DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUG ADVISORY COMMITTEE

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Hilton Washington
620 Perry Parkway
Gaithersburg, Maryland

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Donna Przepiorka, M.D., Ph.D., Chair
Johanna M. Clifford, M.S., RN,
  Executive Secretary

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Michael Bishop, M.D.
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Ralph D'Agostino, Ph.D.
Maha Hussain, M.D.
Jan Buckner, M.D.
Wen-Jen Hwu, M.D.
Joanne Mortimer, M.D.
Michael Perry, M.D.

PATIENT REPRESENTATIVES (VOTING):

Kenneth McDonough (for Genasense)
Natalie Compagni-Portis (for RSR 13 Injection)

FDA STAFF:

Richard Pazdur, M.D.
Grant Williams, M.D.
Robert Temple, M.D.

C O N T E N T S

C O N T E N T S

P R O C E E D I N G S

Opening Remarks

DR. PRZEPIORKA: Good morning to all and welcome to the Food and Drug Administration's Advisory Committee for Oncologic Drugs. My name is Donna Przepiorka. I will be chairing the committee. I just wanted to remind everyone in the audience that the purpose of the individuals on this panel is to serve as independent consultants to the FDA. We do not work for the FDA. We are also not anyone who makes any decisions; we only provide advice.

Our first item on the agenda--we are going to go a little bit out of order. We want to hear first from Congressman Deutsch who has a few words to say.

CONGRESSMAN DEUTSCH: Thank you very much. I appreciate the opportunity to be here. My name is Congressman Peter Deutsch, and I recognize that it is not at every meeting of this committee that you are addressed by a member of Congress. Largely it is in that capacity that I speak to you today,

but it is also in my capacity as an individual who has been personally affected by the specter of melanoma.

On several occasions I have had basal cells removed from my body. Thankfully, they were not malignant but their existence renders me high risk. My dermatologist now evaluates me on a quarterly basis for melanoma and guides me on how to reduce my risk profile. I pray that this risk never materializes but, if it does, I need to know that my physician and I have access to every therapeutic treatment available for this horrible disease. As someone who actually hears people testify in many settings, I am trying to get your attention so actually I have pictures of my kids who both have red hair so, obviously, they are high risk for skin cancer as well especially as having a parent who has been diagnosed with basal cells. They also happen to live in Florida.

Again, most of the people in this room don't live in Florida and I am not exaggerating that the school that they go to and, in fact, the

schools they have gone to since pre-K, do not have hallways. It is one of the unique things about Florida, south Florida in particular so they are literally outside all the time. For anyone who has kids, especially in a setting like south Florida, think about the summer when you try to get your kids to wear suntan lotion. It is not an easy thing to do. So, this is a very real thing. I mean, I have fights with my kids, especially as they have gotten older, about putting suntan lotion on, on a continuous basis.

But it is not just for my kids; it is not for myself that I am here today. It is for all the constituents I represent and all the citizens around the nation. So, it is on their behalf as well that I stand before you today, not to advocate for the approval of this drug but to advocate that the mind set from which you consider this application be your own mind set--clinical physicians dedicated to the welfare of their patients.

What does this mean? That this

application be a referendum on whether you would want this drug available to your patients if they were diagnosed with metastatic melanoma. That is the standard we owe cancer patients and that is the standard government is obligated to uphold.

I did not come here to preach to this committee to the extent me and Congress have had frustration with over-regulation by the FDA. It is not of your doing; quite the opposite. It is people like yourselves who give up your time to guide the FDA. I cannot over-emphasize the importance of your role. You provide the FDA a window that they otherwise do not have, a window into the real world, if you will, a world in which dying cancer patients are desperate for and must be given access to every reasonable treatment that might save their lives.

As you may know, there were two relevant newspaper articles last week that got some attention in Congress. One was an article in The New York Times about a Japanese study published in The New England Journal of Medicine proving the

effectiveness of a drug called UFT in treating a form of lung cancer. What was staggering about the article was that this same technology was rejected in this country by the FDA. In other words, thousands of cancer patients in this country could be dying because the government failed them.

What I later learned was that the FDA rejected this drug even though this very advisory committee composed of your predecessors voted unanimously to approve it and, because the FDA did not accept the recommendations of clinicians, countless Americans lack access to that drug today. That is inexcusable.

In the other article, the Wall Street Journal related to this committee's hearings. It offered no views on whether this drug should be approved but, instead, noted the absence of treatments for metastatic melanoma and a couple of vignettes about the people who took the drug. One of those was an individual names David Bernstein who is scheduled to join us here today. Mr. Bernstein is a fourth grade teacher from a small

town in New Jersey. The article said that Mr. Bernstein's cancer went away and he is alive today, teaching his students in his fourth grade classroom because of the drug before you today.

I am not a physician nor a scientist and I have not studied the clinical data regarding this drug, but I do know this, if you find that this drug is as safe and effective as other available treatments, if it reasonably presents another possible course of treatment, by what right can government deny cancer patients an avenue to save their lives? This is not about a passing illness for which there are other treatments. This is about cancer, an absolutely devastating disease that has in some ways affected nearly every single American. This is about cancer patients who are dying and desperate for a chance to live longer. It is in their interest that we must be foremost in today's hearing.

I flew back to Washington last night to speak to you this morning, however, prior obligations in my district require me to actually

literally turn around right now and return to Florida this morning. I regret that I can't stay here to listen to all of the testimony but I wish to thank this committee for its time, and it has been an honor and pleasure to speak with you this morning.

DR. PRZEPIORKA: Thank you, Congressman Deutsch. Any questions for the Congressman?

[No response]

Thank you, sir.

CONGRESSMAN DEUTSCH: Thank you.

DR. PRZEPIORKA: Next we will hear from a representative from Congressman Ferguson's office.

MR. DELPIZO: My name is Alex Delpizo. I am here representing Congressman Mike Ferguson of New Jersey who, unfortunately, is in New Jersey and couldn't be here with us today.

I am not a scientist or a clinician or a chemist but everyone knows a person whose life has been taken by cancer. For me, that person was my mother. She fought and eventually lost her six-year battle with cancer. However, due to

miracle life-extending drugs she saw two of her children get married and met her three grandchildren. My mother was fortunate enough to experience all of the wonderful things that mothers and grandmothers experience later in life.

As you know, Genasense us used to treat stage 4 metastatic melanoma. Metastatic melanoma is currently a death sentence. When two available therapies treat the disease and the last chemotherapy therapy treatment was approved in 1975, yours is an awesome responsibility. The FDA works every day to ensure that Americans and their food and drug supply are safe. Your decisions on which drugs are approved are based on numbers, and numbers are very important, however, we would never want to approve a placebo. However, an over-emphasis on statistics at the expense of patient needs does a life-threatening disservice. The failure to appreciate mean or median statistical analyses in any size sampling also fails to take into account a patient population that achieved the most dramatic overall response.

Given the devastating nature of this disease and the relatively few treatments available, even marginal increases in life expectancy can clearly be the difference between rapid death and years of life extension for those patients that will see a benefit from this and other drugs.

In closing, I would like to highlight the experience of one of my constituents in Montgomery Township in New Jersey. David Bernstein was diagnosed with skin cancer and prescribed chemotherapy to remove a grape-sized tumor on his chest. Mr. Bernstein opted to supplement the chemotherapy by joining a clinical trial of an experimental drug. Six weeks after his first dose he received the news that his tumor had essentially disappeared. This was two years ago. That experimental drug was Genasense.

For my mother, David Bernstein and for all of those who have been diagnosed with cancer, I respectfully request that you look favorably on Genasense and other new drug applications that can

provide hope for those for whom hope is all they have. Thank you very much.

DR. PRZEPIORKA: Thank you. Again, I would like to ask the folks who are standing along that far wall by the doors to please step outside into the hall, or take a seat, or take a stand at the back wall only, please. You are going to need to vacate that area immediately, please.

We would like to now move on to the first item on the agenda and Johanna Clifford will read the conflict of interest statement. Thank you.

Conflict of Interest Statement

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

Based on the submitted agenda and information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a

conflict of interest at this meeting, with the following exceptions:

In accordance with 18 USC Section 208(b)(3), Dr. Ronald Bukowski has been granted a waiver for serving on a competitor's advisory board on an unrelated matter for which he receives less than $10,000 a year; consulting with the sponsor of dacarbazine on an unrelated matter for which he receives less than $10,000 a year; and, finally, for consulting with a competitor on an unrelated matter for which he receives less than $10,000 a year.

Dr. Maha Hussain has been granted waivers under 18 USC 208(b)(3) and 21 USC 505(n) for unrelated consulting for the co-developed of Genasense for which she receives less than $10,000 a year; and owning stock in the co-developer of Genasense, valued from $25,001 to $50,000.

Dr. Wen-Jen Hwu has been granted a limited waiver under 18 USC 208(b)(3) for her employer's contract with a competitor for an investigator-initiated study of a competing

product. The contrast is less than $100,000 a year. Under the terms of the waiver, Dr. Hwu will be permitted to participate in the committee's discussions of Genasense. She will not, however, be able to vote.

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

We would also like to disclose that Dr. Silvana Martino has been recused from participating in all matters concerning Genta's Genasense.

Lastly, we would like to note for the record that Dr. Antonio Grillo-Lopez, Chairman, Neoplastic and Autoimmune Diseases Research Institute, is participating in this meeting as in industry representative, acting on behalf of regulated industry. He would like to disclose that he is a scientific advisor to Chiron and receives speakers fees from Roche.

In the event that the discussions involve any other products or firms not already on the

agenda for which FDA participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

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

DR. PRZEPIORKA: Thank you. Once again, there are still some folks registered for the open public hearing who have not signed in. I just want to remind you that if you do wish to speak at the open public hearing you will need to sign in at the table outside.

Next, I would like the members of the committee and the other participants to introduce themselves and we will start with Dr. Pazdur.

DR. PAZDUR: Richard Pazdur, Director of the Division of Oncology Drug Products, FDA.

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

DR. FARRELL: Ann Farrell, clinical team leader for Genasense.

DR. KANE: Robert Kane, medical reviewer.

DR. YANG: Peiling Yang, statistical reviewer.

DR. BUKOWSKI: Ron Bukowski, medical oncologist, Cleveland.

DR. BISHOP: Michael Bishop, Experimental Transplantation, Immunology Branch, National Cancer Institute.

DR. HWU: Wen-Jen Hwu, medical oncologist at the Memorial Sloan-Kettering.

DR. TAYLOR: Sarah Taylor, University of Kansas.

DR. REAMAN: Gregory Reaman, George Washington University and Children's National Medical Center.

DR. REDMAN: Bruce Redman, University of Michigan.

MS. CLIFFORD: Johanna Clifford, FDA, executive secretary for this meeting.

DR. PRZEPIORKA: Donna Przepiorka,

University of Tennessee, Memphis.

DR. RODRIGUEZ: Maria Rodriguez, medical oncologist, M.D. Anderson Cancer Center.

DR. DOROSHOW: Jim Doroshow, Division of Cancer Treatment and Diagnosis, NCI.

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

DR. GEORGE: Stephen George, Duke University.

MS. HAYLOCK: Pamela Haylock. I am a nurse and I am at the University of Texas.

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

DR. D'AGOSTINO: Ralph D'Agostino, Boston University biostatistician.

DR. MORTIMER: Joanne Mortimer, medical oncology Eastern Virginia Medical School.

DR. HUSSAIN: Maha Hussain, University of Michigan.

MR. MCDONOUGH: Ken McDonough, patient representative.

DR. GRILLO-LOPEZ: Antonio Grillo-Lopez,

Neoplastic and Autoimmune Diseases Research Institute.

DR. PRZEPIORKA: Thank you to all. I think Dr. Pazdur will open with some remarks.

Opening Remarks

DR. PAZDUR: Thank you very much, Donna. First, I would like to recognize the contributions of four ODAC members who will be leaving the committee after this meeting. These members include our chairman, Donna Przepiorka, John Carpenter, Sarah Taylor and Bruce Redman. We, at the FDA, recognize their efforts at providing us advice at these public meetings and, in addition, we appreciate their valuable assistance throughout the years in providing us with their insights at other FDA meetings and in reviewing and assessing protocols. Our work and the welfare of the American public is greatly facilitated by their hours of work and their talents devoted to these tasks. Again, Donna, John, Sarah and Bruce, we thank you for your efforts, your patience with our phone calls, and advice on some of the most

perplexing issues of drug development. Let me say this, this is not "adios" but "hasta la vista" and it is not "hasta la vista, baby." We will be calling you; we will be in touch; this will be a continuous process that we will be dealing with you over the years, but we do appreciate your kindness and your efforts at helping us with some of the problems that we have at hand.

Let's turn to the issues at hand. This morning's meeting focuses on a drug for the treatment of patients with advanced melanoma who have not received prior chemotherapy. I would like to spend some time addressing issues for you to consider during the presentations provided by the sponsor and the FDA staff. These issues are important to this application but also this afternoon's application and in drug development in general, especially as we have continuing, ongoing discussions and dialogue with the committee on endpoints for drug development.

The FDA has long considered the demonstration of an improved survival as the gold

standard for drug approval. An improvement in survival associated with an acceptable safety profile is of unquestionable clinical benefit. It is assessed daily and is unambiguous. When we, at the FDA, began our discussions with the committee on drug approval we realized that there may be some disadvantages to requiring survival improvement for drug approval. These disadvantages include the confounding of survival analysis by crossover with frequently large patient numbers required to be enrolled on trials for survival, and the long follow-up that may be required in selected oncological diseases.

This trial at hand this morning was originally discussed with the agency to be a trial with a primary endpoint of survival improvement. The trial did not demonstrate an improvement in overall survival. We are asked to evaluate this drug for approval on the basis of secondary endpoints of claimed improvements in progression-free survival or PFS and response rates. Please member that since this drug is added

to a standard therapy we must assess the drug's contribution to that standard therapy and any claimed response rates or claims for PFS advantages represent a combination of the investigational agent and the standard therapy. Hence, we must isolate the efficacy of the drug in assessing the drug's efficacy.

Let's turn our attention to the measurement and assessment of PFS which will be discussed during this meeting on multiple occasions. The assessment of PFS may be difficult and uncertain in unblinded trials with a small effect on this endpoint and where there is a lack of attention to clinical trial issues that are important in measuring and comparing PFS data between treatment arms. These issues include a prospectively defined methodology for assessing, measuring and analyzing PFS. These need to be detailed in the protocol and in the statistical plan. Tumor progression should be carefully defined in the protocol. The FDA and the sponsor should agree prospectively on the protocol, the

case report forms and the statistical analysis plan for PFS. There should be a prespecified analysis plan for handling missing data, especially missed assessment visits. Censoring methods and assessment of progression in non-measurable lesions must be prospectively outlined and agreed upon. Most importantly, visits and radiological assessments should be symmetrical on the study arms to prevent systematic bias. When possible, studies should be blinded. This is especially important when the patient or investigator assessments are included as components of the progression endpoint. If progression is assessed by both the treating physician and an external review panel or an external radiology committee, the protocol should prospectively stipulate whose assessment will be used in defining PFS. This cannot occur after the study data has been examined.

Hence, from a practical perspective, PFS as a primary endpoint for drug approval takes meticulous, prospective planning. The measurement of PFS progression-free survival requires rigor.

This planning is frequently lacking in clinical trials that relegate PFS to a secondary endpoint. Some practical problems outlined above in accurately characterizing the treatment of PFS will be discussed by the FDA reviewers.

Provided an acceptable safety profile, one has to answer the following question, what is the magnitude of the drug's effect on PFS that would be considered clinically relevant? A very small effect may raise questions about the very existence of this effect, especially when the study is unblinded and attention to the symmetry of assessments and handling of missing assessments is not evident.

In answering whether marketing approval should be granted to an agent, two important questions need to be answered. First, does the drug have a convincing effect that can be adequately characterized? Secondly, and this question can only be addressed if the first question is answered in the affirmative, what is the clinical relevance of the effect? This

obviously must take into account a risk-benefit analysis. However, benefit can only be assessed in this equation if it convincingly exists and also can be adequately characterized.

I hope these comments will provide a catalyst for your considerations this morning, this afternoon and tomorrow as we discuss endpoints of drug approval. Donna, I turn the program over to you and I will answer questions after the FDA presentations. Thank you.

DR. PRZEPIORKA: Thank you, Dr. Pazdur. Let's go ahead and begin with the sponsor presentation, with an introduction by Dr. Itri.

Sponsor Presentation

Introduction

[Slide]

DR. ITRI: Dr. Przepiorka, members of the Oncology Drug Advisory Committee, ladies and gentlemen, it is my pleasure, on behalf of Genta, to introduce the agenda and the participants for the presentation of the new drug application for Genasense in combination with dacarbazine for the

treatment of patients with advanced malignant melanoma.

Following my introductory remarks, Dr. John Kirkwood will give an overview of malignant melanoma and available treatments. After Dr. Kirkwood's presentation I will return to the podium and discuss the results of GM301 in detail. At that point, Dr. Frank Haluska will summarize the risks and benefits in the context of the disease we are treating.

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By way of introducing our speakers, Dr. Frank Haluska is from Harvard University and Mass. General Hospital. He is chairman of the CALGB melanoma committee. Dr. John Kirkwood is professor and vice chairman of Medicine at the University of Pittsburgh and is also chairman of the ECOG melanoma committee.

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In addition to our distinguished speakers, we are fortunate to have with us today a number of clinical experts in the field of melanoma,

including Dr. Sanjiv Agarwala from the University of Pittsburgh Cancer Center, Dr. Agop Bedikian from M.D. Anderson Cancer Center, Dr. Paul Chapman from the Memorial Sloan-Kettering Cancer Center, Dr. Robert Conry from the University of Alabama, Dr. Peter Hersey from the University of Newcastle, all the way from Australia, and Dr. Evan Hersh from the University of Arizona Cancer Center.

Drs. Bedikian, Conry, Hersey and Hersh were principal investigators in our study and together are responsible for managing approximately 20 percent of patients who are on our trial. They are available to address any issues you may have regarding patient management in the study. Dr. Janet Wittes, formerly head of statistics at the National Heart, Lung and Blood Institute and currently president of Statistics Collaborative, is available to provide expert biostatistical consultation. Dr. Robert Ford, chief medical officer and founder of RadPharm, is with us to address the intricacies related to the blinded independent review of radiographic studies. I

would like to now invite Dr. John Kirkwood to the podium.

Melanoma Overview

DR. KIRKWOOD: Thank you, Loretta.

[Slide]

Dr. Pazdur, Dr. Przepiorka, members of ODAC and the FDA, I am delighted to speak with you today about a disease that many of us here have spent all of our lives working on.

[Slide]

This is a disease that has risen in epidemic proportions and is 4 percent of new cancers, rising at 5 percent per year. The mortality from this cancer is also rising and most notably for men over 50 for whom there is a 157 percent increase in mortality in just the last decade. The societal impact of this cancer is even more because of its median age of incidence in the late 40s, and it takes a toll in terms of productive life years that exceeds many more frequent cancers, even including prostate cancer.

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In the past 37 years only three agents have been approved for the treatment of this disease in the advanced setting. Not one of these agents was approved on the basis of randomized, controlled Phase 3 trials prior to their approval. None of these agents has ever shown a survival benefit. Approval of these agents was based solely on response rate.

Hydroxyurea, approved in 1967 with a 10 percent response rate, has not been used in the clinical community for 20 years or more.

Dacarbazine, approved in 1975 with a response rate of 23-25 percent, has more recently been summarized in an article to appear next month in the European Journal of Cancer. The response rates that range between 7-13 percent I think are far more accurate assessments of the true response rate to this agent. Most of these were done pre-RECIST criteria and we don't know really what the objective response rate will be in larger trials using the newer RECIST criteria that have been used for the study to be discussed today.

[Slide]

Turning to IL-2, the most recent agent approved for the treatment of metastatic melanoma, the IL-2 NDA pooled 8 Phase 2 small studies. The regimen was not compared in these to any other therapy. The approval was based upon quality of response, durable responses and, given the significant toxicity of this agent, the population that was treated was highly atypical of the general community of patients that we have to deal with in the country at large. The median age was 42 years. The patients had in general no co-morbidity in terms of cardiac or pulmonary disease. Most of the patients who had responses had disease confined to skin, lymph nodes and lung. The toxicity of this regimen is so regularly, predictably severe that, in fact, specialized units are required for the administration of this agent. Its administration is confined to specialized centers in general across the country.

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IL-2 responses were noted in 16 percent of

patients treated, about one-third of whom had surgery to maintain this complete response, and 10 percent partial responses, defined using pre-RECIST criteria. The most salient aspect of the IL-2 benefit in these patients has been the long duration of response observed in some patients. While the median duration of patients treated at large was 9 months, the median duration for patients who achieved complete responses was greater than 5 years. Unfortunately, the number of those complete responses alive is rather small. The drug-related mortality with this treatment in this series was 2 percent, further compromising this relative benefit.

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Over the years there have been many attempts to improve upon the therapeutic benefit of dacarbazine. The largest of the trials conducted in the last five years are summarized in this slide, beginning with the IL-2 experience which was Phase 2 and, therefore, for which no comparator exists.

These include the Dartmouth regimen, adding tamoxafin to BCNU, cisplatin and dacarbazine; two regimens of biochemotherapy including one that the Eastern Cooperative Oncology Group and the Intergroup presented to the ASCO meetings just a year ago, now enrolling 416 patients; and a similarly large study from the EORTC that has not yet been published; as well as a publication just recently in JCO from the French group with a total number of more than 1000 patients in which overall there has been no combination that has shown a statistically significant difference in overall response rate, in complete response rate, in durable response rate or in progression-free survival.

