current design in the study -- and,

clearly, we're still finalizing our conversations with the FDA. As Dr. Pazdur's mentioned, the secondary -- the co-primary endpoint is progression-free survival. We do have neurocognitive function, based on some of the instruments that we tested in the Phase II study, that will be secondary endpoints, but they are currently not powered to the degree that I think would satisfy the Committee. It's a conversation that we can have with the FDA.

DR. HARRINGTON: I think those are very valid co-primary endpoints, but I don't think progression-free survival is quite the same thing here as the apparent symptom relief that we're both seeing and hearing about, and could, in fact, be the basis for the use of the drug even if it did not significantly extend survival. So I guess we would hope that in 2014, we don't find ourselves in a very similar position, where we say, well, we didn't really get a significant p value here for survival, but we have reduced edema, and we have people who apparently have great stories about being able to return to their life, and be stuck again.

DR. PAZDUR: I think we've heard you. We'll discuss this with the sponsor.

DR. WILSON: Any more points?

Well, I think that we're running a little bit ahead of time, so should we just move on to the second voting question?

So the second question is to be voted upon.

Objective response has not been used as the basis for accelerated

approval for GBM. Objective response rate is determined by standard MRI with 25.9 percent and 19.6 percent in two single-arm studies. The median duration of response for responders is 4.2 and 3.9 months, respectively. There were no complete responses.

The question for voting before the Committee is, is the response seen in this application of significant magnitude, that is, clinically meaningful to serve as a surrogate reasonably likely to predict clinical benefit for the purpose of accelerated approval in refractory GBM?

Do any of the members have any comments on this, discussion points?

DR. BARKER: I think I'll go ahead and say that I'm not troubled by the comparison to historical controls. I've seen enough of those historical controls in the last 20 years. This is something different.

DR. LOEFFLER: I also think it's important to understand that when you treat a brain tumor, even if you sterilized every tumor cell in the brain, the brain is never normal again. The blood-brain barrier is disrupted forever from surgery, radiation, in particular. The fact that you don't see a complete response or even a dramatic partial response -- and we know from lymphomas, often, patients who rendered disease free for years and years and years still have abnormal FLAIR changes and enhancement patterns.

So it's a different disease than a large-cell lymphoma of the mediastinum, where you're looking for often a complete radiographic response. You'll never seen that no matter what therapies we develop in the next 20

years. So I think these results are dramatic as a caregiver for patients with brain tumors.

DR. LYMAN: Perhaps Richard can put some light on this.

I think it may relate back to that workshop, but at some point, a benchmark of 30 percent response, I thought, was introduced in discussions there.

Is that a recollection of anybody?

DR. BARKER: I actually went through the manuscript last night. Dr. Buckner on page 15 said 3 percent. Dr. Fine on page 23 said 15 percent or 20 percent.

DR. LYMAN: So we have perfect agreement, in other words.

DR. BARKER: Yes. There wasn't -- we weren't asked for a number that was a consensus, and we didn't give one.

DR. PAZDUR: I think this is quite difficult to do because, obviously, for each drug, it depends on a risk/benefit, the toxicities of it, the confidence that you have in the point estimates, the 95 percent confidence intervals surrounding it.

If anything, I would have to say, with the data that we've had -- and I think it's important for people to realize, this was one of the first applications -- or one of the few applications, I should say, that we reviewed all of the x-rays independently. So even though the numbers were not exactly in one study, we did see it in -- our numbers did match with the other one. I

think there's a high degree of confidence in what we're reading here as achieving a response by the criteria were met out.

DR. WILSON: I would say that just on the face value, based on what I've seen with other agents in this disease, that a response rate of 20 to 25 percent is a very robust number. And so, to me, what we've been struggling with more is, are these responses -- will they reflect clinical benefit. But I personally think that if, in fact, they do, this is a very good number.

Yes, Dr. Curt?

DR. CURT: I just want clarification from the Agency.

How important is the magnitude of the unmet medical need in the advice that we give you?

DR. PAZDUR: It should bear into consideration, obviously.

DR. WILSON: Well, I won't have you sit here and be tortured by silence. So if I hear no more thoughts, maybe we can then go on to voting.

We will be using the new electronic voting system for this meeting. Each of you have three voting buttons on your microphone labeled yes, no and abstain. Once we begin the vote, please press the button that corresponds to your vote. After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. I will read the vote from the screen into the record. Next, we will go around the room, and each individual who voted will state their name and vote into the record, as well as provide a reason why they voted as they did.