[Slide]

I appeared last before this committee in 1999 in relationship to metastatic melanoma. In that setting, it was to introduce the application for temozolomide. This is an oral equivalent of dacarbazine that I think no one questions was equivalent to dacarbazine. The committee did not

vote to approve that agent which achieved equivalency in a trial that had been targeted upon superiority. But since that time I think it has to be admitted that temozolomide has been the most widely used drug in the community across the country. The FDA briefing that you have before you suggests that Genasense is, in fact, comparable to temozolomide. I would argue that it is not.

The overall response rate for the temozolomide application was not significantly different. The complete responses, identical; the durable responses, not detailed; and the differences in progression-free survival with an asymmetrical interval of assessment for the two arms, as Dr. Pazdur has just spoken about, significant but 11 days.

The other major difference about temozolomide is that this agent was already going to be available to the community at large for trial exploration, and the agent that we are going to discuss today will not be available if it is not approved today.

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In summary, despite more than 25 years of work and low response rates with the single agent dacarbazine, this agent remains the reference standard for the field. No single cytotoxic drug nor any biological agent or combination has been shown to be superior to single agent dacarbazine in relation to survival.

Relative to dacarbazine, no large randomized, multicenter comparative study has ever shown a statistically significant benefit in overall response rate, in complete response rate or in progression-free.

High-dose IL-2 is a useful agent that many of us use for selected patients who lack significant co-morbidity and who are willing to accept its side effects. This drug is not suitable for the majority of patients who present to us with metastatic melanoma and is particularly unsuited for patients who are elderly.

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I would conclude that metastatic melanoma,

upon which I have focused the last 33 years of my work, is a drug-refractory neoplasm. We need new agents desperately. Thank you.

Study GM301

DR. ITRI: Thank you, Dr. Kirkwood.

[Slide]

Genasense is an example of a new class of drugs called antisense. Antisense is fundamentally a protein knockout strategy. Genasense inhibits Bcl-2 production. Bcl-2 is a protein and is believed to be an important mediator of cancer cell resistance to chemotherapy. Genasense is administered for 5 days before chemotherapy, reduces Bcl-2 production and renders the cancer cell more susceptible to chemotherapy. In this way, Genasense is postulated to enhance the efficacy of chemotherapy.

[Slide]

Bcl-2 is ubiquitously expressed by melanoma cells. Five days of continuous IV therapy with Genasense prior to the administration of DTIC resulted in approximately 70 percent reduction in

Bcl-2 levels in melanoma cells taken from patients before and after Genasense treatment. These results provided the rationale for a Phase 3 study in patients with advanced malignant melanoma.

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This study is the largest randomized trial ever conducted in patients with advanced malignant melanoma. It was an open-label, multicenter trial involving 139 investigational sites in 9 countries around the world.

The primary endpoint was overall survival and the secondary endpoints included progression-free survival, antitumor responses using computer calculated RECIST based on evaluations of site tumor measurements; durable responses which were defined as responses lasting longer than 6 months; and, of course, safety in all patients.

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Patients received either DTIC at the standard dose of 1000 mg/m^2 or the same dose of DTIC preceded by a 5-day continuous infusion of

Genasense at a dose of 7 mg/kg/day. Patients were stratified according to the three major prognostic factors for melanoma, ECOG performance status 0 or 1-2; the presence or absence of liver metastases; and normal or elevated LDH levels. Patients could receive up to 8 cycles during a treatment phase which were administered every 21 days. Restarting evaluations were performed at the end of every two cycles.

It is important to note that the timing of interval measurements were fixed and similar in both arms, and they were prospectively defined with FDA agreement, with the temozolomide review issues clearly in mind. Crossover was not permitted from the DTIC arm into the Genasense arm, and follow-up was continued for 2 years in both arms of the study. Patients on the Genasense arm only could receive up to an additional 8 cycles of the combination therapy in extension protocol GM214 if they achieved at least stable disease by the end of the treatment phase and it was considered to be in the best interest of the patient, in consultation

with the treating physician.

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The statistical assumptions for this study were based on an overall median survival for DTIC of 6 months which was derived from published reviews. Genasense was postulated to add an additional 2 months, for total a median survival of 8 months; 750 patients would provide 90 percent power to see a difference between groups, with an alpha level of 0.05. It was assumed that accrual would be constant at 30 patients per month. In agreement with FDA, an analysis was planned when at least 508 deaths had occurred on the study.

[Slide]

The two groups were balanced for age and gender. The median age of patients in this study was 60 years but patients ranged in age from 16 to 93. Approximately 40 percent of our patients in this study were greater than 65 years of age and, remarkably, more than 10 percent were more than 75 years of age.

[Slide]

The two groups were equally balanced with regard to baseline performance status and approximately half of all patients were symptomatic at baseline.

[Slide]

Similarly, the two groups were balanced with respect to the major prognostic indicators including time from initial diagnosis, LDH/disease site distribution and prior immunotherapy which consisted primarily of alpha interferon administered as an adjuvant therapy in both groups.

[Slide]

Forty patients who were randomized into the study did not receive treatment. The primary reason for this is that in the DTIC arm some patients, later being randomized to the standard of care, were unwilling to travel or withdrew consent once they learned they would not be receiving experimental therapy. The amount of DTIC delivered to both groups was equivalent. Overall, the addition of Genasense did not require dose reduction of DTIC.

[Slide]

This is a summary of the efficacy parameters which, taken together, provide evidence for the benefit of combining Genasense with DTIC. I will discuss each of these in more detail in following slides.

Although not statistically significant, improvement in overall survival was noted for the Genasense group. Statistically significant improvement was noted in both progression-free survival and response rates, and I will shortly be showing you some interesting updated results regarding complete responses in this study. We also saw a positive trend in patients with durable responses.

[Slide]

The FDA has raised a number of considerations for the committee's review. These include response rate concordance; the impact of interval assessments on progression-free survival; the impact of missing data on progression-free survival; baseline differences in prognostic

factors; and the influence of non-U.S. sites on response rate. I will address each of these issues separately in the appropriate sections of my presentation.

[Slide]

This Kaplan-Meier plot of overall survival shows that both arms outperformed expectations. DTIC was associated with a 7.9 month median survival as opposed to the expected 6 months, and Genasense treatment resulted in a 9.1 month median survival. These differences were not statistically significant. Please note that the overall survival curves begin to separate at 6 months and the median follow-up at the time of database lock was 7 months.

[Slide]

The addition of Genasense was associated with an overall response rate of 11.7 percent as compared to 6.8 percent for DTIC alone. This difference is significant, with a p value of 0.019. Use of the stringent RECIST measurement system has historically reduced response rates in other

studies by 25-50 percent when compared to investigator determinations.

[Slide]

It is appropriate at this point to discuss how responses were calculated in this study. The investigators did not determine response. Investigators measured lesions and entered these data onto an electronic case report form. The computer then calculated whether the response met criteria for RECIST. RadPharm was only contracted to review responding patients. The sponsor was provided with measurements of target lesions and evaluations of non-target lesions by RadPharm. These measurements were also assessed by the same computer algorithm using RECIST criteria. RadPharm reviewers were blinded as to the treatment arm and all clinical information in which tumors had been selected by the sites as target lesions. All marks made by the sites on x-rays were removed.

There are three major reasons why RadPharm readings might not have been strictly concordant with the site measurements. These include the

evaluation of different target lesions with different measurements, the absence of important clinical information regarding preexisting lesions and controversy regarding the reporting of normal or residual lymph node tissue.

[Slide]

The patient on this slide had extensive liver metastasis at baseline which resolved completely during treatment. This patient has remained in complete clinical remission for approximately three years.

[Slide]

Due to the presence of a persisting liver lesion in the same patient, RadPharm was unable to confirm a complete response. By procedure, RadPharm was unaware that this was a documented preexisting cystic lesion that was benign. This patient is being cared for by Dr. Hersey who is here with us today and can answer any questions you might have regarding her treatment course.

[Slide]

In the next case, which demonstrates how

the absence of medical history can confound concordance, a biopsy-proven metastatic lesion of the frontal sinus was read by RadPharm as incidental sinusitis. Because this patient had undergone a Caldwell Luck enterotomy with removal of the inferior turbinate due to metastatic melanoma, RadPharm reasonably assumed that this was an infectious process and did not confirm the response.

[Slide]

Because RECIST criteria do not provide guidance for the interpretation of normal lymph nodal architecture at the site of previous disease, RadPharm could not confirm complete response in the next case and several others like it. Despite complete regression of the tumor next to the blood vessel, here, RadPharm could only assign partial response due to the presence of small residua.

The PET scan results for this same patient confirmed complete clinical response and shows no residual evidence of a viable signal post treatment. The FDA did not review any of these

x-rays and based their concordance judgments solely on raw measurements in percent reductions provided by the sponsor at their request. I urge the committee to address questions regarding radiographic reviews to Dr. Robert Ford, who is here with us today as an expert consultant in radiology and who personally reviewed all of these films.

[Slide]

Seventy-one responding patients were evaluated by RadPharm and 60 of these were considered to be evaluable; 11 patients were not evaluable due to the poor quality of photographs or films or the absence of lesions which could be considered measurable by RadPharm. Five of these cases occurred in the Genasense arm and 6 occurred in the DTIC arm.

Point-to-point concordance for two time point evaluations were available for 38 patients and give the concordant rate of 63 percent which is consistent with literature citations for evaluations of this nature. Two additional

responding patients were confirmed to be responses but were assessed differently by the site and by RadPharm. Eight cases were consistent at a single evaluation and were within 10 percent of response at the second evaluation. Four patients, such as the ones I have previously described to you, were easily explained by the absence of appropriate medical history. If we include only the 40 responders confirmed by RadPharm and agreed to by the FDA on treatment comparison, Genasense is completely consistent to DTIC as demonstrated by odds ratios. If only those 40 responses considered to be confirmed by both RadPharm and the FDA are included, odds ratios reveal a 91 percent improvement in response rate by RadPharm compared to an 82 Percent improvement in response for Genasense as reported in the NDA.

[Slide]

These cases were randomly selected by FDA and included 40 cases in each arm of the study. X-rays were collected from around the world and included assessments which occurred in the

follow-up period after NDA cutoff. As a consequence of this unplanned review of cases, RadPharm was able to identify additional responses which occurred in the follow-up period after NDA cutoff. These important clinical findings prompted Genta to evaluate all patients in follow-up who met RECIST criteria for response during at least one time point during the treatment phase and all patients who ended the treatment phase without disease progression and who had received no intervening therapy.

[Slide]

As with response, we observed good concordance regarding the conclusions about time to progression between the investigational site assessments and RadPharm determinations. When the site assessments and RadPharm determinations for time to progression are compared, both showed a benefit for the Genasense group. RadPharm assessments of time to progression in the Genasense group were generally longer than the site assessments.

[Slide]

Six additional responses have been identified which occurred in the follow-up period after the NDA submission and all were in the Genasense group. Only complete responses are reported since they are the ones most unequivocally associated with clinical benefit and constitute a result not commonly observed with single-agent DTIC. Three of these complete responses were upgraded from the partial response category and 3 were patients with long-standing stable disease. Information regarding these additional responding patients was submitted to the FDA on April 9th of this year.

It is important to note that the submitted database has not been updated or altered in any way, nor are we attempting to change the data provided in our NDA. We wish simply to inform you of important and frankly unanticipated clinical findings. These responses all occurred in the absence of other intervening therapies and have been documented by duplicate CT scans using the

same RECIST criteria as specified in the protocol. The physicians caring for several of these patients are here with us today and are able to answer any questions you may have directly.

[Slide]

Complete responses were evenly distributed by gender and generally exhibited the same demographic pattern as the overall population. Importantly, one-third of the responses occurred in patients with elevated LDH and half were observed in the worst AJCC prognostic categories, M1b and M1c.

[Slide]

Survival for the complete responders ranges from 15 months to more than 3 years on the Genasense arm, and 19 to 21 months on the DTIC arm. The plus signs denote ongoing responses. Two patients have died, one on each arm of the study.

[Slide]

The evolution of the complete responders on this study is shown in this slide. The two responding DTIC patients are shown in yellow for

comparison. The solid bar denotes the database cutoff of August 1, 2003 and is the information contained in the NDA. The dotted line denotes the date of the FDA inquiry that precipitated review in the follow-up period after database cutoff.

As you can see, partial responses tend to occur later in the Genasense arm and evolved over time into complete responses. Three of the Genasense responses, similar to what has been described for IL-2, have been surgically maintained. Once again, all responses were based on strict RECIST criteria with duplicate measurements and no patient received intervening therapy.

[Slide]

Returning now to the data previously reported in the NDA database, the duration of response is presented using a box-and-whisker plot on this slide. The red line denotes the median. The top of the box is the boundary of the third quartile and the bottom is the boundary of the first quartile. As you can see, the medians are

similar but an important difference is observed in the third quartile, resulting in a longer mean duration of response in patients who received Genasense.

[Slide]

Durable responses, defined as responses lasting at least 6 months, were more than doubled in the Genasense group, as shown in this slide.

[Slide]

Median progression-free survival for the Genasense group was 74 days as compared to 49 days for the DTIC group. The relative risk of having progressive disease or death was reduced by approximately 27 percent in the Genasense arm. These differences are highly significant, with a p value of 0.0003.

Time to progression was performed as a sensitivity analysis for progression-free survival. The results were very similar and showed approximately a 27 percent reduction in the risk of progressive disease. In this analysis, 11 patients who died without documented disease progression

were censored to the day of last lesion measurement. These 11 patients constitute the only difference between progression-free survival and time to progression in this study, and explain why the two curves are so similar.

[Slide]

Genta conducted multiple sensitivity analyses to address possible biases in the calculation of progression-free survival. In all instances the hazard ratios remained stable and all were statistically significant, attesting to the robustness of the observation. The most common concerns regarding progression-free survival analyses include the impact of scheduled assessment and missing data which can potentially be a source of bias. Several of the methods used by Genta address these issues and all confirm the conclusion derived from the original planned analysis.

[Slide]

FDA has performed four analyses using interval censoring techniques. Hazard ratios are not reported for this method. Approach number one

specifically addresses the issue of assessment schedule bias and remains statistically significant in favor of Genasense. Approaches two, three and four address both assessment schedule and missing data biases taken together. Approaches two and three remain statistically significant in favor of Genasense. Only approach four, which represents a rather extreme case assumption, and I will show you an example of this on the next slide, resulted in an insignificant p value and would have resulted in the deletion of almost half of the data.

[Slide]

Using this example of patient data by interval censoring technique number four all of the data in yellow would have been thrown out because the investigator failed to repeatedly record the absence of brain metastases. I would encourage committee members to address any questions you might have for the sponsor regarding this analysis technique to Dr. Janet Wittes.

[Slide]

In order to address FDA concerns about

potential differences for baseline variables to affect efficacy endpoints, progression-free survival results and response rates were adjusted for the variables of age, gender and AJCC LDH disease site criteria. Results show that both hazard ratios and odds ratios remain stable and all results remain statistically significant. Thus, there was no apparent impact of potential baseline imbalances on results.

[Slide]

An additional concern has been raised regarding benefit for patients in the United States when response rates are examined by country. This tree plot shows that confidence limits overlap and point estimates are similar for the United States and non-United States. There is, of course, expected variability in some countries with small sample sizes but no evidence exists that the beneficial effect of the Genasense combination is different in the United States than it is outside the United States.

[Slide]

In summary, we have demonstrated radiographic concordance and superiority of Genasense regardless of who reviews the x-rays. Progression-free survival was not biased by missing data or interval assessment irregularities. No effect on endpoints was observed related to baseline demographic variables and similar benefit was observed for both U.S. and non-U.S. patients on the study.

[Slide]

Turning now to safety, adverse events were generally increased in the Genasense arm, as can be expected with add-on therapy. The committee is referred to the briefing document provided by the sponsor for details of adverse events. Importantly, no new or unexpected adverse events were observed in the study which have not been seen with DTIC alone. We did see an increase in the incidence of fever, which is a well-known effect related to Genasense as a single agent, as well as an increase in neutropenia, thrombocytopenia and catheter-related complications. Safety data were

regularly and carefully monitored by an independent drug safety monitoring board who at no point identified any safety concerns in the study.

[Slide]

There is an increased incidence of grade 3-4, as well as serious events of thrombocytopenia in the Genasense arm. The word "serious" in this context is defined in its regulatory context and generally means the need for hospitalization or the prolongation of hospitalization. However, bleeding, which is the major clinical consequence of this laboratory abnormality with grade 3-4 bleeding, serious bleeding--serious bleeding related to thrombocytopenia, shows no difference between the arms. Similarly, the number of patients who required platelet transfusions with the absolute number of units transfused were no different between the two treatment arms.

[Slide]

Neutropenia exhibited a similar pattern as thrombocytopenia. The incidence of grade 3-4 and serious events was increased in the Genasense arm.

Although higher in the Genasense arm and largely related to the presence of a central line, the incidence of grade 3-4 and serious neutropenic infections was generally low in both groups.

[Slide]

Not surprisingly, catheter-related complications occurred almost solely in the Genasense arm and the incidence was consistent to that reported in the literature for central venous catheters. Injection site infections occurred in approximately 4 percent of patients and thrombotic events occurred in approximately 2 percent of patients receiving Genasense, whereas injection site reactions occurred only in the DTIC group where peripheral lines are generally used for DTIC administration. Two patients in the Genasense arm received their 5-day Genasense dose in 5 hours due to a mis-programming of the pump. Both of these patients experienced nausea, fever and thrombocytopenia. Both patients recovered completely within 48 hours and had no sequelae related to the overdose. Both patients went on to

receive the additional cycles of therapy and one of these patients has achieved a PR after 7 additional cycles of treatment. We are hopeful that subcutaneous and other alternative dosing methods in development will mitigate the need for a central line and its attendant complications.

[Slide]

Adverse events leading to discontinuation were increased in the Genasense arm. However, the majority of events in both arms were related to disease progression. In this study disease progression could be reported as an adverse event. Importantly, adverse events resulting in death and deaths which occurred within 30 days of the last dose of study drug were no different between the two treatment arms.

[Slide]

In summary, this study was the largest randomized trial ever completed in patients with advanced malignant melanoma. The study was carefully conducted; showed internally consistent results; and demonstrated compelling clinical

benefit.

We believe that we have addressed all of the study questions given to ODAC for consideration. Finally, we believe that the study shows consistent clinical benefit, which will be summarized by Dr. Frank Haluska in his closing remarks.

In closing, I would like to thank the patients and their families, the physicians, the nurses and the site coordinators who made the study possible. I would also like to thank the dedicated and professional employees of Genta who worked tirelessly to contribute to the treatment of cancer patients. Thank you for your attention. Dr. Haluska?

Clinical Benefit Summary

DR. HALUSKA: Thank you, Dr. Itri.

[Slide]

My task today is to provide you with a summary of the data that you have just seen, that I think have been so clearly presented, as well as an overview and some context for the clinical trial.

[Slide]

I think the best way to do this is to in our minds assume the role of ODAC and if I were a member of ODAC right now I would have two major questions. The first of these is that the sponsor here has failed to meet the primary endpoint of the study, which is survival--can I still approve this drug? I think the answer to that question is an emphatic yes. Dr. Pazdur has already commented that although meeting a survival endpoint is desirable and is the gold standard, the failure to do so does not preclude approval, and I think that is germane here.

I addition, I think it is important to consider the recent regulatory history of the melanoma field, specifically with regard to IL-2 and temozolomide. IL-2, as you know, was approved several years ago based on the rate, the quality and the duration of the responses, data that we are presenting here, and I think these data are stronger because they are the result of a randomized, prospective trial, albeit with

secondary endpoints.

The other drug that I think is relevant is temozolomide and, as Dr. Kirkwood has already explained, the data are better for Genta than for the temozolomide submission as well. So, I think that this drug is approvable despite the failure to meet the primary endpoint.

The second question that must be on your mind is do the secondary endpoints confer or support the conferral of clinical benefit? Are they strong enough to support approval of this drug? I do think that significant clinical benefit is strongly suggested by these data. So, let's consider that.

[Slide]

These are I think the most important endpoints of this study. Again, I want to stress that they were prospectively identified as opposed to, for instance, IL-2s which were the result of Phase 2 data.

The first of them is the overall response rate. The overall response rate approaches 12

percent versus 6.8 percent in the DTIC arm. This is an improvement. In this field, no improvement with statistical significance has ever been demonstrated in response rate for advanced melanoma.

We have demonstrated improvement in complete responses, 11 versus 2. This is significant as well and, again, this has not been demonstrated in a reaction study. I think the IL-2 experience is relevant to both of these. As I said, IL-2 was approved on the basis of the rate, the quality and the duration of survival. We have, in this trial, 9 patients that are alive, an increment that is not seen in the DTIC trial, and I want to point out that IL-2 was approved on the basis of 10. So, this is certainly in keeping with previous decisions that have been made.

The final issue is progression-free survival, 74 versus 49 days, nearly an additional month for patients who are presenting to their oncologist. That is an extra visit a patient can come to their oncologist without having been told

that their disease is progressing. This, to my mind, is clinical benefit.

[Slide]

What is the context of these findings? These are the data from the five largest randomized trials that have been conducted in melanoma and the trial in front of you today is the largest. There are 2019 patients that have been treated on these trials and until today there has never been a significant clinical improvement for any of the measures that we are discussing today. Response rate has not been shown to be improved and it is shown to be improved here. Complete responses have never been documented in a randomized study to be improved and they are improved here. And, progression-free survival has never been shown to be improved and it is improved here. I think this trial sets itself apart from the progress in the field in the last few years and I think that is why it requires your careful consideration today.

[Slide]

To summarize that, patients value

responses and value complete responses. The FDA in the past has made it clear that these are important criteria to consider and, in fact, there are no melanoma drugs approved that have been approved on any other criteria.

You might ask is a 10 percent response rate, or the order of magnitude of 10 percent, important to patients and I think it is with, I think, the recent approval history and data on responses in other malignancies, particularly in lung cancer. The IRESSA experience that has recently been clarified with data published last week suggests that a 10 percent response rate is clinically important. We understand the biological basis of some of these responses and a 10 percent response rate can certainly change the field; it can certainly change a patient's life. So, I do not think that a 10 percent response rate in and of itself argues against approval.

What about the magnitude of time to progression? A month, I think, is important. Data that Carey Kilbridge and my colleagues have

examined with regard to how melanoma patients view their experience strongly suggest that any additional time without being told their disease is progressing or without the presence of disease is important to them. In my opinion, what the sponsors have shown today constitutes clinical benefit for the melanoma patient.

[Slide]

What about safety? When we research a treatment for our patients we do it based on an evaluation of risk versus benefit. What are the risks of this therapy? The sponsor has shown that there are no new or unexpected adverse events concomitant to treatment with DTIC and Genasense. There is no difference in the treatment-related deaths between the two arms. There is an increase in fever, neutropenia and thrombocytopenia. Some of this is likely due to catheter-related complications and this is certainly not the only agent on the market or potentially on the market that would be administered with a pump.

Finally, Genasense is still better

tolerated than other alternatives for melanoma patients and, again, I think a review of the literature is germane here.

[Slide]

These are three of the trials for which we have good safety data in comparison to the trial in front of you today. They demonstrate that the rate of complications for the DTIC arm is certainly similar to what was seen in other studies with regard to grade 3 or 4 neutropenia and grade 3 and 4 thrombocytopenia, and certainly the rates of complications that can be attributed to the combination of Genasense and DTIC are less than what we see with other alternatives for melanoma patients. I think that argues that this is a safe combination and the risk-benefit analysis is completely reasonable to be attributed to therapy.

[Slide]

Conclusions--I think this is a novel drug. It is the first of a class of agents that has been shown to be efficacious by several measures. It takes into account our genetic understanding of

this disease. It is in keeping with the movement in the field broadly for targeted therapy and I think that should be taken into consideration.

It confers a clinical benefit with DTIC by multiple measures that I think have been reliably demonstrated in this large clinical trial that include response rate, complete responses and progression-free survival. And, it has a predictable and manageable safety profile.

[Slide]

Melanoma is refractory to current front-line therapy. You have heard and I think you will hear further today that we need new agents. This product is safe; it is effective when combined with DTIC to treat stage 4 melanoma. In other words, this drug works. I think it is up to you to define today what "works" means but I don't think we can discard the randomized trial demonstrated improvement in response rate, in progression-free survival and in complete response rate.

A final comment--I am supposed to be here as a dispassionate expert, scientifically objective

and clinically removed but I don't think I can completely play that role because I do take care of melanoma patients. The melanoma field has been criticized for trying to consistently hit the clinical home run. But this represents progress. It is incremental progress. It is not a clinical home run but it is incremental progress, and if we are ultimately going to make real progress in this disease to cure it, it will require the accumulation of incremental progress. Allow us to make incremental progress; make this drug available to our patients. Thank you.

DR. PRZEPIORKA: We are going to hold questions for the first presentation until the FDA presentation has been completed. Dr. Kane, if you could begin? Thank you.

FDA Presentation

Medical Review

DR. KANE: Thank you.

[Slide]

Good morning. My name is Robert Kane. I am the medical reviewer for this NDA and I will be

presenting the FDA review along with Dr. Peiling Yang, our statistical reviewer.

[Slide]

I would like to recognize our primary review team members for this NDA.

[Slide]

Randomized, controlled trials prospectively designed with clear, quantitative endpoints statistically analyzed provide the basis to assess the merits of new drugs. Clinical judgment translates these findings for best patient care. Our presentation today will include requirements for new drug approval based on federal law and regulations; aspects of ODAC review of temozolomide which are relevant to today; the FDA examination of the Genasense, oblimersen, NDA; and concluding remarks.

[Slide]

In the FD&C Act of 1962 substantial evidence of effectiveness was required by Congress. This was defined as evidence from adequate and well-controlled investigations, generally

understood to mean at least two such studies for new drug approval.

[Slide]

The FDAMA legislation in 1997 indicated that one trial may suffice for approval with confirmatory evidence. The guidance document on effectiveness in 1998 indicated that for a single trial to suffice it should be of excellent design, internally consistent with highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and a confirmatory study might be difficult to do for ethical reasons.

[Slide]

New drug approval can take two forms. For regular approval a sponsor needs to show clinical benefit. Accelerated approval uses a surrogate endpoint reasonably likely to predict clinical benefit and requires subsequent confirmation of the benefit.

[Slide]

Here are the currently approved drugs for

metastatic melanoma. In the past response rate was the primary basis, as you have seen and as you have already heard, for hydroxyurea and for dacarbazine. Survival times were, and continue to remain, in the range of 5 to 9 months. More recently, improvements in the quantity or the quality of survival have served as the basis for approval. Also as you have heard, the aldesleukin, interleukin-2, approval was heavily related to the very long complete responders, some in excess of 5 years. Complete responses will be abbreviated as CRs on this slide.

[Slide]

I would like to remind the committee that the evidence for interferon supported approval for its adjuvant use although it is often used in the treatment for metastatic disease. The temozolomide evaluation by ODAC in 1999 is relevant and instructive for today's review.

[Slide]

This NDA contained one main open-label study, the primary endpoint of which was survival

time. It was designed to show a 3-month survival benefit for temozolomide alone over DTIC alone. Secondary endpoints were progression-free survival, abbreviated here as PFS, and response rate, RR.

[Slide]

The results of this study showed no survival benefit for temozolomide over DTIC. Median survivals were 7.7 versus 6.4 months. For progression-free survival the difference was found to be highly statistically significant with a log-rank p value of 0.002. However, the median progression-free survival difference was only 11 days. When an ample size is chosen for a survival endpoint the statistical significance of small differences in early endpoints can appear magnified. Response rates were not significantly different.

[Slide]

Temozolomide was not approved. The study failed to demonstrate the primary endpoint of survival benefit. Progression-free survival, a secondary endpoint, was of small magnitude at best.

No symptomatic benefit was observed and a proposed post hoc 6-month survival analysis was not convincing.

[Slide]

For Genta's NDA, here are the important study dates. The Phase 3 protocol began in July, 2000. The data cutoff date was August 1, 2003, and this represents excellent accrual to the study. On December 8, 2003 the NDA was submitted for FDA review.

[Slide]

Genta has just presented their trial design. I would like to emphasize a couple of points. This was a very large, multicenter, multinational, unblinded study. This was an add-on of Genasense to DTIC. Prolonged central venous access is required for the 5-day infusions of Genasense. Genasense may be abbreviated as G or G3139 on our slides. The protocol specified an independent review, a blinded group, to assess responders. Also, the ability to deal with an ambulatory infusion pump was required.

[Slide]

The primary endpoint was survival. The design was to detect a superiority in survival. The protocol included seven secondary endpoints, listed here.

[Slide]

The trial design was to identify a 2-month median improvement in survival time from 6 months with DTIC alone to 8 months for the addition of Genasense to DTIC. The primary analysis for the trial was to be the unadjusted log-rank analysis for the intent-to-treat population.

[Slide]

The study disposition of patients showed that less than half the patients were still on therapy after the first assessment about day 42. Most patients went off study because of progressive disease; 44 percent remained on study after the first assessment. As I mentioned, the data cutoff date was August 1 and analysis occurred at 535 deaths.

[Slide]

In the primary endpoint analysis, using the protocol-specified analysis with the intent-to-treat population, no survival benefit was demonstrated by adding Genasense to DTIC treatment versus DTIC alone. These are the actual survival results. As you have already seen, the hazard ratio was 0.89 and the log rang p value for the survival difference was 0.18.

Dr. Peiling Yang will now provide a more detailed examination of the progression-free survival.

Statistical Review

DR. YANG: Thank you, Dr. Kane.

[Slide]

As seen in Dr. Kane's presentation, the study failed to demonstrate efficacy in the primary endpoint of overall survival at a two-sided alpha level of 0.05. From a statistical perspective, an efficacy demonstration based on any other endpoint, such as progression-free survival, would only infer a false-positive error rate. Despite this concern, the secondary endpoint, progression-free survival,

was evaluated and the important question is regarding progression-free survival.

[Slide]

We have doubt regarding the applicant's findings and, second, as Dr. Kane will be discussing, there are questions regarding its clinical significance. This will be summarized in this presentation.

[Slide]

My review of the progression-free survival is as follows, review of applicant's analyses and results; then the major FDA concern about assessment times; then additional FDA concerns.

Let's first review the applicant's analysis and results. Progression-free survival was defined as time from the data of randomization to the date of disease progression or death. The data of disease progression was recorded as the assessment date when disease progression was documented. If the assessment was on different days, then the latest date among all assessments was used by this applicant to represent the

assessment date in that cycle.

[Slide]

This slide summarizes the applicant's results. The protocol specified as secondary efficacy analysis or progression-free survival was the log-rank test with the missing data imputed by the last observation carried forward method. The p value based on this approach was very small. However, in a large trial a small p value can be observed even if the treatment effect is small. During the review process FDA requested the applicant to analyze the data using a different approach by censoring patients at the last assessment date when at least 50 percent of target lesions were measured if the disease had not progressed yet. The p value based on this approach was also very small. However, when analyzed by this approach the observed median progression-free survival in the combination therapy dropped by 13 days and in the control arm dropped by only 1 day, as presented in this table.

[Slide]

An important question is raised while interpreting the results of the analysis of progression-free survival. Is the applicant's finding a true finding?

[Slide]

FDA has a major concern in evaluation of progression-free survival, that is, imbalance in observed lesion assessment times between treatment arms. The next few slides address this concern.

[Slide]

Lesions were to be measured every 6 weeks during the treatment phase. In practice, this did not always occur. Even when they were assessing the planned cycles there were still differences in timing between the two arms. Because this is a very large open-label trial involving two different regimens, one administered on 6 days and the other only 1 day and because the claimed difference was very small, FDA was concerned that the observed differences in progression-free survival might be affected by systematic bias. One potential bias could be caused by differences in the time of

lesion assessments.

[Slide]

We must remember a critical difference between the analysis of survival and of lesion progression. The date of death, represented by the star, will not change regardless of the evaluation schedule. With progression measurement, however, the date we assign for progression is usually the date of a scheduled visit occurring sometime after the actual progression date. It should not be surprising that assessing progression at longer intervals leads to a longer time to progression.

[Slide]

To address this concern FDA summarized the time from the date of randomization to each of the first 3 observed assessments in this pivotal trial. Included in this summary are those assessments which occurred by the time of disease progression or death and where there was at least one target lesion measurement. The observed median times from randomization to each of these assessments were obtained for each treatment arm. They were 48

versus 43 days to the first assessment; 94 versus 87 days to the second assessment; and 137 versus 129 days to the third assessment. The p values for the log-rank test comparing the entire curves were also obtained for each assessment. Note that the difference in timing of lesion assessments shows striking statistical significance, with p values of the same order of magnitude as the claimed difference in progression-free survival. This finding raises a concern that all or some of the observed progression-free survival difference were caused by this systematic bias in lesion assessment times.

[Slide]

These are the times to the first assessment curves. Please note that these are not time to disease progression curves. The blue curve represents the combination therapy and the red one represents DTIC alone. On the horizontal axis we have the time from randomization to the first assessment in days. On the vertical axis we have the proportion of patients who had the first

assessment later at a given time. As seen here, the blue curve stayed above the red curve all along, suggesting a systematic delay in the first assessment time in the combination treatment arm.

[Slide]

Similar patterns were observed in the time to the second assessment curves.

[Slide]

And to the third assessment curves.

[Slide]

Imbalance in assessment times may have impact in several ways on the analysis of progression-free survival. The first impact is that bias may be introduced in estimating progression-free survival. Second, with a large trial even a small imbalance between treatment arms may lead to incorrect conclusions.

[Slide]

This slide illustrates the first impact. A hypothetical example is given here to illustrate how imbalance may be introduced in estimating progression-free survival. In this example,

suppose that the actual day of disease progression was day 35 post randomization for both patients, one in the control arm and the other in the experimental arm. However, the first assessment for the patient in the control arm was on day 42 and for the patient in the experimental arm it was on day 48. The recorded days of disease-free progression will be on days 42 and 48 respectively. These recorded days, not day 35, will be the observations used in the analysis.

[Slide]

This slide illustrates the impact of systematic bias by a simulation study. In the simulation study progression-free survival was generated from identical distribution in both arms with a median of 50 days and 300 subjects in each arm. However, a systematic increase by 2 days in assessment times in one arm was introduced. In 98 percent of the 5000 simulations p values were less than 0.05. This illustrates that even with a small imbalance in assessment times between two arms the chance of falsely concluding treatment effect can

be very high when, in fact, there is no treatment effect at all, also the chance of incorrectly concluding increases as the sample size increases.

[Slide]

An additional FDA concern is about missing data. Missing data was observed in both treatment arms, especially for non-target lesions which also had an influence on the determination of disease progression. In this study lesion assessments were not always performed in planned cycles. Also, lesions were assessed at baseline or assessed post baseline. In the presence of missing data bias could be introduced in estimating treatment effects, especially in an open-label study as this is. This is a common problem in assessing progression in most of the studies.

[Slide]

This slide summarizes the progression-free survival findings. The claimed progression-free survival benefit in the combination therapy over DTIC alone may not be a true finding because of imbalance in assessment times between treatment

arms. The true progression-free survival benefit of the combination therapy over DTIC therapy alone was confounded by imbalance in assessment times between treatment arms. Thus, true treatment effect with respect to progression-free survival cannot be isolated. The chance of falsely inferring progression-free survival benefit could be high. Even if there was, indeed, no benefit, it will be magnified by increasing the sample size. Missing data is always a concern in oncology studies evaluating progression as an endpoint. The confidence in the amount of difference in progression-free survival is diminished in the presence of missing data and may allow introduction of bias, especially in an open-label study.

[Slide]

Finally from a statistical perspective, this large randomized, open-label study failed to demonstrate the protocol specified primary efficacy based on the overall survival benefit with respect to the secondary efficacy analysis of progression-free survival because of systematic

bias in ascertainment. It is not clear whether the benefit of progression-free survival in the combination therapy over DTIC alone exists. If it exists, the magnitude is uncertain. Also, there are multiplicity issues with analyses conducted to support the efficacy. Dr. Kane will address the clinical relevance.

Clinical Relevance

DR. KANE: Dr. Yang has provided a detailed assessment of some of the concerns related to progression-free survival.

[Slide]

To summarize these concerns, assessments in this study were done at 6-week intervals. The progression-free survival difference, however, was only in the range of 2-3 weeks. The progression-free survival difference is highly statistically significant but may be fully accounted for by asymmetry in the timing of assessments between the two arms. The magnitude of the effect size is uncertain. The real problem is what is the clinical relevance.

[Slide]

The Division examined all of the secondary endpoints of the protocol for the possibility of patient benefit, given the fact that the overall survival analysis failed.

[Slide]

We will next look at the response rates among the secondary endpoints. The data submitted at the time of the original NDA submission and analysis, as has been presented here, indicated that the Genta investigator-determined responses were derived from an algorithm using tumor measurements from the case report forms. In that examination, 11.7 percent of patients were reported as responders to the combination versus 6.8 percent with DTIC alone. The p value for this difference was 0.018 and the actual difference was just under 5 percent.

The study protocol also called for a blinded independent review and confirmation for all responders. The protocol stated that all radiographs, as well as photographs of cutaneous

lesions, were to be provided to this review group. The blinded independent reviewers, as you have heard, reported different response rates, 6.7 percent response for the combination versus 3.6 percent for DTIC alone, a difference of 3.1 percent and of borderline significance. Ordinarily, adjudication by an independent review is considered to be the definitive response rate.

[Slide]

Some of this discordance may be due to technical difficulties, such as providing the independent review group with the appropriate images. However, we must point out that 5 complete responses, which constituted all of the responses in the initial NDA submission identified by the Genta site investigators--there were 3 in the combination arm and 2 in the DTIC alone arm. None was adjudicated as complete responses by the independent review. Forty-four percent of the responders by the Genta site investigators were determined as not assessable or unconfirmed by the independent review. For 49 percent there was full

concordance for the response category between Genta and the independent review.

[Slide]

You have also heard that on April 9th--a couple of weeks ago--Genta provided new data on responders. This new data is being examined. There are problems with data that is developed outside of the study protocol. There can be ascertainment bias between arms when an analysis is not prospectively planned. Subsequent therapies, such as surgery not being part of the protocol treatment, may not be applied symmetrically.

[Slide]

Turning to duration of response, another secondary endpoint, this is Genta's analysis. This data is skewed data and, therefore, we refer to the median to describe it and the medians are quite similar.

[Slide]

For durable response rate Genta has provided this analysis. This was a prespecified secondary endpoint. The difference was not

significant.

[Slide]

Performance status is a measure of functional capacity. There were no differences in performance status observed between study arms to suggest a benefit for adding Genasense to the DTIC.

[Slide]

For tumor-related symptoms, there were no differences in symptoms observed between study arms during the treatment.

[Slide]

This slide introduces the adverse events which represent the toxicity safety endpoint for the study. You have heard from Dr. Itri that the grade 3-4 adverse events, the serious adverse events, and the adverse events leading to discontinuation all were increased with the addition of Genasense to DTIC. Since the DTIC doses were the same, the increased toxicity is likely due to the Genasense.

[Slide]

This represents the hematologic toxicity

which you have already heard. There was more grade 3-4 neutropenia and thrombocytopenia on the combination arm.

[Slide]

For non-hematologic toxicity, all adverse events were more frequent on the combination arm with the addition of Genasense.

[Slide]

In total, there were 18 patients with upper extremity thrombosis on the combination arm compared to 3 on the DTIC alone arm.

[Slide]

In summary, the Genasense trial failed to achieve its primary protocol-specified endpoint. No survival benefit was demonstrated with the addition of Genasense to DTIC compared to DTIC alone. The efficacy of the control arm, DTIC alone, is consistent with that of other studies.

[Slide]

Looking again at the secondary endpoints, these are usually considered to be exploratory and for progression-free survival there is no precedent

for progression-free survival as evidence of clinical benefit for metastatic melanoma. This may not be a true finding. The progression-free survival difference between the two arms may be 13 or 25 days depending on which censoring technique is chosen for missing data. The clinical relevance is uncertain.

[Slide]

For response rate, the difference from DTIC alone may be in the range of 3-5 percent. No complete responses in the original NDA submission were confirmed by the independent blinded review committee. The clinical relevance of this result is uncertain. Thus far, response rates in these ranges have not conferred survival benefits for metastatic melanoma. For the durable response rate, no significant difference. Response durations were practically identical.

[Slide]

For performance status no benefit was observed from the addition of Genasense to DTIC over DTIC alone. Symptomatic benefit was no

different. There is greater toxicity with the Genasense combination than for DTIC alone. Thank you.

Questions from the Committee

DR. PRZEPIORKA: Thank you for the review. We are now going to open the session for questions to either the sponsor or to the FDA. Dr. Cheson?

DR. CHESON: I am sure the 11 or so patients out there still in remission will be disturbed to know that modeling suggests that they shouldn't be there. We have heard some difficult, complicated analyses of modeling suggesting that what we heard from the elegant presentation from Dr. Itri and her co-workers might not be as clinically relevant. So, we have one side suggesting one set of outcomes showing clinical benefit, then the computer modeling and the FDA suggesting perhaps that these are not reliable. I would like to hear from the company, from Dr. Wittes, their side of this spin.

DR. WITTES: The issue about the potential for bias that can come from interval censoring and

from missing data we knew about and, in fact, looked at--I need the slide, yes, that is the one.

[Slide]

In fact, that is why we did some of the sensitivity analyses. These sensitivity analyses look at three different kinds of things, the missing data and the interval censoring, and the last three are the ones that look at interval censoring, the by-cycle analysis, the assumed progressive disease, back to the scheduled visit--these are three different ways of trying to adjust for the interval censoring. What you see is some changes in hazard ratio but quite similar to what they were before and then statistically significant p values.

[Slide]

Next slide, CC49--the FDA's approach for interval censoring, which is a method due to Michael Fay, is a non-parametric approach. It is a score statistic and, again, the p value remains statistically significant. So, yes, there certainly is a differential time to measurement in

the two groups but analyses that adjust for that time still show a statistically significant benefit.

DR. PRZEPIORKA: Dr. D'Agostino?

DR. D'AGOSTINO: Janet, the procedure the FDA used is not unreasonable. I am asking a question but it is a set of assumptions that could, in fact, underlie some of the differences we see, and I guess the point that the FDA was making, I thought, was that you could chip away at these differences not only in statistical significance but magnitude of difference, clinical difference, and that I think should be taken into account with the interpretation of these techniques.

DR. WITTES: I agree, Ralph, but can we go back to that 49?