So if there are no further discussions on this question, we will now begin the voting process. Please press the button on the microphone that corresponds to your vote.

(Pause in the proceedings.)

DR. WILSON: Thank you. The vote is now complete.

(Applause)

DR. WILSON: For the record, yes, 10 votes; no, zero votes; abstain, zero votes.

(Applause)

DR. WILSON: May I ask, starting on the left, for the first voting member to begin and give us their vote, which we already know, and give us the reason why they voted as they did. And please state your name.

DR. BARKER: Fred Barker. I voted yes. I view this as a bet on the success of the randomized trial that we've been told is planned, and I feel confident enough that that will display a clinical benefit to vote yes.

DR. LINK: I voted yes because I believe that this response rate, whatever is responding and however ambiguous; but interpretations of the MRIs are significant and, certainly, substantially better than almost anything else that has been seen in this tumor in the last 30 years.

DR. HARRINGTON: I voted yes despite the uncertainty in the data. I also agree that we are seeing some activity here and that the risk/benefit profile is very much in favor of the drug.

DR. RICHARDSON: I voted yes. I think patients do appear to benefit from this. I'm uncertain just what the cause is for that benefit, whether it's more on the basis of vascular permeability effects versus tumor effects. But, clearly, I think there is some improved -- well, let me put it this way. I think they do get benefit from this, and I vote yes for that reason.

DR. WILSON: Wyndham Wilson. I voted yes. I felt that the totality of the data raised a reasonable likelihood of clinical benefit. I also felt that edema in a closed space, such as the brain, does have side effects, and those effects we know are ameliorated through steroids. So even if there's not a survival advantage, I feel there is a reasonable likelihood that these radiographic changes will be reflected in improved quality of life.

DR. LYMAN: Gary Lyman. I also voted yes. Despite the uncertainty as to the reasons for the imaging responses that we're seeing, they seem to be net beneficial, in a net beneficial direction. I also believe that these responses are reasonably likely to predict a clinical benefit, hopefully to be confirmed in large randomized trials, net benefit. Although I am concerned about the serious toxicities that occur, it most likely outweighs that risk and will lead either to improved survival or quality-adjusted survival.

MS. MASON: Virginia Mason, and I voted yes. I'm excited to see something on the market available for patients who don't have a lot of options. And for me, it looks like the risk/benefit profile makes it worthwhile to pursue.

MS. ALMGREN: Peggy Almgren. I voted yes. I think the benefits definitely outweigh the risks. I'd like patient accessibility for this, and also, even to further advance this to look at the stabilization of a tumor because I think if you have a stabilized brain tumor, it's significant. And I think that's something that's being overlooked, but maybe we can progress to include that as a positive response.

DR. LOEFFLER: Jay Loeffler. I voted yes. I think this represents a new generation of molecules to treat our patients with brain tumors. And I'm actually confident that the Phase III trial's going to be positive. I think it's going to increase the effectiveness of radiation and chemotherapy when it's given as part of the initial therapy. And I think -- as I said earlier, I am optimistic that that will be a positive trial.

DR. KIERAN: Mark Kieran. I also voted yes for a number of reasons, most of which we've heard. Population is clearly in need with relatively limited options. And I think we agreed that we would take that into account, that the data is certainly encouraging on multiple fronts. No one individual data point was a home run, but with respect to overall response, six-month, progression-free survival, decrease in steroid use, all, certainly, I think lead us in the correct direction.

I think the comparison data that Dr. Prados showed over multiple studies, some of which were concurrent that don't do nearly as well, tell us that we may be on to something here. It would be a shame to ignore it. I

think the safety data, although not completely negative -- there's no such thing as a drug with no toxicity -- it certainly seemed appropriate for this patient population, so something that I think doesn't -- I think the risk component isn't high enough to overwhelm the positive components.

Certainly, the independent results from Howie Fine's study I think can't be ignored, given that they were completely independent and arrived at the same conclusion; and laud the FDA and the company for developing a trial which it sounds like may still be developing in terms of goals to answer the question in a more definitive way. But like many of the others, I think that the answer is going to be positive, not just with respect to symptom management, but I think also to disease outcome.

DR. WILSON: All right. Thank you all, and let me thank you all for taking the time, the ODAC Committee, today. The meeting is adjourned.

(Whereupon, the proceedings at 2:16 p.m. were concluded.)