[Slide]

Here is the chipping away. I mean, the chipping away is to look at both the interval censoring and the missing data. I think if you approach four, which is the one that is most chipped, if you look at what that does, it is the

Michael Fay approach to interval censoring plus a very conservative method for missing data, and let me describe that a little bit because I think it is important to know what happens here.

There are basically three kinds of missing data. There are those that Dr. Itri showed where there is an assessment, it is clear and then you don't keep on looking at that--the no lesion. That is one source. There is another kind of missing data where you have an assessment. At the next assessment you don't measure that lesion and then subsequent to that you do measure it and there is no progression. So, to me, that isn't really missing. If you take away those two and leave the missing data where you really can't know whether there is an assessment or not, this method becomes an 0-3 again. So, I think if you chip it away you still get evidence of benefit in progression-free survival.

The other thing to remember is that from the point of view of complete responses there is no issue at all about either interval censoring or

missing data.

DR. PRZEPIORKA: Dr. D'Agostino?

DR. D'AGOSTINO: But just again though, we are left in the dilemma of how do you respond to the data as collected, as the assessments were made and so forth, and there is uncertainty in terms of how comfortable some of us are with the p values. I think also with a large study you can generate very large p values with small differences and maybe some of that is here also. Again, p values are important but there is clinical significance the way these numbers draw closer together by, I think, relatively comfortable assumptions that is of concern I think.

DR. WITTES: I think someone else should address the clinical significance.

DR. PRZEPIORKA: Dr. Temple?

DR. TEMPLE: Janet, one of the things about 0.003 is that you don't worry about adjustment for multiplicity and stuff like that. It kind of blows you away. But with the smaller p values that you get from some of the other things

you did that might become an issue. Do you have a view as to how one should take into account the fact that this is not the primary endpoint? It is one of at least several things one could have done. What would you say the right kind of adjustment would be in a case like that, assuming that some of the closer to 0.05 p values were the ones that might count?

DR. WITTES: Yes, I don't know the answer to that. I mean, if the question is what is the type-1 error of this study, I think one can't really answer that question. Of course, one looks at consistency. One worries about the potential for bias and, again, I feel that those complete responses kind of avoid--they become a different kind of criterion. But if you ask me what is the type-1 error rate, I don't know.

DR. PRZEPIORKA: Dr. D'Agostino?

DR. D'AGOSTINO: Just again, when you look at the secondary endpoints after you have a failure in the primary endpoint, the whole interpretation--just to reinforce what you just

said, no one around this table is going to be able to put a real p value on any of these things that we have given that the primary didn't turn out to be statistically significant.

DR. PRZEPIORKA: Any other questions from the committee? Dr. Hwu?

DR. HWU: I have a question for Dr. Itri regarding the design of this trial, especially the regimen used in this large trial for the experimental arm. The initial scientific indication of this incremental improvement in the treatment of melanoma was based on the Phase 1 and 2 trial, which was published in Lancet by Jansen and colleagues in 2000. The Phase 1 and 2 trial design was extremely careful. They screened the patients who had shown in tissue increased expression of Bcl-2. Also, the pharmacokinetic study was done very carefully and was a clinical correlate of the tissues at the level of decrease of Bcl-2 expression. Also, there is correlation with responses.

The regimen used in that trial was very,

very reasonable in design. They were giving infusion on day 1 to day 14, continuous infusion. Clearly by day 5 the Bcl-2 expression was maximally down-regulated. DTIC was given from day 5 to 9 in divided doses of 200 mg/m 2 every day for 5 days. In other words, when DTIC is infused in patients, the G31 and 39 Genasense treatment also continues.

Now, the response was clearly shown in the M1a group, the patient with skin metastases or lymph node metastases. No response was noted in the lung or visceral organs. However, the responses were impressive. Even one patient who had prior DTIC had a partial response.

My question to Dr. Itri is why we changed the protocol which has clearly demonstrated scientifically that it worked as a target therapy and now we have changed to 5-day infusion of Genasense followed by 1 infusion of DTIC and even forgot that DTIC is not an active chemotherapy agent by itself; it requires hepatic activation to its active metabolite MTIC? We do know that the company provided a pharmacokinetic study that, yes,

the continuous infusion of Genasense that achieved the maximal plateau level within 10 hours if you were giving it at the 7 mg/kg/hour rate--I am sorry, per kilogram--however, once the infusion stopped, less than 10 hours later the level for the Genasense clearly dropped to what we call the biological active level of I think 1 mcg/L.

So, I would like to know before we launch this large Phase 3 trial are there any other Phase 2 studies, other than the safety, well-tolerated 5-day infusion by 1 day of DTIC, that have shown that there is tissue correlation and also efficacy as shown by the Phase 1 and 2 trial. Thank you.

DR. WALL: I am Dr. Ray Wall, from Genta. Dr. Hwu, I think I will take a whack at those questions since I was around at the time the study was done and took it with Dr. Haluska down to FDA, and Dr. Itri was not.

The Genasense study was informative. I would point out to the committee it was a Phase 1 studies that looked at a couple of different doses of Genasense at that time and also looked at a

couple of different routes of administration, both subcutaneous administration as well as continuous IV infusion. So, it was Phase 1 and it was a total of 12 patients. It was published in Lancet in year 2000.

What we had found both in that study and also in a variety of other studies, some of which are presented in your briefing book, are a couple of things with respect to the biological activity of the drug. The pharmacokinetics are very well described and I will skip them for the time being.

What we see in human tumor cells subsequent to administration of Genasense is that the onset of the down-regulation of Bcl-2 at the protein level, not the RNA level but of the protein level seems to occur at least as early as day 3 and is maximal at day 5. The one other thing that had been a very, very important driver of our clinical schedule is that the continued administration of Genasense beyond day 5, if the dose is not changed you do not seem to get any further down-regulation of Bcl-2 at the protein level.

I didn't bring a lot of blots in my back pocket here but I think I can show you one from a melanoma patient, if I can have MA-25, please?

[Slide]

This is a Phase 1 study looking at a very, very low dose. This is a dose that is about 20 percent of our Phase 3 doses, and this is from the Jansen study looking at continuous infusion over a 14-day period. Again, you see maximal down-regulation by about day 5 and, despite the fact that the infusion is continued, you don't see any further decrease in the down-regulation of Bcl-2 protein effect. These are human tumor cells, serial biopsies of patients with malignant melanoma.

So, from these data and from other data that have been obtained from a variety of other patients and other cells, both malignant cells as well as normal cells, that molecular information has been used to drive the clinical studies, including the one that you have seen today.

So a couple of things, one is we use

rather short infusions to maximize the down-regulation of Bcl-2 so that that effect is maximal at the time that chemotherapy is administered and we don't continue beyond. Dr. Tony Tolcher, who actually is in the audience, has done some of the best scheduling work but, again, modeling preclinically, suggesting that when you administer Genasense with chemotherapy the effect is maximized when you administer Genasense in advance of chemotherapy. The second thing that he has shown is that there seems to be no advantage to overlapping Genasense with chemotherapy. The final observation from the Tolcher lab is that if you reverse the sequence, if you give Genasense after chemotherapy is administered, then you basically eliminate the synergistic effect. So, the constellation of these kinds of pharmacodynamic events have driven the schedules that you have seen here today in Phase 3.

DR. PRZEPIORKA: Before you leave the podium, just one more question to follow-up, how long is the effect once the infusion is

discontinued?

DR. WALL: As was pointed out, the half-life of this drug is around 3-4 hours and fundamentally disappears probably by about 10-12 hours. The data are a little fragmentary and mostly derived from in vitro cell culture studies, but it does look like the half-life of Bcl-2 protein is in the order of 16 to about 22 hours. So, you would expect that if you get complete shut-down of Bcl-2 production by knocking out the messenger RNA, then pharmacokinetically within 5 half-lives or so you should have no protein within the cell, and recovery would be equally as rapid as soon as it is shut back on.

DR. PRZEPIORKA: Dr. Temple?

DR. TEMPLE: Dr. Itri or others, there was a lot of discussion about the responses. You clearly had two different ways of calculating responses, one based on investigators and the other based on RadPharm. My presumption was that the RadPharm analysis existed because the study was open and that is a common thing to do, to have a

blinded analysis of the response rates. In your presentation though I gather you were disappointed with what RadPharm produced and you considered it inaccurate. Could you clarify the intended role, what happened and whether you think there ought to be a further blinded analysis, or what? This is a somewhat unusual situation and it wasn't clear what the original intent was. As Dr. Kane said, usually when you have a group like that, they are the primary analysis. Was that not true? Just what was the arrangement?

DR. ITRI: That was not true here.

DR. TEMPLE: Then why did you do it?

DR. ITRI: The response per statistical analysis plan was RECIST measurements based on investigational site measurements that were then calculated by computer to see whether or not they met criteria for a partial response or a complete response. That is primary and that is what is reported.

The use of RadPharm--and I think it is important to note that it was only responding

patients that they looked at so if we were going to rely on RadPharm to actually give us a response rate for the study they would have had to review everyone. They were really used by us for quality control purposes. We wanted to make sure that the relative numbers we were seeing were consistent with what has been reported in the literature; that the concordance rates weren't really out of whack. I think that the best person to speak about this is Dr. Ford because he can put this into real context and explain what the literature shows, and really how we stack up in terms of other studies that have utilized a similar review. Is that okay?

DR. TEMPLE: Anything is okay, but you have two somewhat separate, somewhat different calculations based on the ones that went to them. Usually that is distressing and I guess the further question I have is do you have some way of resolving this? Should this be subjected to another blinded review where people get the whole files, or something? I mean, as it is, you can see why it is sort of troublesome. For example, all of

the complete responses they didn't think were complete responses although you feel that complete responses are very important for the reasons Dr. Cheson mentioned earlier. That is troublesome, and now you have found more which we haven't had a chance to review yet, but the same problem could arise there too. So, it does seem important to figure out what it all means.

DR. ITRI: I really think you need to talk to Dr. Ford about this.

DR. TEMPLE: Whatever you like.

DR. ITRI: But the other issue is that, you know, if the agency would like us to submit these x-rays for review and if that would make you more comfortable, we would be totally willing to do that. We believe that what is being called lack of concordance really relates to the fact that Dr. Ford is going to elucidate now. And, it would not be a problem; we would be so happy to sit with anyone and give you the clinical data that supports this because these are real and the patients are alive, most importantly. So, we would welcome a

chance to sit down and review these x-rays.

DR. TEMPLE: While you are at that, that is the second question I was going to ask you and maybe you want to answer them both. The survival curves don't seem to have different tails on them. So, I am a little confused about where the long-term survivors you are referring to come from if they are not in the survival curve, or maybe the curve has been extended.

DR. ITRI: We provided update survival information to the agency--

DR. TEMPLE: I just need the one you showed though.

DR. ITRI: Well, that was an early cutoff so we don't really know what the tail is doing. That was the 7-month median.

DR. TEMPLE: It is really Dr. Cheson's question I am following up on, if there were a small subset of people that got really important responses, wouldn't you see a difference in where the tails end up?

DR. ITRI: It might be too early to see it

on that curve.

DR. TEMPLE: Well, that means they are in both groups then. There are long-term survivors in both groups. Is that right?

DR. ITRI: There are some long-term survivors.

DR. WITTES: It depends on the nature of the censoring, where the censoring is. So, some of that could be showing up before the edge of the tail occurs because they haven't been followed long enough. I mean, the fact that they come together doesn't eviscerate the point. You have to look at where the specific events occurred relative to censoring.

DR. TEMPLE: That is fair enough. There was reference to at least some people who were getting really spectacular benefits and I would have thought that would show up as curves where the flat part is here on one and the flat part is below on the other.

DR. WITTES: They are censored.

DR. TEMPLE: They are censored because

they haven't been on long enough--

DR. WITTES: It is like three years.

DR. FORD: Well, thank you very much for the opportunity to address the committee on this topic, the topic at hand being how does an investigator who sees the patient on a daily basis or a regular basis assess response compared to how an independent review facility would assess response in the same patient in a remote location, not having access to the clinical information.

I think that there is little written in the medical literature about this topic, but there are two particular studies that I would like to review kind of as a background for this discussion. The first was a study that was published in the Annals of Oncology in 1997. The author was a radiologist and that was a review of a 100-patient ovarian cancer trial. In that review there were 24 claimed responders who were reviewed by an independent review facility and in that instance there were 14 patients who were concordant, that is, deemed to be responders by the independent

review facility and deemed to be concordant with the investigator.

There was a second study that was done, also published in 1997 in the Journal of Clinical Oncology. It was a review of a renal cell trial where there were 133 subjects who were reviewed. In that review an independent review facility reviewed those studies and the responses were concordant in 62 out of those reviews. In that article you can see the concordance, that is, site same PR to independent review facility saying PR was approximately 60 percent, and in the second study it was lower, on the order of 48 percent.

Now, with that as a background, there is a significant difference in the methodologies in which those reviews were performed. That is, in those examples the investigators who enrolled the patients in the trial were actually part of the review process. A radiologist sat down with the films, made the measurements and reviewed the images in concert with the physicians who knew much more about that patient, that is, had the

additional clinical history that the radiologists would have at the time of the review.

Now, that as a background, discussing the current study, the current study was a radiology only review. When it was performed there was no clinical information provided. In that instance, even in that particular setting the concordance was 63 percent. So, 63 percent of the time that the investigators assessed the response on this trial, the independent review facility assessed the same response.

DR. TEMPLE: When they are different how do you know which one is right? When they are different, non-concordant, how do you decide which one is right? I am sure I understand that different groups will reach different conclusions. Sometimes these special committees have a tie-breaker when they don't agree. But what is one supposed to do that when they are non-concordant? How do you decide which is true?

DR. FORD: Well, in this particular setting the investigator-determined response was

chosen.

DR. TEMPLE: When? I mean, was this prospectively defined in the protocol how any discrepancies were going to be handed?

DR. ITRI: Yes, it was.

DR. TEMPLE: So, the protocol was clear that the investigator-determined conclusion, or the analysis based on the investigator--

DR. ITRI: The investigator measurements were fed into the computer and that is what was to be used for determination of response.

DR. PRZEPIORKA: Dr. Rodriguez?

DR. RODRIGUEZ: Yes, this is a follow-up to the question by Dr. Hwu because I didn't hear the response to part of her question, that is, you know, this is a biologically targeted agent and one assumes that one is going to look for the appropriate target or that one would select patients who are appropriate to be treated with this drug. I didn't hear whether all patients entering on the study were screened, if their tumors were screened for expression of Bcl-2 or if

there had been an attempt to quantitate category of patients because, obviously, some patients are going to be appropriate for trial and others are not. Was that done?

DR. WALL: That is a very good question. Can I have slide MA-18, please?

[Slide]

The challenge with Bcl-2 is the ubiquity of Bcl-2 expression in melanoma. So, this is not comparable, for instance, with HER2 expression in breast cancer in which the incidence of expression in advanced cases is on the order of 20, 25 percent so that you would not want to treat 100 percent of women. You could theoretically benefit 25 percent so the absolute response rate would be 5 percent of your total. In general, we chose melanoma because of the very, very high prevalence of expression which in these studies, whether you look at immunohistochemistry, which is the blue bars, or RT-PCR of excised specimen, you are talking about something in the range of 90, 95 percent expression of tumors.

So, the kinds of correlations that you are going to be able to make with respect to over-expression we thought, going into this study, were going to be extremely limited due to the very high prevalence of baseline expression. Again, it certainly influenced our choice of melanoma as one of the early targets for this particular disease. After that it is not clear where you could go if you were going to look at percentage down-regulation. That meant serial biopsies of fresh tissues from multiple sites, handled very, very carefully, centrally managed, exponential increases in cost and ability to manage--that simply overwhelmed us as a small company. So, we figured we would pick a big tumor in which would be an unquestioned level of very, very high expression at baseline but it did preclude the ability to make subset selections based on--at least at the stage we were dealing with this in 2000--Bcl-2 expression per se.

DR. PRZEPIORKA: Dr. Hwu?

DR. HWU: I agree that choosing melanoma

as this malignancy is very important based on what we know of Bcl-2 over-expression. My question to you that you didn't answer is based on your current regimen with some 300 patients. Have you any data to show that it clearly reproduced your finding in the previous Phase 1 and 2 using completely different regimens?

DR. WALL: Well, the Phase 1 study, as you know, did not show correlations. It really was not appropriately powered to look for correlations between baseline Bcl-2 expression and percentage of down-regulation. That is very difficult to model even preclinically. I am not sure I am answering your question.

DR. HWU: I don't agree that that is not the conclusion from the publication. Clearly the CR person that has the highest incremental decrease of Bcl-2 is the percentage of decrease; it is not the total amount of expression. That is what I learned from the paper.

DR. WALL: I think you need to keep in mind that it is a Phase 1 study. That patient got

a rather low dose. The majority of patients were actually not serially sampled. And, the ability to make inferences with respect to those kinds of correlations with a total N of 12 is I think very problematic.

DR. HWU: To make a correction, the patient got the highest dose level of 6.5 and she had 70 percent--

DR. WALL: And that blot was shown to you, by the way.

DR. HWU: --and the patient had never received any chemotherapy prior either.

[Slide]

DR. WALL: Right, and here is the blot from that patient that Dr. Itri showed. I think the major point, however, is with an N of 1 in a sample size of 12 in a Phase 1 study we didn't feel like we could make inferences. I would say that one of the advantages of being an oncologist is that you can fall back on issues related to maximally tolerable dose and we felt that the dose used in this study for the Phase 3 study was

comfortably above the threshold that we needed to achieve down-regulation of Bcl-2, which is a dose just above what this particular patient got. Did that happen in 300 patient? We don't have that information. The willingness of patients to be serially sectioned for us to obtain this information on a fresh basis is rather limited and it was simply not part of the study. It overwhelmed our capabilities in year 2000 and was not done.

DR. PRZEPIORKA: If Dr. Tolcher is here, I have a question. In the in vitro studies is there a threshold amount of Bcl-2 that needs to be down-regulated to in order for the chemotherapy to show synergy?

DR. TOLCHER: That is a very good question and it is not well addressed. Most of the models are, you know, somewhat artificial and in vitro versus in vivo really has no strict correlation. We functioned for a period of time with the assumption that 1 mcg/mL is probably the minimum effective concentration. In almost all of the

studies published to date we have a steady state concentration of 5 mcg/mL as an average. So, based on the work that was done preclinically, published by Martin Gleave and others, we are well above what we would need in the in vitro setting but, again, the major caution always is that it is hard to relate what are the necessary concentrations in vitro to what are the necessary plasma concentrations for maximal effect. Does that answer your question?

DR. PRZEPIORKA: I guess I was asking what is the amount of Bcl-2 intracellularly that we need to get the level down to in order to see the synergy with chemotherapy.

DR. TOLCHER: An excellent question. You know, the issue is that it is dynamic so one doesn't know necessarily. You are lowering it so that you essentially are shifting the equilibrium in favor of apoptosis. You clearly do not need to extinguish all the Bcl-2 to have a pronounced effect in vivo. In fact, you probably only have to drop it below some threshold and that threshold is

unknown. It gets more complex as well in that there is a diversity of Bcl-2 expression in different tumors.

So, what I would say is that it is not necessarily a simple equation where you have to drop it below X amount. It may be very dependent on the chemotherapy that is given with it. So, it is not clear. The certainty is that we do know that you do not have to extinguish all the Bcl-2 to have a synergistic effect preclinically.

DR. PRZEPIORKA: Thank you. Dr. Bishop?

DR. BISHOP: I am relatively new to all this so I don't know if this question is appropriate or not but I am going to turn it to Dr. Kirkwood and Dr. Haluska. You made passionate pleas for the treatment of metastatic melanoma in this randomized study. So, would this treatment, Genasense plus DTIC, become the standard of care in the control arm for future CALGB and ECOG studies respectively?

DR. HALUSKA: I think that is a reasonable proposition. I think that the context of this

trial's conduct is that we have never shown any of these improvements and I think we shouldn't lose site of the fact that we are chipping away, as has been articulated, at numbers that have not been able to be chipped at away before because they haven't existed. So, I think that that is a decision to be made by the community, but an improvement clinically like we have seen should be the standard against which other stage 4 therapies will be compared. I think that is reasonable.

DR. BISHOP: Let me make it more specific then. In your future randomized trials will this become the control arm? The data with DTIC we know is not very impressive yet that is the community standard outside of immunotherapy. So, as you plan your future trials, and you believe these results are impressive enough, will that become the control with which new therapies will be developed and compared to?

DR. HALUSKA: I wish we had new therapies to compare to now. I would have to say that it is hard to view the future when those new therapies

become available. The landscape for drug development for melanoma right now includes other targeted therapies. None of them is at the stage where we would choose a comparison arm like this but the short answer to your question is yes.

DR. PRZEPIORKA: Dr. Kirkwood?

DR. KIRKWOOD: I agree with Frank's conclusion so I think this is an incremental advance. I think this is something that we have been trying to do in the studies that I reviewed and have not succeeded to do. Obviously, if one were going to take survival as an endpoint in a future study it could still be dacarbazine but I think that we are talking here about response rate and we don't have anything that has reliably before shown response rates and complete response rates incrementally advanced as this has, with the single exception of high dose IL-2, which we have spoken about previously.

DR. HALUSKA: Something else occurs to me. I don't think it is the agency's job to support our research endeavors strictly. I mean, their job is,

as I understand it, to make agents available for public consumption. But, clearly, these decisions do affect our research and we have, for reasons that are not clear to any of us who work in melanoma, been very unsuccessful in improving overall survival. I don't believe that as long as we hold that out as the only endpoint that we can meet that we are going to meet it because it has been such an impediment. But there is nothing in my mind that prevents small improvements in these sorts of endpoints from accumulating with addition of different agents and you can envision a variety of other things that you could add Genasense to that might also prove additive to the responses and progression-free survival we have seen today. Ultimately, that is how I think we are going to make real progress with the survival endpoint in this field.

DR. PRZEPIORKA: Dr. Redman?

DR. REDMAN: Thank you but Dr. Kirkwood answered my question.

DR. PRZEPIORKA: Other questions from the

committee? Dr. Tolcher, could you please come back to the microphone? We need to have you identify your affiliation, please, for the record.

DR. TOLCHER: Sure. I came actually today without personal compensation by Genta or any of the pharmaceutical sponsors, although my travel arrangements have been paid for Genta. I have been the principal investigator on three clinical studies and have acted as an occasional advisor to Genta and Aventis and have been compensated with honoraria for those less than $10,000.

DR. PRZEPIORKA: Thank you. Hearing no other questions, we will break for ten minutes and return at 10:40 to begin the open public hearing. We will need to begin the afternoon session on time so please be on time for the next part.

[Brief recess]

Open Public Hearing

DR. PRZEPIORKA: If we could have the doors closed, please, we will begin the second half of this session. This is the open public hearing and we actually had many individuals who wanted to

speak this morning and, in order to give everyone who is registered a chance to participate and to be fair to all, we will be following some fairly strict procedures. We have a timer. Each speaker has been allotted two minutes and at the end of the two minutes we will ask that speaker to return to their seat and the next speaker to immediately begin. Due to considerations of fairness and these restrictions of time, only speakers who have registered will be allowed to come to the podium.

Both the FDA 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, the FDA believes that it is important to understand the context of an individual's presentation. For this reason, the FDA encourages 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 the sponsor's payment for your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, the FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any financial relationships at all. If you choose not to address the issue of financial relationships at the beginning of your statement it will not preclude you from speaking.

Thank you all for your participation in this portion of the meeting, and our first speaker is Gail Graham, who is chairman and president of the William S. Graham Foundation for Melanoma Research.

MS. GRAHAM: Good morning. Yes, I am chair and president of the William S. Graham Foundation for Melanoma Research. We are widely known as the "Billy" Foundation. Please also note that I am here to represent not any particular therapy or pharmaceutical company though in the past we have accepted financial donations to our

programs at the Foundation from Chiron, Maxim, Genta, Antigenics and Schering. However, I have paid my own expenses in order to address you here today.

The phone rang and I answered a call that would change my life and the life of our beloved family. Over ten years ago a doctor called our home and told us that our beloved son had stage 4 melanoma. "Mrs. Graham, your son has three to six months to live." That was the beginning of my journey into every mother's nightmare, watching your only son disappear before your very eyes.

I was told then, ten years ago, that there wasn't anything that could be done for him and no one prepares you on how to tell your child that there is no hope, nothing that could even extend his life for an extra month or two.

Now, ten years later, what has truly happened to give patients new hope? What do you say to patients and their families now? We want patients to have choices, choices from the onset of their diagnosis not as a second matter of recourse.

Over those ten years, over 300,000 people have been diagnosed with malignant melanoma in the United States and have had to face that diagnosis and have extremely limited offerings available to them for treatments, and it is long past time that something be done to offer hope, the hope that they deserve.

I am here also to represent the dozens of phone calls that we get on a daily and monthly basis...

[Audio system malfunction]

DR. PRZEPIORKA: I am sorry, but thank you very much for your comments. R.M. Sutton please.

MR. SUTTON: No financial involvement. I am of clinical relevance--I am free, I am alive, I am here after my doctor gave me about a month and a half and because of prior medical problems no treatment available, but this trial which has blessed me with time to spend with my son, my daughter-in-law, my daughter, my son-in-law. With all due respect, should my doctor have waited a thousand or so years until all the kinks were worked out? If we were licensing aviation today,

would we have to wait for the law of gravity to be revealed to be assured that we would never fall from the sky?

I am 77. I expect to live another 23 years. My mother died at 99. I want to see, among many other things, my granddaughter get married and eventually greet my great grandchildren. I pray on bended knee you approve it so others like me who have been diagnosed with melanoma--thank you, I have a secure place in heaven to join my late wife but, thanks to Genasense, thankfully not just now. You can give life, hope and achievement. I hope to write a book on dreams of reality, limited only by my imagination, inspiration and time. Thank you.

DR. PRZEPIORKA: Thank you, Mr. Sutton, very much. Davie Bernstein, please.

MR. BERNSTEIN: My name is David Bernstein. I paid my own way here. I have taken time off from work in order to address you here today. I am 51 years old, a husband, father of two little girls, a fourth grade teacher in New Jersey. Two years ago I was diagnosed with stage 4 melanoma

after discovering a lump in my chest. We were devastated. We had found the disease had already spread to my lungs.

I sought a group at Thomas Jefferson University Hospital in Philadelphia to be treated. We discussed various options for treatment, all of which included going on various forms of chemotherapy. I learned that DTIC was the standard care although it was described as having very limited results. My doctor also told me about a clinical trial they were conducted for a drug called Genasense. I qualified for the trial, feeling oddly lucky that my tumor was large enough, and received Genasense with DTIC.

Genasense was administered through an automatic pump that I wore like a fanny-pack for five days, followed by a one-hour infusion of DTIC. After six weeks, or two treatment cycles, I got a CT scan to monitor the size of my tumor. The scan showed that my tumor had already begun to shrink. I remained on the therapy for a total of 16 treatments and was scanned every six weeks, each

one coming back clear of tumors. Throughout my treatment, I was very well supported by the team at Thomas Jefferson that included my oncologist, Dr. Sato, and Tracy Newhalls, the clinical liaison.

I stopped treatment in August, 2003 and have remained tumor-free since then. I am here today because I received Genasense in this study. Genasense now needs to be made available to the thousands of people like me who have received or will have received the diagnosis of advanced melanoma. People need to know that there is hope for this disease in the form of new drugs. Genasense worked for me and others should have the same chance I did. Thank you.

DR. PRZEPIORKA: Thank you very much for your words. Erica Weiss, please.

MS. WEISS: Good morning. My name is Erica Weiss and I am the director of patient education and outreach for the Wellness Community. For the record, The Wellness Community will receive an unrestricted educational grant from Genta and Aventis. However, I received no compensation for

my presence here today.

By way of background, the Wellness Community is a national non-profit organization that provides free services for people with cancer by way of support, education and hope. Our programs include professionally facilitated support groups, educational programs on nutrition, mind, body--programs like this. We aim to help people affected by cancer regain a sense of control over their lives, feel less isolated and restore a sense of hope for the future regardless of the stage or type of their disease. Last year we served about 30,000 people with cancer, including people with melanoma.

At the Wellness Community we have learned a great deal from the people we serve and we really value the importance of an educated and empowered patient, and since we feel that people with cancer often feel stigmatized, alone and overwhelmed with grief, they feel stronger and more hopeful when they have more options available for their disease.

When a cancer like melanoma results in 80

percent of skin cancer deaths and when limited treatment is available for advanced melanoma, it is clear that we are in great need of new treatment options and better access to those treatments. At this time we have the opportunity to expand the chance that these families have in their daily fight for life and we feel strongly about supporting that opportunity, assuming that the treatment promise has manageable side effects, assuming there is progression-free survival time, even if only for a few weeks or months, and other positive outcomes.

I ask today that you carefully consider the plight of people with melanoma and understand the range of both physiological and psychological issues that they face daily. Please take a leadership role in considering the approval for a broader range of treatments based on sound science and answers to hard questions, and then encourage patients to be informed, empowered and possibly optimistic about the potential for a longer, healthier life. Thank you.

DR. PRZEPIORKA: Thank you very much. Dr. Anna Pavlick, please.

DR. PAVLICK: Good morning. Thank you for allowing me to address the committee. I am one of the clinical investigators on this trial. I have received no financial compensation for coming down here, however, I do receive research support through Genta and Aventis.

I am actually here on behalf of my patient. This is Mrs. Kovati. Mrs. Kovati was my first patient to be enrolled on the Genta trial in my institution. She was told by a few other melanoma oncologists that she had six months to live and there were no options for her. She came to me four and a half years ago in a wheelchair, with a leg full of melanoma, large pelvic adenopathy and multiple tumors in her abdomen and said, "I'm only 56 years old. I don't want to die. Help me." I explained to her that we had this clinical trial available to her and told her full-well I was not sure if this was going to help her, however, we knew what her alternative was, so

she went on study.

She was featured in CURE magazine last summer because, I am proud to say, Mrs. Kovati had a complete response. She now remains three and a half years out of therapy in a continued complete response; has been able to get out of her wheelchair. She no longer walks with any assistive devices. She was able to dance at her son's wedding a year and a half ago, and she was unable to come down here today to be with us because she is now experiencing the birth of her grandchild, the first one that she thought she would never-ever see.

I felt it was on her part and on the part of all the other melanoma patients that I treat that I needed to come down here and tell you what a wonderful experience it has been for me to work with this new drug that truly holds hope for patients who have absolutely no options. Thank you.

DR. PRZEPIORKA: Thank you very much. Dr. Lawrence Green, please.

DR. GREEN: I have no financial disclosures to report.

[Slide]

My name is Lawrence Green. I am a dermatologist and dermosurgeon in private practice in Montgomery County. I also teach a weekly dermosurgery clinic at George Washington University to the dermatologist residents.

I am here today as a professional member of the Skin Cancer Foundation specifically because I have an interest in skin cancer.

[Slide]

Skin Cancer Foundation is the only national organization that is non-profit, dedicated solely to eradicating the world's most common malignancy, which is skin cancer and it has been around for 25 years, educating the public, among other things. Despite these ongoing efforts, as you know, the incidence of skin cancer, especially melanoma, continues to rise at an alarming rate.

[Slide]

One in three cancers this year will be

skin cancer which translates to 1.3 million new cases of skin cancer in the United States this year. Basically, that means that 20 percent of the population in the United States will develop skin cancer in their lifetime.

[Slide]

One person dies every hour from melanoma. In fact, if you look at it, melanoma is basically the most common cancer in women between the ages of 25 and 35.

[Slide]

In light of these abysmal statistics, it is painfully clear that providing public education messages on sun protection, skin cancer prevention and early skin cancer detection is not enough. The Skin Cancer Foundation is speaking here today, and I am speaking on behalf of it, as part of its patient advocacy mission to support skin cancer research and the latest advancements in effective treatments for its constituents.

[Slide]

Sadly, there are currently very few

effective treatments available for late stage melanoma patients. Therefore, if this new treatment shows promise, on behalf of myself and The Skin Cancer Foundations, the many patients and their families who have been affected by melanoma, we encourage this committee to carefully consider it. Thank you.

DR. PRZEPIORKA: Thank you, Dr. Green. Diane Murphy, please.

MS. MURPHY: Thank you for allowing me to come before this scientific panel to urge fast approval for Genta's drug Genasense. Three years ago I was diagnosed with stage 4 melanoma, and Dr. Hersh, at the Arizona Cancer Clinic in Tucson, told me that without treatment statistics would show that I had around nine months to live. This was shocking news for me because as a family we have been living on organic food, drinking bottled water, exercising, staying away from chemicals and doing whatever else we thought would give us a healthy life. So, how could this lead to a golf ball sized tumor?

I was biopsied, diagnosed and, thankfully, referred to Dr. Hersh. I was considering no treatment at all but Dr. Hersh persevered, suggesting that I was a good candidate for the experimental Phase 3 drug, which I did agree to try if, for no other reason, although it might not help me it would help someone down the road.

It did help. As my doctor told me, I have a complete response to my treatment and can now enjoy celebrating my big 70th birthday, which I did by, among other things, buying shares of Genta.

[Laughter]

Hopefully, none of you today making a decision on this drug has ever had friends or loved ones sitting in a chemo treatment room. It is the saddest and most depressing place to spend time. You can smell the fear, the misery, hopelessness and anger, and see the fatigue in all their faces under all the green hats hiding their bald heads. Help for each and every one of the patients is hearing the word "remission" and that is what Genta's drug gave me, and I am here to encourage

you to pass this drug for approval.

In closing, I want to thank God and the people in my life, my husband Jim who is always there 24/7, for hundreds of prayers from friends and acquaintances, both known and unknown, Dr. Hersh who truly is a healer in the greatest sense of the word and my oncology nurse, Cindy who encouraged me to get through each treatment day. I pray that all the poor souls going through this dreadful disease can have the same care, support team and access to the latest drugs such as Genta's Genasense. Thank you.

DR. PRZEPIORKA: Thank you very much, Ms. Murphy. Dr. Asher Chanan-Khan, please.

DR. CHANAN-KHAN: Hi. I have received honoraria for a speaking engagement. I have received clinical trial support from Genta and have not been compensated for anything for today's meeting.

I would like to thank the committee for allowing me to voice my opinion in the matter of Genasense. I come here from Russell Park in

Buffalo, New York, where I am entrusted with the care of patients with multiple melanoma and chronic lymphocytic leukemia. I am one of the clinical investigators involved in the studies exploring the role of Genasense in these incurable and rather frustrating diseases.

The NCI identified these as orphan diseases, thus, emphasizing the need for developing new and novel therapeutic options. Based on my personal experience as a clinician and as an investigator, I am able to comfortably state that the agent is safe and well tolerated during these clinical trials that I am conducting. No long-term side effects in the patients that I have treated have been noted. In fact, with this drug a number of patients with CLL and multiple melanoma have benefited clinically and continue to benefit as of today.

In conclusion, I therefore feel that this is a safe drug with a predictable and manageable side effect profile, and it does bring hope to a lot of patients in my clinic who are facing an

incurable cancer. Thank you.

DR. PRZEPIORKA: Thank you very much. Dr. Tolcher, please.

DR. TOLCHER: I am a medical oncologist in a cancer therapy research center. I have given my disclosures already. I am an investigator with one of the larger clinical experiences with oblimersen, having treated 63 patients in 288 courses of oblimersen during the conduct of 3 clinical studies. This includes one patient who received the maximum of 25 courses of this agent.

The toxicity profile of oblimersen is modest and largely predictable. The majority of adverse events experienced by patients are related to the chemotherapy itself and, again, are predictable for that chemotherapy agent. They do not require any special management above that of what a standard medical oncologist provides.

For those toxicities that can be attributed to oblimersen alone, they include a transient lymphopenia, pyrexia that occurs during the infusion but can be treated with standard

antipruritics, and complications of the central venous catheter. Patients with these toxicities can be safely retreated with the agent without evidence of cumulative increases or increases in the severity of these toxicities.

Interestingly, and I think really importantly, patient acceptance of the oblimersen treatment and its inherent cumbersome pump is high due to the low incidence of adverse events associated with oblimersen. From a clinical perspective, oblimersen can be safely and feasibly administered to patients with cytotoxic chemotherapy over many multiple courses. Thank you.

DR. PRZEPIORKA: Thank you, Dr. Tolcher. Dr. Patrick Cobb, please.

DR. COBB: Patrick Cobb, I am medical oncologist from Montana. I receive research grants from both Aventis and Genta. I have not been compensated for my time.

We have participated in a trial of Genasense in CLL and I will address some of the

safety concerns about it. We have treated three patients with this. All these patients had disease refractory to fludarabine chemotherapy. One patient received six courses of this and had no toxicity greater than grade 2 and remains in complete remission two years later. Another patient was treated with the same regimen and had an Aspergillus lung infection at the beginning of his course and went into complete remission after only one course and continued in complete remission after two years. He relapsed a while back and is receiving another course of Genasense now.

In summary, we found Genasense to be a very well tolerated drug when it was given to our patients with chronic lymphocytic leukemia. As a clinical oncologist I see a lot of patients with metastatic melanoma and, as you have already heard this morning, there are very limited options for their treatment and we need more treatment options. From the data we have seen presented today, it appears that Genasense is both a safe and an effective drug. Thank you.

DR. PRZEPIORKA: Thank you, Dr. Cobb. Harrison Blanton, please.

MS. BLANTON: Betty Blanton, from Shelby, North Carolina. I came at the request of my oncologist, with no compensation but I have discussed travel expenses with Genta.

I came to Carolina Regional Medical Center in Charlotte in October, 1995 after my melanoma reappeared following two previous melanoma surgeries. Later in my treatments as the disease progressed surgery was no longer a viable option. When your oncologist tells you that you have metastasized melanoma for which there is no surgery, thankfully, my family and I considered the best course and we decided that to be the Genasense trial, as was suggested by Dr. Gary Fernad of Carolina Health System.

I began with the trial in January, 2003 with eight cycles. My last was in July, 2003. My gratitude goes to my three sons who have provided, and still do, transportation since I live an hour from Charlotte. I received the Genasense

continuously for five days and then would go back for my DTIC. The Genasense treatment was not a bad experience, although a little trying to dress and keeping the wires intact was something interesting which I am sure the women can relate to. During that time I was referred to by my friends as the lady with the fanny-pack.

On days five of the Genasense treatment I did go back to Charlotte and received my DTIC. If I followed the medication for nausea as directed, I was able to function normally all the time. There were times when anemia was a problem but this was addressed by the doctor and his team. Sometimes a transfusion was needed but on most days I was able to do my normal office work in the mornings as a church secretary and teach piano in the afternoons, both of which I have enjoyed for over 50 years now. On Sundays I play the organ at the church. Out of those eight cycles of treatments only one Sunday I was not able to play.

I have nine grandchildren and two great grandchildren. They are, indeed, my life as each

of you share with your families. But I am here today because, I believe, the Genasense trial was a success for me. I am still able to work, enjoy my family and continue to live independently, and it is my hope that this experience will have an impact on the lives of others who know melanoma personally.

DR. PRZEPIORKA: Thank you very much. Dr. Jonathan Lewis, please.

DR. LEWIS: Distinguished members of the committee, good morning. My name is Jonathan Lewis. I come before you wearing two hats. For more than eight years I worked as a surgical oncologist at Sloan-Kettering. Although I still follow patients, the second hat I wear is developing cancer drugs in the context of a private start-up company. I have no financial interest at all in Genta. They have not paid me anything; they have not asked me to be here. Their CEO, Ray Morrell, referred many melanoma patients to me while we both worked at Memorial. I have only had sporadic contact with him for several years; I have

not spoken to him for at least six months.

I speak to you today because this committee's decision is important in the context of both the science and art of treating melanoma patients and the science and art of cancer drug development. I have been involved in the care of thousands of melanoma patients at Memorial. I have treated well over a thousand, and I have also conducted and been part of many experimental clinical studies in this disease.

As we have heard, stage 4 melanoma is an extraordinarily difficult problem. As I interpret these data presented today, it strikes me that despite the fact that the study clearly missed the statistical primary endpoint, every single analysis, including response rate, progression-free survival and survival demonstrates an advantage for those patients receiving the test agent. I understand that statistical improvement in survival is the gold standard but I am, nonetheless, very focused on the observation that Genasense shows effectiveness in the setting of a hundred percent

lethal disease. In the context of the disease, all of these are very likely to be clinically meaningful.

I am here today in part because a patient of mine with stage 4 melanoma is sitting in the audience. He is a highly decorated, allegedly retired senior FBI agent who has served this country extraordinarily. His care has involved a lot of the science and art. I have been through the data with him and he has a tremendous amount of common sense, wisdom and understanding and, on reviewing these data, he asked me how can this drug not be approved. I am grateful for your time. Thank you very much.

DR. PRZEPIORKA: Thank you. Cathy Liebermann, please.

MS. LIEBERMANN: Good morning. My name is Cathy Liebermann and I am a two-time cancer survivor. I am here with my daughter Lisa and her husband Aaron to share our family struggle with melanoma.

After reading about this meeting last week

in the Wall Street Journal we felt obligated to be here today, and we paid our expenses to do so. Our story begins in 1996 when I was undergoing chemotherapy for Hodgkin's disease. My husband Mark's primary concern at that time was my treatment and helping me with my battle. All the while Mark ignored a growth on his scalp. Because the growth was pink and perfectly round, Mark did not think it urgent to see a doctor. However, months later he was diagnosed with melanoma and the lesion was removed. We were elated that the pathology results showed no disease in Mark's lymph nodes and no further treatment was needed.

Six years later, in February 2003, metastatic melanoma was confirmed. We sought the advice of experts that included Dr. John Kirkwood and a family friend, Dr. Jerome Groupman, who referred us to Drs. Michael Atkins and John Richards. Mark then proceeded with four cycles of biochemotherapy. In July he walked down the aisle with Lisa at her wedding.

Only two months later tumors began to grow

again. It was then that Genasense was recommended to us. We were disappointed when Dr. Richards informed that the Genasense trial was no longer enrolling patients so Mark began other treatment instead in November. On January 10th Mark died at the age of 54.

There is no way to know if Genasense would have helped Mark but based on the trial results I believe that had Mark taken this drug he might be standing here with us today. Lisa, Aaron and I are here to plead with you to vote in favor of Genasense for all those who suffer with this disease and for their families who just want a few more days, weeks or months with their loved ones. Thank you for listening.

Committee Discussion

DR. PRZEPIORKA: I have no other individuals registered. I do want to apologize on behalf of the committee to Ms. Graham for the sound going off before she completed her statement. We have asked if she wished to make any additional comments and I understand she does not. If you

need to change your mind now, please feel free. Otherwise, we will go on with the rest of our meeting but we do apologize to Ms. Graham.

The next item on the agenda is the questions posed from the FDA to the committee. We have all received these previously. They include a rather lengthy prologue which Dr. Pazdur has chosen not to review for us. So, we can go straight to page three and we will be voting on questions one, two and three and question four is for discussion only. Let me start with question number one, given the thrombocytopenia concerns noted above, does the committee believe that the small observed differences in the response rates, that is, less than 5 percent, and in progression-free survival, the difference in median days between arms of 13 days with a p value of 0.006, represent real effects of Genasense when added to DTIC?

I am going to ask for discussion for a few minutes before we actually go around and take a vote. So, if anybody has any comments on this question, please feel free.

DR. GRILLO-LOPEZ: I have a point of order. I think the question needs to be worded differently because the way it is worded it is biased towards the analysis of the data by the FDA. I think we need to consider as a committee both the FDA's analysis as well as the sponsor's analysis. So, I would say that the qualification of the differences as small should be taken out and the 13 days, which comes from the FDA analysis, should be taken out.

DR. PRZEPIORKA: Dr. Pazdur, do you accept the changes in your question, or Dr. Temple?

DR. TEMPLE: The committee obviously is supposed to consider all the data it heard. It heard more than one assessment of both of those things and, obviously, can consider both.

DR. PAZDUR: I share that, and as I pointed out in my initial comments, I think what one has to take a look at is the individual contribution that the drug is making. Remember, we are dealing with a combination of a drug so one has to take a look at the delta also.

DR. PRZEPIORKA: Thank you for accommodating this need so a more unbiased question perhaps would be, given the concerns noted above, does the committee believe that the observed differences in response rate and progression-free survival represent real effects of Genasense when added to DTIC? Dr. D'Agostino?

DR. D'AGOSTINO: I noted that the second question picks up the ordering of the analysis. Are we supposed to take question one as if we use some sort of clinical judgment, are these effects substantial, ignoring the fact that we may not be able to attach any statistical significance to them?

DR. PRZEPIORKA: The answer would be yes. Dr. Hwu?

DR. HWU: I would like to review a little bit the background of the treatment of advanced metastatic melanoma. In the last 30 years we have made very small progress. The single-agent chemotherapy gradually evolved into the combination chemotherapy and also the development of

immunotherapy and the combination of a biochemotherapy involving the interferon interleukin and the chemotherapy. That evolvement is primarily based on the findings of the pilot and Phase 2 studies. Those trials have clearly demonstrated that when you combine several agents the response rate definitely increased, in some cases double or triple, especially with biochemotherapy. Yes, the price you pay is very high; it is toxic. However, in the Phase 3 trials none of those combination therapies has demonstrated that even with the response rate the difference is clinically significant but there is no impact on the outcome of the survival, not statistically significant.

So, in year 2002 we started the AJCC staging system which clearly separates the patients with stage 4 disease into three prognostic groups, M1a, which has disease in the skin and the lymph nodes; M1b, which can have soft tissue and the lymph nodes but also has lung metastasis; and M1c is the patients who have visceral disease other

than lung or with elevated LDH. The reason those patients were categorized in three groups is really based on their survival. The data is from over 1000 patients from nine major cancer centers. Irrespective of what their treatment was, the median survival for M1a is 16 months; the M1b group is 14 months because their survival is correlated with M1a for the first year and then that becomes consistent with the M1c group. The M1c group has the shortest median survival of 7 months or less if you have brain metastasis which is less than 6 months.

So, clearly, if we want to make any impact on the survival of the patients with stage 4 disease we have to make the treatment more effective for the M1c group. I have to congratulate the sponsors of this study that they did not exclude the patients with M1c which is a very, very bad group. However, it was not balanced on the two arms. The M1c group has more patients, 253 on the DTIC alone group--257, and in the experimental group there were 226. The imbalance

was also seen in stage M1a. On DTIC it was 50 patients and the experimental arm had 61 patients.

So, what is the outcome when you compare that everybody is getting the DTIC and only the experimental arm is getting the experimental drug? So, which group benefits the most by adding the experimental drug? It is not surprising to see that most of the patient benefit is with the M1a group because it was clearly shown in the previous Phase 1/2 trial that patients who had responded well to the Genasense plus DTIC is the group with lymph node and also skin metastases. So, in this study the M1a group in the experimental arm--13 patients had a response, objective response as compared to DTIC with 6 patients.

In the M1b group 16 out of 96 patients responded to the experimental group and 9 out of 75 in the DTIC alone group. However, in M1c 16 out of 226 patients responded to the experimental drug as compared to 11 out of 227 of DTIC alone.

So, I definitely say yes, there is activity of this drug when it is compared with

DTIC. Are we going to make any difference in prolonging survival of our patients? Believe me, I desperately want to have some drug that can help with my patients. After 15 years in this field I cry every time when I lose a patient; I feel it is a personal defect. But, unfortunately, this drug is not the answer, at least the way it is administered. We are helping the best prognostic group of patients and I hope that with continued effort we will eventually help the group of M1c patients. Thank you.

DR. PRZEPIORKA: Dr. Cheson?

DR. CHESON: Yes, first of all to follow-up on what you were saying, it is clear that with these biotherapeutics, or however we categorize this drug, that we don't have a clue as to the optimal way to use them. We base it on cell lines, pharmacodynamic things, but that doesn't mean that this is the best way to do it. My concern is that if we consider this unapprovable the drug is going to die and we will never figure out how to use it, and how to apply it better, and

how to study it better in other diseases as well as melanoma, melanoma being one of the two diseases increasing in frequency; the other being lymphoma--we have to get our plug in there.

The other point I want to make is that I sat here a few months ago at another ODAC meeting, and this was mentioned earlier, and saw another drug approved with a response rate for which the lower limits of the confidence interval was 5.4 percent with two huge negative Phase 3 trials without even a twinkle of progression-free survival, without any suggested difference of long-term survivors. To me, these results are a lot more encouraging than that drug that was approved at a prior meeting. And, that is all I have to say about point number one.

DR. PRZEPIORKA: Dr. D'Agostino?

DR. D'AGOSTINO: Why will the drug die? You don't think the company will pick it up with the promising results here? The studies are too expensive?

DR. CHESON: You know, I have no

conversations with the company about that or anything else but with a small company that has devoted a lot of resources into a particular drug, if it doesn't get approved then, based on economics etc., drugs tend to fade away.

DR. PRZEPIORKA: Dr. Temple?

DR. TEMPLE: Not to state the obvious, but really we need to know from you whether you think it works, not whether you feel bad for the company or feel bad for the state of oncology development.

DR. CHESON: No, that is not the point. I do think it works. I think there is a strong signal here but I think, as with that other drug, we don't know the optimal way to use it. But there is a signal here. I do believe the progression-free survival data, as we will get to in the next point. This committee discussed last time, and may discuss tomorrow, that progression-free survival may perhaps be the better endpoint and, had this trial been started today instead of several years ago, they would have been recommended to use progression-free survival and we

might not have been having this sort of discussion.

DR. TEMPLE: But this question is about whether you believe there is a difference in progression-free survival. The importance of it really is what the second question is.

DR. CHESON: Well, I will vote yes on that when it comes to my time to vote.

DR. TEMPLE: Okay. Even though the question has been modified appropriately because we don't want to put bias in it, you do need to tell us what you think of the various comments that various people have made about the difference in time of assessment and whether those shake you or not. That is what this question is.

DR. CHESON: I will leave that to Dr. George who is about to ask a question.

DR. GEORGE: I have a number of comments about this. To me, some of this is rather disturbing and I guess that is why we have it before the committee. If it were easy we wouldn't see it.

The general strategy of when the primary

endpoint is not met and looking at secondary endpoints is bothersome from a regulatory point view point and scientific view point just on the surface. That is, one way it could have been done--of course, we wouldn't be talking about this, at least in the same way if the primary endpoint had been progression-free survival and more tightly done with the measurements. But, you know, one way it could have been done would have been a bigger study, of course, but you could have said, all right, we are going to look at the primary endpoint and the secondary endpoints and we are going to make adjustments. The adjustments basically are we have to be more sure of the results, therefore, we have to have a much bigger study. Of course, this is already a large study.

So, getting back to the point, there wasn't an advantage in survival. There may have been some signal there. That is, some very small percentage of patients, those who achieve a CR, may be the long-term survivors and may, in fact, be different in the really long term. That is, you

might have--what?--if you look at the survival curves at about 20 months they are identical but there is some evidence obviously both from the testimonials and from the data that there are some patients who are making it beyond that.

But to pick up that kind of difference, of course, is very, very difficult and takes huge sample sizes and that is sort of out of the question here. But what is bothering some people here is that they are thinking there might be something here but it just isn't clear.

Just to make my own point on this, it is clear that the overall survival, from a regulatory view point, wasn't significant. I am very suspicious of the progression-free survival. I didn't get the data myself, of course, and go over all this but I am very worried by the differential measurement timing and the effect of this, the potential effect of this on attenuating that result, maybe attenuating it down to a point where there is really essentially no difference between the two.

So, I am sort of left at looking at these response rates and then I hear that there is this question about whether this independent assessment of the response rate--there is some question about that and, again, I am not clear on what it all means. It sounded plausible that maybe if this independent group had had more of the background clinical information it wouldn't have been so discrepant, but the fact is it was discrepant. So, I am struggling with all these things in the face of what might be a promising agent but probably at a very low level.

DR. PAZDUR: I just wanted to emphasize why we drew up these questions the way we did. If you remember my opening comments, we first have to make sure that there is a biological effect. What is the effect of this drug on the endpoint that we are entertaining, and then how adequately characterized is that effect? We have to answer that question first before we go and discuss the clinical relevance because the clinical relevance of a certain drug brings in the risk-benefit

relationship and, as I pointed out, benefit cannot be discussed unless it is adequately characterized, and this is the sense of the questions and why we are asking them in the way we are.

DR. PRZEPIORKA: I would just then like to ask if we could split question 1 into 1A and 1B.

DR. PAZDUR: That would be fine.

DR. PRZEPIORKA: So, 1A being the difference in response rate is pretty objective and I think we can address that. I am just sorry to hear that the study was not designed truly based on the best way determined in this Phase 1 study, as Dr. Hwu pointed out earlier, and also that there is really no biological correlate that was looked at, going instead straight from a Phase 1 to a Phase 3. So, there is a huge number of design issues which I think really limited the difference in response rate that we are seeing here.

I have to agree with Dr. George that there is a tremendous bias ascertainment here with the progression-free survival data and that is why I would like to ask that these two questions be

answered separately. Dr. D'Agostino, you had more comments?

DR. D'AGOSTINO: In some sense I was going to endorse what was said. I mean, we have to understand, if I am understanding correctly, that these were secondary outcomes we are looking at, and sort of the way that one would rigorously define these and then ascertain them is somewhat missing. So, I am stuck, as you point out, with the difficulty with progression-free survival and how that can move around depending on some assumptions.

I am also concerned with the response rate in terms of how rigorous that was. I am quite surprised that the outside independent group was somehow or other only there for quality control, and the quality control was somehow or other not able to work because it wasn't given all the data. I find those aspects of the study to really bother me in terms of how do we interpret these relatively small numbers.

DR. PRZEPIORKA: Dr. Taylor?

DR. TAYLOR: I guess I have a concern about progression-free survival in that there are some patients who have very slow growing tumors and, if you are going to use that as a measurement, in particular people with the soft tissue type disease, I think you have to know how rapidly they were progressing before they were treated, and if you have someone who had very slow growing disease that might be impacted on that.

The second thing that as a clinician I have seen is that melanoma is a particularly unpredictable disease. Although its response to chemotherapy has been dismal, I have patients whom we put on tamoxafin studies and who are now 20 years out in complete remissions. So, it makes it very hard for me to not be concerned when I see small numbers of patients getting benefit about whether it is truly the drug or the natural history of that particular melanoma.

DR. PRZEPIORKA: Dr. Bukowski?

DR. BUKOWSKI: The issue of response rates I think is an important one to consider. We have

looked in melanoma, and I believe I am correct here, in randomized trials where we have added biological agents to chemotherapy and have seen increments in response rates in the past that were significantly higher than the chemotherapy alone. Unfortunately, those studies demonstrated no benefit in terms of survival or other secondary effects.

So, I think we have to keep this in mind as we consider this particular drug. There is an increment in response here that may be a signal but we have seen this before without the signal of survival being met. Melanoma is not unique in this situation, obviously, but this is a concern when you look at response rates and we are saying response is one measure of drug effect here and we have seen this before in this disease.

DR. PRZEPIORKA: Before we go on to the vote, are there any other comments from the committee? Dr. Rodriguez?

DR. RODRIGUEZ: I share similar concerns that have already been voiced with regards to the

PFS endpoint and that there clearly was some difference in the timing to assessment of that endpoint.

I think as a clinician there is one thing that can't be argued and that is, as I look at this data, the arm that got Genasense clearly had more complete remissions. I am staring at that and I can't let that go. I mean, we have seen some of the survivors here today and one can't argue with the living.

We all know as oncologists that we will never get to a cure unless one gets a complete remission. So, it is intriguing to me that it seems that this drug probably improves on the quality of response rather than the overall total response or DTIC. The question is what makes the people who did get the complete responses different than the other patients. I am so disappointed, like Dr. Hwu, that we don't have anything that correlates that will point us to the appropriate patients for whom this drug is indicated.

DR. PRZEPIORKA: Dr. Reaman?

DR. REAMAN: I regret that we have sort of brought up the past in a prior meeting of this committee but, unfortunately, it has been brought up and there was a suggestion to approve an agent with a response rate that was of a similar magnitude. I feel that we are being called upon to make a similar decision again with a hint of a response with an agent that may disappear if it is not approved at this committee meeting.

Also, I am troubled by the fact that the response rates and the methods for independent review were as troublesome in this study, but I just feel like we are between a rock and a hard place in trying to answer the first part of question one.

DR. PRZEPIORKA: Dr. Pazdur?

DR. PAZDUR: I would just like to comment that when we talk about response rates, remember that the "other" drug that you mentioned was a single agent that produced that 10 percent response rate. We are talking about a combination therapy and, therefore, one has to take a look at that

combination.

Also, I think it is very important that we perhaps discuss this issue more about the complete responses. Remember, 3 of the proposed 11 complete responses were surgically induced. As far as my recollection of the protocol, there was no uniform statement about how surgery was going to be applied. This is really a very down-the-line analysis. There is a great deal of subjective bias. We all know who are surgical candidates and who are not surgical candidates.

To the patients, I fully understand the importance of complete responses and whether they get it by surgery plus chemotherapy or chemotherapy alone probably may not matter to them. What we are addressing here though is a drug effect, and I think it is important that we take a look really at those surgically induced complete responses really as partial responses, if they were in fact, that would then render them disease-free by surgery. I think that would be a more appropriate way of really suggesting this entire issue.

But this whole idea of surgery intervening here--granted, it is very important--there is a higher degree of subjectivity and unless that is handled in a prospective manner on both arms of the study it is really hard to ascertain how many complete responses, especially when people are following these patients out for prolonged periods of time--the symmetry of follow-up has to be similar.

DR. PRZEPIORKA: Dr. Hwu?

DR. HWU: Regarding the response rates to the single agent in the other Phase 3 trial, we have to remember that although the response rate is similar to this study, in that study it allowed 20 percent of the patients with brain metastases and on the DTIC arm all the 20 patients who had brain metastases did not respond as compared to the 5 percent response. So, you have to discount those 20 patients in that study.

DR. PRZEPIORKA: Thank you. If there are no other burning issues I would like to call the question. Dr. Lopez?

DR. GRILLO-LOPEZ: Grillo-Lopez. At the end of the session today we really have to address question number five which, regardless of all of the above, is should Genasense be approved and made available to the patients who need it? That relates to what Dr. Pazdur and Dr. Temple just said. We need to give a recommendation on whether or not there is an effect and if that effect is important enough to merit approval of this agent, and that question is not asked so I would ask that we add that as question number five.

DR. PAZDUR: That is patient access and I think that is a different question. There are obviously access mechanisms available through expanded access programs. We are asking basically about issues here that are defined in our questions. If you would like to discuss that at the end, please feel free to do so.

DR. PRZEPIORKA: Dr. Temple, do you have any brief comments before we take a vote?

DR. TEMPLE: I just have one thing. Maybe you will find it distracting. There is some sense

that there is a small fraction of the population that has a very special response and maybe, indeed, that is true. But in the two figures that we have seen that look at that, namely progression-free survival and survival itself, the curves at about 700 days are right on top of each other. In fact, for progression-free survival Genasense is slightly below. So, maybe the continued data will show that there is an excess of long-term survivors but at least in the data we have seen so far it is very hard to discern this hyper-responder group. I don't know whether that is lack of maturity of the data and when the last 10 percent of the people are looked at something will turn up but, at least in those figures, there is no hint of that and I just wondered what everybody thinks about that in light of the possibility that there might be some people who get particularly good responses.

DR. PAZDUR: I think it is also important that people are cognizant, when they talk about these responses, these complete responses, that the N in the treatment arm is quite high. We are

talking about, whether one wants to say 8 responses, 10 responses, how many patients were in that arm.

DR. PRZEPIORKA: So the survival issue actually falls under question two I think and we will discuss that in just a few moments. Dr. Cheson, you had some other comments?

DR. CHESON: Just one comment about that. Didn't they stop collecting survivor data at a certain point for these curves and, therefore, we don't know if they were censored--what?--at two years or something and we don't know what goes on beyond that.

DR. TEMPLE: That is what I am saying. As far as the data that we have been presented, you don't see that tail on the curve looking different. In fact, they are right on top of each other. Maybe with the final values on everybody you will see something but I don't see that yet, even though there are obviously some people who had good responses to either the drug or the combination.

DR. PRZEPIORKA: Let's go ahead with the

vote and we are going to simply start at one end of the table and go around. Dr. Grillo-Lopez and Dr. Wen Jen-Hwu are not voting members but everyone else should give a yes, no or abstain.

Question 1A would be does the committee believe that the observed differences in response rate represent a real effect of Genasense when added to DTIC? Dr. Bukowski, we will start with you.

DR. BUKOWSKI: No.

DR. BISHOP: Yes.

DR. PRZEPIORKA: Dr. Taylor?

DR. TAYLOR: No.

DR. REAMAN: Yes.

DR. REDMAN: Yes.

DR. PRZEPIORKA: Yes.

DR. RODRIGUEZ: Yes.

DR. DOROSHOW: Yes.

DR. CHESON: Yes.

DR. GEORGE: Yes.

MS. HAYLOCK: Yes.

DR. CARPENTER: Yes.

DR. D'AGOSTINO: No.
DR. MORTIMER: No.
DR. HUSSAIN: No.
MR. MCDONOUGH: Yes.
DR. GRILLO-LOPEZ: I am a non-voting member but I would vote yes if I were allowed to.
[Laughter]
So, the end of the vote says 11 yes and 5 no. Question 1B would be does the committee believe that the observed difference in progression-free survival represents a real effect of Genasense when added to DTIC? We will start with Mr. McDonough and go the other way.
MR. MCDONOUGH: Yes.
DR. HUSSAIN: No.
DR. MORTIMER: No.
DR. D'AGOSTINO: No.
DR. CARPENTER: No.
MS. HAYLOCK: Yes.
DR. GEORGE: No.
DR. CHESON: Yes.
DR. DOROSHOW: No.

DR. RODRIGUEZ: No.

DR. PRZEPIORKA: No.

DR. REDMAN: Yes.

DR. REAMAN: No.

DR. TAYLOR: No.

DR. BISHOP: No.

DR. BUKOWSKI: No.

DR. PRZEPIORKA: The final vote is 6 yes and 10 no. Let's move on to question two. Do the results of the study, in particular the difference in response rate and/or progression-free survival for the combination of Genasense and DTIC versus DTIC alone, in the absence of a survival improvement, provide substantial evidence of effectiveness that outweighs the increased toxicity of administering the Genasense for the treatment of patients with metastatic melanoma who have not received prior chemotherapy?

While the members of the committee are thinking about comments, I personally have two. One is that I know the folks at the FDA have seen me say, "yes, I'm a pro PFS kind of person" with

the exception of when the experiment is not done very critically. So, progression-free survival I think has to be considered a valid endpoint in melanoma for which there is no drug that shows a benefit for survival. There is no question about that.

The other issue has to do with the administration. As was pointed out, this is a drug added to another drug and Genasense is administered by continuous infusion requiring a pump and a catheter and is not given as a pill. I think that actually also weighs with regard to what I was thinking.

I have just been handed a recount. On question 1B the recount is four yes and 12 no. Thank you to the folks who went through the tape and listened to everyone once again. Other comments on question two? Dr. D'Agostino?

DR. D'AGOSTINO: I think we do, in responding to question two, have to remember what the objective of the study was. The objective of the study was to have a primary outcome of survival

and some secondary outcomes, of which two are mentioned here. The survival was not significant and I am concerned or confused about where the separation comes from. Maybe later data will show us that but it is sort of beyond the study time period and heaven knows what other things were going on. So, again, to focus it, we did have survival as the primary outcome. It wasn't significant and the secondary outcomes weren't obtained, at least the progression wasn't obtained in the clearest fashion. So, I think we have concerns that the study didn't meet its objective.

DR. PRZEPIORKA: Dr. Lopez?

DR. GRILLO-LOPEZ: Grillo-Lopez; Lopez is my mother's last name.

DR. PRZEPIORKA: I stand corrected, thank you.

DR. GRILLO-LOPEZ: Thank you. At the December meeting of this committee we discussed endpoints primarily in the setting of lung cancer. But as I recall, our recommendation to the FDA was to apply and utilize progression-free survival in

preference to overall survival in most settings. There are some exceptions. So, this protocol was probably written four or five years ago and discussed with the agency, and maybe at that time overall survival was favored.

Now, those of you who are not familiar with how primary endpoints are chosen should understand that the sponsor meets with the agency and there are discussions around protocol design, the choice of endpoints and the statistical design of the study. And, it is not entirely up to the sponsor to choose the endpoints. The agency, of course, has a strong influence on what the primary and secondary endpoints are. I think it is important, since it is an overriding concern for a number of people here, the issue of not having met the primary endpoint--I think it is important to know how the agency and the sponsor arrived at the decision for that primary endpoint and whether or not that would have been the sponsor's first choice.

DR. PRZEPIORKA: Dr. Temple?

DR. TEMPLE: Well, we have been bringing the question of what the endpoint should be to various deliberations of the advisory committee for--I don't know, probably ten years; for a long time. One of the problems that we recognize is that many trials have crossover and if there is going to be crossover you have very little hope of showing a survival effect. We understand that. That is a serious problem.

The other thing is that if death occurs long after progression the numbers of people you have to have in a trial to show a difference start to get huge even if you retain the whole benefit. But all of those conversations have reflected the fact that disease-free survival has to be done scrupulously, with great care, preferably in a blinded study because it is subject to bias, and it is not just a simple matter of which do you like. I think that is what Rick said at the beginning, and that has always been part of the discussion too. Whether people were influenced by the endpoints that we like or not, if somebody were

setting out to really do disease-free survival I have to believe it would be done differently, and that is part of the context too.

DR. GRILLO-LOPEZ: I think a lot of us don't like overall survival and that is the discussion that we had in December. Some of the things that have to count against overall survival as an endpoint were mentioned by Dr. Pazdur earlier. It is a biased endpoint and those biases, by the way, were not mentioned by--

DR. TEMPLE: Why is survival a biased endpoint?

DR. GRILLO-LOPEZ: Let's go back to the December meeting. Survival as an endpoint depends on an event, death. That event, if it relates 100 percent exclusively to the disease, is useful. But that is not reality. In the majority of patients it doesn't relate 100 percent to the disease. It depends on complications of the disease or the treatment. It depends on co-morbidity, it depends on a variety--don't interrupt me; I am not finished, Dr. Pazdur. Please turn off your

microphone. Let me talk. You interrupted me once before and that is enough. Okay?

The event is, in fact, something that can be manipulated. It can be manipulated depending on, one, the supportive care the patient receives or does not receive. The patient may die earlier or later because of that. That introduces a bias. The event also depends on a death being certified by a physician who may or may not be the primary physician, who may or may not know the patient and the natural history of his disease. So, if a physician is seeing the patient for a first time at the deathbed and know the patient has cancer may say the cause of death, cancer. Maybe the patient had an MI or pulmonary embolism. So, there are many ways in which overall survival is a biased endpoint, which is why progression-free survival, despite all of the problems that have been mentioned here today about its measurement, is a preferred endpoint because it is measurable.

DR. TEMPLE: There are statisticians in the room. Most people wouldn't call bias in any of

those things. That is an unusual use of the term.

DR. PRZEPIORKA: If we could continue with the discussion on question two which regards a risk-benefit ratio, does the benefit, the small benefit that has been seen in this particular study outweigh the toxicities and the trouble with giving everything by continuous infusion? Dr. Carpenter?

DR. CARPENTER: I thought it was worth noting, in response to Dr. Temple's comments, that long survival could confuse things because it causes a death and could muddy the endpoint. Long survival is not an issue in this study, at least from what we have now. Since there is no other therapy which dependably prolongs survival in melanoma, I think a crossover effect in this population is extremely unlikely.

DR. PRZEPIORKA: Dr. D'Agostino?

DR. D'AGOSTINO: I just can't let the death be a biased endpoint. I am sorry to eat up the time on the committee but I wish all studies had such a firm endpoint. The death is all-cause mortality; it is not cancer-related mortality.

Right? So, we are not talking about mistakes, and I hope that the investigators don't give differential treatment to subjects depending on what treatment they are on. So, the biases that might be generated by care I hope really are not an issue.

DR. PRZEPIORKA: Any other comments regarding the toxicity and risk-benefit ratio? Dr. George?

DR. GEORGE: I will pass.

DR. PRZEPIORKA: Dr. Hwu?

DR. HWU: We spent the last three decades trying to find standard care or better treatment and I believe all my colleagues in the field feel that the only way to establish better treatment is through a Phase 3 trial with an endpoint of improved survival, not any other means because, clearly, we have gone through this for years and years and improved response does not translate into improved survival. The endpoint has to be survival, overall survival.

DR. PRZEPIORKA: Dr. Redman?

DR. REDMAN: Just for my clarification because I really need things simplified, question one that I answered already is basically saying is there a difference and do you believe the difference is real. Question two is asking us is it of clinical benefit.

DR. PAZDUR: That is the approval question.

DR. PRZEPIORKA: Other comments? If not, I will call the question. Do the results of this study, in particular differences in response rate and/or progression-free survival for the combination of Genasense plus DTIC versus DTIC alone, in the absence of a survival improvement, provide substantial evidence of effectiveness that outweighs the increased toxicity of administering Genasense for the treatment of patients with metastatic melanoma who have not received prior chemotherapy? We will start with Dr. Bukowski, please.

DR. BUKOWSKI: No.

DR. BISHOP: No.

DR. TAYLOR: No.
DR. REAMAN: No.
DR. REDMAN: No.
DR. PRZEPIORKA: No.
DR. RODRIGUEZ: No.
DR. DOROSHOW: No.
DR. CHESON: Yes.
DR. GEORGE: No.
MS. HAYLOCK: Yes.
DR. CARPENTER: No.
DR. D'AGOSTINO: No.
DR. MORTIMER: No.
DR. HUSSAIN: No.
MR. MCDONOUGH: Yes.
DR. PRZEPIORKA: The final vote then is three yes and 13 no. The third question has a rather lengthy prologue. For regular approval of a drug for metastatic melanoma, the FDA has considered an improvement in survival and/or disease symptoms to constitute clinical benefit. However, in the December ODAC discussion considerable interest was expressed in

progression-free survival as an endpoint in some settings, particularly where crossover to other treatment could obscure a potential survival benefit. In the metastatic melanoma setting, do you believe that a progression-free survival benefit of some magnitude represents clinical benefit that could support regular drug approval, even in the absence of an effect on survival?

We have initiated some discussion and I will just throw my two cents in here and say absolutely, in a disease where there is no drug that confers a survival benefit having a progression-free survival, getting patients off chemotherapy for some period of time or at least away from the stigma of having active disease is a clinical benefit. Any other comments from the committee? Dr. George?

DR. GEORGE: Just a comment I made actually at the last meeting when we discussed this has to do with the crossover effect issue that people seem to obsess about quite a bit. The real point about that is that if there is something that

happens later that affects the outcome, then you still can look at survival. That is, there still is an answer. The answer may not be what you wanted to answer, that is, did this therapy prolong survival if I didn't give anything else later or if I absolutely controlled everything precisely the same way beyond this point? But is the real-world answer that in the current setting with available therapies that are so-called salvage therapies sometimes and other things, it may not work with respect to survival or it may work but the answer is still a good one for that therapy. Having said that, I still think that progression-free survival, done properly, is in fact a very good way to do it.

DR. PRZEPIORKA: Dr. Carpenter?

DR. CARPENTER: I just second that.

DR. PRZEPIORKA: Dr. Grillo-Lopez?

DR. GRILLO-LOPEZ: It is important to consider that for the majority of agents that come before the FDA for approval the submission package does not include data as to their optimal use, perhaps the use with a combination therapy that may

have the potential of prolonging survival. Usually this is the early data. It is the first studies done with an agent and you maybe will see evidence of clinical activity but not necessarily the optimal use within the best possible combination of that agent. There are many examples of that.

I will give you rituxan, a product for which I was responsible for clinical development. When we presented the data to the agency we did not have the optimal use of that agent that would prolong overall survival. In fact, that happened only five to six years after the fact when the combination with CHOP has shown that it can increase the cure rate in patients with diffuse lymphoma.

So, again, we have to be careful because that is another problem with overall survival as an endpoint. You seldom receive at the beginning--you, the agency, seldom receive at the beginning the optimal use of the agent, and I think you have to be very careful and look for clinical activity. If it has clinical activity, then it

should be approved and it should go to the medical community that really has the responsibility for finding what the eventual optimal use in combination, and so on, is for that agent.

DR. PRZEPIORKA: Dr. D'Agostino?

DR. D'AGOSTINO: Is it a quality of life issue that you are suggesting by using this variable that the individual removes a stigma?

DR. PAZDUR: let me just jump in here. Do I have permission to speak?

DR. PRZEPIORKA: Yes, sir.

DR. PAZDUR: Thank you. The issue here is that we really brought this to the committee because we really wanted to illustrate problems of time to progression or progression-free survival. In order for this to have rigor it has to be adequately measured and prospectively defined. The points that I was trying to get across that I wrote last night and read to you is that this is really almost a harder endpoint to do correctly. It requires robustness. It probably requires that the pharmaceutical sponsors actually meet with their

investigators and emphasize to them how to handle missing data. The symmetry of assessments have to be there. It actually is a much more difficult endpoint to assess.

Now, getting back to Dr. D'Agostino's question, I think one of the fundamental issues that you have to answer, and here again it comes back to question number four, which is almost an unanswerable question because it is in the eyes of the beholder--what is the magnitude? What is the benefit of delaying progression of a disease? Here, again, in any analysis of survival with a conventional toxicity profile, we have really not answered that question if it was statistically significant with an acceptable toxicity profile. But when you are dealing with a progression endpoint, I think one has to ask oneself what is the benefit in light of the toxicity, even if the toxicity is what one would encounter in a standard chemotherapy drug.

The other issue that we have been discussing with sponsors as we move away and we

have to ask ourselves why we should move away in individual disease, and Bob brought this up, is whether it is a problem with crossover. Is the disease of such sufficient natural history that is so long that a survival endpoint might not make sense to bring up? Is the trial so big that it is unmanageable to do? Why does one want to substitute PFS for survival? That may be an individual disease setting that that needs to be discussed, and that is why we are approaching these disease by disease rather than just making a uniform policy that we will no longer look at survival; we will look at progression-free survival.

The other issues that we have discussed with sponsors is that we really like the studies to be powered at least for survival, not that that would necessarily be an approval endpoint, but it is something that I think we have to look at eventually. We could approve a drug, for example, on progression-free survival but if we never power the study for survival we will never know whether

any of our treatments have a survival advantage and that would really put medical oncology behind significantly.

The other issue, finally, is power on trials. To power a trial requires a degree of guesstimation and frequently we have seen trials that come to this committee as under-powered trials. At least if we power for survival, one would hope that a progression-free survival would be adequately powered even with the uncertainties that exist there.

DR. PRZEPIORKA: Dr. Redman?

DR. REDMAN: I agree that progression-free survival is probably important and I think one of the problems is the p value. If someone says I am going to power a trial to prove that for patients getting drug X the progression-free interval is three weeks greater and they had a p value with six zeroes in front of it, the question is, no matter how rigorously it was done, how clinically relevant that is. I guess it comes down to the point, and it is not very scientific, that you will know it

when you see it.

DR. PRZEPIORKA: Dr. Temple?

DR. TEMPLE: A couple of other points while we are discussing this, there has never been any question that if someone had data on time to symptomatic progression that would be a clinically meaningful endpoint. Despite our saying that at a hundred end-of-Phase 2 conferences we have been very unsuccessful at getting anybody to look at that. I just want to make the advert that even after someone progresses radiologically you could still measure time to symptomatic progression, especially if there isn't anything very good to transfer the patient to. So, that is one pitch.

The second this is sort of a practical matter. When you calculate the increase in sample size that is needed to show survival, even if the effect on survival was the same as the effect on time to progression, if death occurs considerably after progression the effect size gets depressingly small. So, if you had a hazard ratio of 0.8 at 10 months and survival goes to 20 months that same

difference becomes a hazard ratio of 0.9 and the sample size implications become quite daunting. That is a practical concern but it could mean that trials in that setting would have to be just enormous, and that is another reason we are thinking about disease-free survival.

DR. PRZEPIORKA: Just to come back to a question that Dr. D'Agostino asked me earlier, you raised the issue of symptomatic relapse and I still have great concerns that depression and anxiety are truly symptoms that we wish to address. Dr. Carpenter?

DR. CARPENTER: I think how much one is willing to accept a progression-free survival endpoint is going to be inevitably tied to question four but a couple of simple examples help to modify the way one might think about it. In this application that we are discussing the issues were all with a possible increase in progression-free survival on the order of magnitude of a month or less, no matter which projection you look at. If you were talking about something in the 3-6 month

interval I would be surprised if the tenor of the discussions was not different and if the difference in survival, even if it was small, would not become secondary. The more we get into drugs that act by biological mechanisms that may not shrink tumors but which might stop growth so you may get long periods and if you get relief of symptoms and prolonged freedom from progression, I think it would be an unusual person who won't think that is a benefit.

The question in this particular application was whether they have really met some kind of endpoint that would be satisfactory. Could one accept unequivocally that they have met that or not, and the votes are there.

DR. PRZEPIORKA: Ms. Haylock?

MS. HAYLOCK: Let's see, all the numbers I think kind of obscure the reality of what melanoma patients face and I think of all the kinds of cancers, the dying process in melanoma is sometimes long and drawn out and fairly awful. So, I think that symptomatic progression is important just in

terms of the things that people do go through if their treatment fails overall.

So, I think the cure versus control issue we are looking at in this particular kind of cancer, like a lot of cancers, is more of a chronic disease entity and how do we control those chronic symptoms for longer periods of time and give people quality for whatever time they have left--I think that is sort of lost in all the numbers, particularly lost when people just look at death as the sentinel event in this.

DR. PRZEPIORKA: If there are no other questions I will ask for a vote. Question number three, in metastatic melanoma, do you believe that a progression-free survival benefit of some magnitude represents clinical benefit that could support regular drug approval, even in the absence of an effect on survival? Mr. McDonough?

MR. MCDONOUGH: Yes.

DR. HUSSAIN: Yes.

DR. MORTIMER: Yes.

DR. D'AGOSTINO: Yes.

DR. CARPENTER: Yes.

MS. HAYLOCK: Yes.

DR. GEORGE: Yes.

DR. CHESON: Yes.

DR. DOROSHOW: Yes.

DR. RODRIGUEZ: Yes.

DR. PRZEPIORKA: Yes.

DR. REDMAN: Yes.

DR. REAMAN: Yes.

DR. TAYLOR: Yes.

DR. BISHOP: Yes.

DR. BUKOWSKI: Yes.

DR. PRZEPIORKA: It is unanimous, yes. The last question for discussion, which we have had a tremendous amount about is, if yes, please discuss what magnitude of improvement in this endpoint would be required to demonstrate clinical benefit and whether this would depend on the toxicity of the treatment.

I will just start by saying not just toxicity of the treatment but the way the drug is administered, and in this situation where the drug

was administered by continuous infusion for a patient population who had no other alternative, like many diabetics who are on a fanny-pack right now, I don't think the patients would mind having the fanny-pack for the rest of their life if it meant they would actually get a clinical benefit from it. So, for this particular setting how the drug is administered is less of an issue because of the background.

Other comments regarding this question from the committee? Hearing none, Dr. Temple and Dr. Pazdur, do you have any other questions you need advice on from us?

DR. PAZDUR: No.

DR. PRZEPIORKA: Thank you. I call this meeting adjourned then. We will meet here promptly at 12:45 to begin the second session. Thank you.

[Whereupon, the proceedings were recessed for lunch, to reconvene at 12:45 p.m.]

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

DR. PRZEPIORKA: In the interest of time, we will start the meeting and we will have a few people in and out during the course of the day, and I apologize but we do want to stay on time as much as possible.

This afternoon we will be discussing RSR13 and we want to start with a conflict of interest statement. I understand there are no conflicts of interest for the group for this afternoon. Please refer to this morning's statement if you want more information.

Because we have moved around a bit and there are new individuals who have joined us for this particular meeting, I would like to go ahead and allow the committee to introduce themselves once again and if we could start with Ms. Portis.

MS. COMPAGNI-PORTIS: Natalie Compagni-Portis. I am a patient representative.

DR. MORTIMER: Joanne Mortimer, medical oncology, Eastern Virginia Medical School.

DR. HUSSAIN: Maha Hussain, medical

oncology, University of Michigan.

DR. D'AGOSTINO: Ralph D'Agostino, Boston University, biostatistician.

DR. BUKOWSKI: Ronald Bukowski, medical oncologist, Cleveland Clinic.

DR. BUCKNER: Jan Buckner, medical oncology, Mayo Clinic, Rochester, Minnesota.

DR. MARTINO: Silvana Martino, medical oncology, the John Wayne Cancer Institute.

DR. TAYLOR: Sarah Taylor, medical oncology, Palliative Care, University of Kansas.

DR. REAMAN: Gregory Reaman, pediatric oncologist, George Washington University and the Children's Hospital.

DR. REDMAN: Bruce Redman, medical oncologist, University of Michigan.

MS. CLIFFORD: Johanna Clifford, FDA, executive secretary to this meeting.

DR. PRZEPIORKA: Donna Przepiorka, hematology, University of Tennessee, Memphis.

DR. RODRIGUEZ: Maria Rodriguez, medical oncologist, M.D. Anderson Cancer Center.

DR. DOROSHOW: Jim Doroshow, Division of Cancer Treatment and Diagnosis, NCI.

DR. GEORGE: Stephen George, Duke University.

MS. HAYLOCK: Pamela Haylock, oncology nurse.

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

DR. RIDENHOUR: Kevin Ridenhour, medical reviewer, FDA.

DR. SRIDHARA: Rajeshwari Sridhara, statistical reviewer, FDA.

DR. DAGHER: Ramzi Dagher, medical team leader, FDA.

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

DR. PAZDUR: Richard Pazdur, Director, Oncology Drugs.

DR. TEMPLE: Bob Temple, Office Director.

DR. GRILLO-LOPEZ: Antonio Grillo-Lopez, Neoplastic and Autoimmune Diseases Research Institute.

DR. PRZEPIORKA: Thank you and welcome to all. I just again want to remind everyone in the room, as well as on the committee, that this is a committee that serves as consultants to the FDA. We are not employed by the FDA or the U.S. government. We do not make any decisions here; we simply provide advice to the FDA.

We will start the presentations this afternoon with Dr. Pablo Cagnoni, from Allos, to introduce the topic.

Sponsor Presentation

Introduction

DR. CAGNONI: Good afternoon, Dr. Przepiorka, ladies and gentlemen.

[Slide]

My name is Pablo Cagnoni and I am representing Allos Therapeutics today for this presentation to the Oncologic Drugs Advisory Committee for the new drug application for RSR13 as an adjunct to whole brain radiation therapy for patients with breast cancer and brain metastases.

[Slide]

Our agenda for today is shown here. After a brief introduction Dr. John Suh will provide an overview of brain metastasis. This will be followed by Dr. Brian Kavanaugh who will provide a review of the mechanism of action of RSR13, early preclinical and clinical data. I will then summarize the efficacy and safety data with our compound and we will have some concluding remarks by Dr. Paul Bunn.

[Slide]

We have a number of experts today available for the question and answer session: Dr. Paul Bunn, Director of the University of Colorado Cancer Center; Dr. Walter Curran, Group Chairman of the Radiation Therapy Oncology Group; Dr. Anthony Elias, Director of the Breast Cancer Program at the University of Colorado.

[Slide]

Dr. Henry Friedman, Director of the Brain Tumor Center at Duke University Medical Center; Dr. Marc Gastonguay, clinical pharmacologist who performed the clinical pharmacokinetic analysis and

population pharmacokinetic analysis for RSR13; Dr. Charles Scott, biostatistician, former statistician from RTOG who conducted the analysis of our RT-08 and served as a design analysis consultant for RT-09; Dr. Baldassarre Stea, Chairman, Radiation Oncology at the University of Arizona, who is a lead enroller in study RT-09.

[Slide]

In addition, we have a number of experts from Allos Therapeutics that will be available to answer questions as well.

[Slide]

We need to acknowledge today that brain metastases in patients with breast cancer represent an unmet medical need. This complication afflicts tens of thousands of patients a year in the U.S. alone. It carries a very high morbidity and nearly uniform mortality. This field has been characterized for the last 25 years by lack of progress in terms of improving the survival of these patients. The data that we will review for you today demonstrates that RSR13 improves the

survival of patients with breast cancer and brain metastases; increases the response rate in the brain in these patients; and has an excellent safety profile in this population.

[Slide]

Our proposed indication for RSR13 is to be administered as an adjunct to whole brain radiation therapy for the treatment of brain metastases originating from breast cancer. Our proposed dosage is RSR13 75-100 mg/kg/day IV over 30 minutes with supplemental oxygen immediately prior to each of 10 fractions of whole brain radiation therapy.

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At this point, I would like to introduce Dr. John Suh. Dr. Suh is Clinical Director of Radiation Oncology and Director of the Gamma Knife Radiosurgery Center from the Brain Tumor Institute and the Cleveland Clinic Foundation. Dr. Suh was the study chair for our pivotal trial RT-09 and he has extensive experience with use of RSR13 in the treatment of brain metastases.

Brain Metastases

DR. SUH: Good afternoon, ladies and gentlemen. It is a pleasure to be here today to talk about brain metastases. As a clinician who focuses his clinical and research efforts on brain tumor patients, I have the opportunity to evaluate and treat a number of these patients. For the past ten years I have been involved in a number of clinical trials related to these patients and hope that after today's discussion you will consider changing the treatment paradigm for patients with breast cancer who develop brain metastases.

[Slide]

In terms of the brain metastasis, its incidence is on the rise. Every year in the United States approximately 170,000 Americans are diagnosed with this condition. It is estimated that 20-40 percent of cancer patients will eventually develop brain metastases. The incidence is thought to be rising secondary to earlier diagnosis of the cancer; better systemic therapy for extracranial disease; and better neuroimaging techniques, the MRI scans.

[Slide]

In terms of breast cancer patients with brain metastases, up to 35,000 patients per year are diagnosed with this disease. It afflicts younger patients. The median age for our study was 53 years of age, and most of these patients are quite functional as well. Systemic agents have provided benefit for extracranial disease. Therefore, to control the brain becomes very important. Current treatment strategies have provide limited benefit and, as a result, more effective treatment options are needed.

[Slide]

This is an example of a an excellent response from radiation therapy. This is a picture of a CT scan of a patient with two very large brain tumors in the frontal area, and after radiation therapy you can see a dramatic response. Unfortunately, this is a very untypical response from radiation therapy and, as a result, we need better therapies for these patients.

[Slide]

In terms of the current treatment strategies for patients with brain metastases, there are a number of treatment strategies depending on the patient and their performance status. Steroids have been shown to increase survival by approximately one month. Anticonvulsant medication is used to prevent seizures. Surgical resection has been shown by several randomized studies to improve survival for patients with single metastases. Stereotactic radiosurgery has been shown by a recent trial to improve survival for patients with a single lesion. Chemotherapy has had limited use thus far. Whole brain radiation therapy has been the gold standard and has been used for over 50 years for treatment of brain metastases.

[Slide]

In terms of the results with whole brain radiation therapy, the mean survival is approximately 4.5 months. it improves and/or stabilizes neurologic function in the majority of these patients. The standard dosing scheme

established by the RTOG is 30 Gy in 10 fractions. There has been no benefit to altered fractionation schemes.

[Slide]

This slide summarizes the lack of progress over the past 20 years for patients with brain metastasis. These are series from the 1970s to the 1990s, looking at various fractionation schemes. If you look at the median survivals overall, they range from about 3-5 months. Therefore, better treatment is needed for these patients.

[Slide]

It is important when analyzing patients with brain metastasis to have common prognostic factors. RTOG performed a recursive partitioning analysis of 1200 patients enrolled in 3 consecutive clinical trials from 1979 to 1993. They came up with 3 classes of patients. The best class of patients is Class I patients, with a KPS of 70 or higher; primary controlled; age less than 65; and no extracranial metastasis, which comprised 20 percent of this database with median survival of

7.1 months.

For Class II patients, these are patients with a KPS of at least 70 and any of the following, controlled primary; extracranial metastases; age greater than or equal to 65. This comprises the majority of the patients in this database; 65 percent survival of only 4.2 months.

For the Class III patients, these are patients with a KPS less than 70; median survival of only 2.3 months, and resulting in poor survival for this group of patients. They are typically excluded from clinical trials.

[Slide]

If you focus on the results of whole brain radiation therapy for patients with breast cancer, these are some recent publications from the late '90s to 2000, looking at 100 patients. You can see here that their median survival has hovered between 4-6 months. The RTOG brain metastasis database that I alluded to, for 113 patients with brain metastases, the median survival was 5.4 months.

This is a retrospective series from the

Cleveland Clinic of 116 patients. When we looked at the one-year survival, it was only 17 percent and two-year survival was only 2 percent.

[Slide]

The recursive partitioning analysis developed at the RTOG was consistent with the control arm of the RT-009 study. As you can see here, for the Class I patients, 7.7 months versus 7.1 months, and for the Class II patients, 4.1 months versus 4.2 months, suggesting that this database is reliable for comparing results.

[Slide]

In conclusion, brain metastases from breast cancer are common. Current treatment strategies yield poor results. Treatment options are available for extracranial metastases. Therefore, it is paramount that we control the disease within the brain to improve survival for these patients, and there is a compelling need for more effective treatment options.

[Slide]

At this point, I would like to introduce

Dr. Brian Kavanaugh, who will talk about the science of RSR13.

The Science of RSR13

DR. KAVANAUGH: Thank you, John. It is an honor to be here today. I have been working with RSR13 for ten years. I participated in the preclinical evaluation. I served as the PI for the Phase 1 study in cancer patients and I have enrolled patients on both the Phase 2 and Phase 3 studies that you will be hearing about today.

[Slide]

In this section we will review several topics, first of all, a brief refresher on tumor hypoxia and its particular importance in radiotherapy. We will explain how and why RSR13 was designed. We will explain how RSR13 improves tumor oxygen delivery and, thus, radiosensitizes solid tumors. And, we will share some key observations when the agent was first taken into the clinic.

[Slide]

Oxygen has long been recognized to be the

purest and most efficient radiosensitizer. Ionizing radiation introduces free radicals which, in the presence of oxygen, are stabilized. When cancer cells are treated with radiotherapy in oxygenated conditions the effect of radiation is roughly tripled when compared with treatment with radiation in hypoxic settings. There are pockets of hypoxia or low pO-2 to varying extent in all solid tumors. The reason this exists is that supply simply doesn't keep up with demand in hyper-metabolic areas. It is possible to measure directly in the clinic the degree of tumor hypoxia present in certain solid tumors and in all cases where this has been performed there is a direct correlation between the extent of hypoxia and the outcome after radiotherapy. Specifically, the more hypoxic the tumor is the lower the chance of controlling with radiation.

I should just add one more point, that it is essential for the oxygen to be present at the moment of radiation. The radiation-induced free radicals that are generated in the absence of

oxygen have a half-life of 10 -5 or 10-9 seconds and with oxygen present this half-life is extended to the range of milliseconds. Nevertheless, it is important for oxygen to be present at the moment that radiation is given.

[Slide]

To consider hypoxia in breast cancer in particular, these data represent thousands of individual point measurements of pO-2 within tumors in a cohort of breast cancer patients. On the X axis is the tissue oxygen pressure and on the Y axis is the frequency with which a value and the range shown on the X axis was observed.

You can see that fully 15 percent of the measurements were less than 5 mmHg and this would be an extent of hypoxia expected to cause substantial radioresistance. Now, it is technically very challenging to obtain pO-2 measurements clinically in tumors, and particularly difficult in the brain. So, there are far fewer data particularly with brain metastasis but what is available would suggest that the rate of hypoxia is

probably even higher when tumors have spread to the brain.

[Slide]

In the early 1980s Professor Don Abraham and the Nobel Laureate Max Perutz set out on a mission to design agents which would have therapeutic benefit by modifying the properties of hemoglobin, and RSR13 is the product of their collaboration.

As you can see here, RSR13 binds within the central water cavity of hemoglobin and exerts an effect on hemoglobin through a process called allosteric modification. Under the influence of RSR13 hemoglobin is changed in its properties. Specifically, the binding affinity between hemoglobin and oxygen is reduced.

[Slide]

I will illustrate that for you in this graph. You will recall that under ordinary conditions, represented here by the black curve, there is an approximately sigmoidal relationship between pO-2 in the bloodstream and the percent of

saturation of all available hemoglobin binding sites. RSR13 has the property of shifting this curve right-ward. We can easily quantify this effect in terms of the p50. The p50 is defined as a pO-2 at which there is 50 percent saturation of all available hemoglobin sites. We have calculated in other studies that an increase in p50 of 10 mmHg is expected to have a major improvement on tumor oxygen delivery and, thus, radiosensitization.

But before we leave this slide, let me share one other particularly important point regarding the reason why supplemental oxygen is given to patients who receive RSR13. At sea level under ordinary conditions you will recall that the pO-2 of arterial blood is typically in the range of 90-100 mmHg. Under normal conditions there would be expected to be 96-98 percent or so saturation of hemoglobin binding sites. Adding additional oxygen in that setting is unlikely to yield any noticeable benefit because the blood is already carrying as much oxygen as possible into the peripheral circulation. Under the influence of RSR13, in

order to exploit the agent to its maximal effect, we want there to be as high as possible saturation of blood leaving the lungs and entering the peripheral circulation. That is why we give supplemental oxygen to achieve pO-2s in the range of 120 or more so that blood leaving the lungs is going to be at a very high level of oxygen saturation.

[Slide]

There have been numerous clinical studies to establish both the proof of principle and the establishment of the radiosensitizing effect of this agent and I will share with you a couple of examples.

In this situation, using a rodent mammary carcinoma, the experimental endpoint was percent of tumor oxygen pO-2 readings below 5 mmHg. You can see in the yellow bar that under controlled conditions this particular tumor is roughly 50 percent hypoxic. Oxygen has only a modest effect, and I should add that in animals the reason for a modest effect in oxygen in this kind of experiment

is because they are anesthetized and there is a certain amount of hyperventilation. It is not expected to have that much effect in humans. The addition of RSR13 has an even stronger effect than oxygen alone, and the combination of RSR13 and supplemental oxygen essentially abolishes all measurable tumor hypoxia. This effect on tumor oxygen levels translates directly into radiosensitizing properties.

[Slide]

Again using a rodent model in the lab, the experimental endpoint here is the clonogenic survival fraction after in vivo exposure. With RSR13 alone and oxygen, you can see that there is no appreciable effect on tumor cell surviving fraction because the agent itself is not directly cytotoxic. Radiation has, of course, an expected effect in terms of reducing tumor cell survival fraction, but the combination of RSR13 and oxygen will meaningfully sensitize cells to radiation and have a pronounced additional radiosensitizing effect.

This proof of principle and radiosensitizing effect has demonstrated in non-small cell lung cancers also and, in fact, for all solid tumors tested in the lab that RSR13 can exert a radiosensitizing effect.

[Slide]

The first instance in which this agent was taken into humans was in a study of healthy volunteers. The targeted pharmacodynamic endpoint was an increase of p50 of 10 mmHg which, as I have already mentioned, is expected to have a meaningful improvement in tumor oxygen delivery.

A Phase 1 study was conducted of 19 patients in which RSR13 was given in doses ranging from 10 up to 100 mg/kg using a single intravenous dose. The observation was an increase in p50 of 10 mmHg achieved consistently at a dose of 100 mg/kg.

[Slide]

A few observations about the pharmacokinetics of RSR13, its volume of distribution is a vascular compartment. Half the drug is gone within red blood cells and the other

half is in plasma, most of it bound to plasma proteins. The half-life in red blood cells is 4.5 hours. The drug is partially glucuronidated in the liver and then both the parent compound and the metabolites formed are excreted through the kidneys.

[Slide]

The pharmacokinetic and pharmacodynamic parameters analyzed in several studies have been combined and the results are shown here. In four separate studies involving both the healthy volunteers and a broad range of cancer patients, the pharmacokinetic parameter of mean red blood cell concentration was assayed and directly compared with the mean p50 increase or pharmacodynamic effect. The eight data points on this particular graph represent the averages of those two groups of patients either receiving 75 mg/kg or 100 mg/kg in the four individual studies.

What you notice is a linear correlation between these two parameters. On the X axis again is the mean red blood cell concentration. In order

to achieve our desired pharmacodynamic effect, an increase of 10 mmHg, we need to achieve in red blood cells a concentration on the order of 480 mcg/mL.

[Slide]

Let me just summarize that tumor hypoxia has long been recognized to be a major cause of radioresistance. RSR13 has the properties of reducing tumor hypoxia and increasing radiosensitivity. The pharmacodynamic effect of the agent is easily quantified by characterizing the increase in p50. There is a linear correlation between the drug concentration and the pharmacodynamic effect. And, RSR13, at a dose of 100 mg/kg, was selected for future study based on its ability to induce the desired p50 increase.

[Slide]

Now I will let Dr. Cagnoni present to you the clinical efficacy results.

Clinical Efficacy Results

DR. CAGNONI: Thank you, Dr. Kavanaugh.

[Slide]

Today's presentation is a culmination of almost ten years of clinical development of RSR13. This was initiated with filing IND 48-171 in 1995. This was followed by the human volunteer study that Dr. Kavanaugh described and, in turn, that was followed by Phase 1 studies in combination with radiation therapy. Our pivotal study in patients with brain metastases started enrollment in February of 2000, completed enrollment in July 2002 and the present NDA was submitted in December of 2002.

[Slide]

Before we describe the results of the Phase 2 and Phase 3 studies, it is important to understand how RSR13 is administered relative to radiation in both studies. On arrival to the clinic oxygen and pulse oximetry for monitoring are initiated. RSR13 is administered through a central venous access device over a 30-minute infusion in both studies. Both studies mandated that patients be radiated within 30 minutes of completing the RSR13 infusion. After radiation therapy was

administered patients were monitored as the oxygen was tapered, and they were released from the clinic when oxygen saturation at room was acceptable. The same process was repeated daily for 10 days.

[Slide]

Our Phase 2 study in patients with brain metastases is study number RT-08. It enrolled 69 patients. It was an open-label study and 21 of the patients in this study had breast cancer, 39 had non-small cell lung cancer and 9 patients had other tumor types. Patients were enrolled at 17 sites in the U.S. and Canada. The primary endpoint of the study was survival. To use as a comparison group we selected the RTOG brain metastasis database that Dr. Suh summarized for you earlier.

[Slide]

When we compared the results of the RT-08 Class II patients with the RTOG database Class II patients, we see the following results: In yellow are the RSR13 patients with a median survival of 6.4 months and in red is the median survival of 4.11 with the patients in the RTOG brain metastasis

database.

[Slide]

We then compared these two groups by tumor type within the Class II patients, and in breast cancer of the RTOG database there was a median survival of 5.4 months and in the RSR13-treated patients the median survival was 9.7 months. In the lung cancer population the survival was 3.9 and 6.4 months respectively.

[Slide]

As a result of this study a pivotal trial was initiated, study number RT-09. This was a Phase 3 randomized, open-label, comparative study of standard whole brain radiation therapy with supplemental oxygen, with or without RSR13, in patients with brain metastases. The study chairs were Dr. John Suh, from the Cleveland Clinic, and Dr. Edward Shaw from Lake Forest University.

[Slide]

The key eligibility criteria for RT-09 are summarized here. Patients had to have a KPS of at least 70. In other words, Class II patients were

excluded. The excluded histologies were small-cell lung cancer, non-Hodgkin's lymphoma and germ cell cancer. No prior therapy for brain metastases was allowed, with the exception of partial resection. In other words, patients had to have measurable disease after resection. All patients had to have adequate hematologic, renal, hepatic and pulmonary function, including resting and exercise oxygen saturation of at least 90 percent on room air.

[Slide]

This was a 1:1 randomization. It was an open-label study. All patients received standard whole brain radiation therapy, 3 Gy fractions for 10 days for a total of 30 Gy. Both arms received supplemental oxygen and patients were randomized to receive or not RSR13. At the time of randomization patients were stratified using RPA class and tumor type.

The primary endpoint of RT-09 was survival. The study had 85 percent power to detect a difference in all patients and 75 percent power to detect a difference in the lung/breast

co-primary population. These are the only two populations for which the alpha spending and the log-rank test was calculated.

[Slide]

RT-09 was amended three times, generating four protocol versions. The key amendment in the study is amendment two. Amendment two took place between versions two and three. At the time of the amendment 222 patients had been enrolled in the study. The key components of the amendment were to expand the sample size up to 538 patients; to define the lung/breast co-primary population as a co-primary population for analysis; and it expanded the dosing adjustment guideline of RSR13 for patients receiving antihypertensive medications, including also weight and gender. This amendment was discussed with the FDA at the time and concurrence was reached on the approvability of this co-primary population.

[Slide]

The dosing adjustment guideline is summarized here. Using the weight cutoff of 70 kg

for women and 95 kg for men, the study divided patients in high weight/low weight categories. According to the guideline, high weight patients were to receive an initial dose of RSR13 of 75 mg/kg and low weight patients were to receive a dose of RSR13 of 100 mg/kg.

[Slide]

For the primary endpoint of survival we assumed that 20 percent of the patients would be RPA Class I. We expected a median survival time in the control arm of 4.57 months and a 35 percent improvement over this would have been a median survival of 6.17 months in the RSR13 arm. The analysis of the study was determined by a number of events, with a minimum follow-up of 6 months and minimum number of events or 402 patients had to occur in all patients and the minimum number of events of 308 had to occur in the lung cancer/breast cancer co-primary population.

[Slide]

The analysis of survival following the statistical analysis plan, which was completed

prior to the completion of enrollment, defined that the primary method for survival analysis would be an unadjusted log-rank. The primary population for analysis of survival would be comprised of the eligible patients. For the co-primary population of lung and breast cancer patients a modified Bonferroni adjustment was described Both the protocol and the SAP specified the Cox multiple regression analysis would be conducted.

[Slide]

The benefits of this type of analysis are summarized here. Adjusted analyses, such as Cox or stratified log-rank, provide the most accurate treatment estimate in heterogeneous populations. As we will see in the presentation, the population of patients in RT-09 was clearly very heterogeneous. It is important to remember that omitting strong covariates can reduce the power of the study to detect treatment effects.

[Slide]

To this effect, prespecification of the Cox model was performed in the protocol and

expanded in the statistical analysis plan. Seven covariates, in yellow, were specified in the protocol and were derived from the literature. In addition to this, ten more covariates were added in the statistical analysis plan. The top six in yellow are derived from the literature as well. The bottom four were specific to the study to take into account the mechanism of action of RSR13 and, i the case of the weight category to take into account the dosing adjustment guideline.

[Slide]

RT-09 had five secondary endpoints. The objective of RSR13 is to improve local therapy in the brain, therefore, the most important secondary endpoint in the study is response rate in the brain. Other secondary endpoints were time to radiographic tumor progression in the brain and to clinical tumor progression in the brain, cause of death and quality of life.

[Slide]

For the radiologic evaluation the following was mandated by the protocol, all

patients had to have a CAT scan or MRI of the brain at baseline. The follow-up had to be done with the same test a month after whole brain radiation day 10, 3 months after day 10 and every 3 months thereafter until progression. All CAT scans and MRIs were centrally and independently reviewed by a team of radiologists at the Neuroimaging Core Laboratory at the Cleveland Clinic. The reviewers were blinded to study arm and treatment outcome.

[Slide]

Let me now review the results of RT-09, 538 patients were randomized in 82 sites in the U.S., Europe, Israel, Australia and Canada; 267 patients were randomized to the control arm and 271 to the RSR13 arm.

[Slide]

The two arms were well balanced for gender, RPA class, age and tumor type.

[Slide]

RSR13 did not impair the administration of standard whole brain radiation therapy in this population and 95 percent of the patients in the

control arm and 94 percent of the patients in the RSR13 arm received all 10 doses of whole brain radiation, with the mean number of doses in each arm of 9.9 and 9.8. Eighty percent of the patients in the RSR13 arm received at least 7 doses of RSR13, with a mean number of doses of 8.4.

[Slide]

According to the statistical analysis plan and following ICH guidelines, the primary population for survival analysis was to be comprised of the eligible patients. Accordingly, a blinded neuroradiology review was conducted to determine eligibility and 22 patients were identified in this review. In addition, one patient with small-cell lung cancer was also excluded from this analysis. Overall, this represents a rate of ineligibility of only 4.3 percent.

[Slide]

The Kaplan-Meier curve shows the overall survival for all eligible patients in this study. In yellow we see the RSR13-treated patients and in

red the control arm. The median survival in the control was 4.4 months and in the RSR13 arm was 5.4 months. This represents a hazard ratio of 0.7 by unadjusted log-rank, and when these results were updated with an additional follow-up of a year the hazard ratio is consistent with the initial analysis.

[Slide]

In the population of eligible lung cancer/breast cancer patients, which is the co-primary population for analysis, the median survival in the control arm was 4.4 months with an improvement of 38 percent, and a median survival of 6 months in the RSR13-treated patients. By log-rank this is a hazard ratio of 0.81 with a p value of 0.07. When these results were updated with an additional follow-up of a year the hazard ratio is consistent with a p value of 0.05. In yellow we see the RSR13-treated patients and in red the control arm, with an early separation of the curves and separation through the median.

[Slide]

The protocol and the SAP specified the conduction of a Cox multiple regression analysis that had 17 prespecified covariates. Of the 17 covariates, 7 were found to be predictive of outcome in RT-09, and they are listed here. Those 7 covariates are KPS, extent of extracranial disease, prior brain resection, primary site, age, gender and baseline hemoglobin. When all 17 covariates are incorporated in the model as described in the SAP, the hazard ratio shows a 22 percent reduction in the risk of death in favor or the RSR13-treated patients, with a p value of 0.01.

[Slide]

In the eligible lung cancer/breast cancer co-primary population the same analysis was conducted following the SAP. The covariates that were predictive of outcome in this population were KPS, extent of extracranial disease, prior resection, age and gender. When all 17 covariates are incorporated in the analysis the hazard ratio shows a 24 percent reduction in the risk of death, with a p value of 0.017.

[Slide]

In addition, to confirm the results of the Cox, we ran a stratified log-rank survival analysis, including in this analysis the three strongest covariates detected in the study. Those are KPS, prior resection and extent of extracranial disease. When this analysis was done in all patients a hazard ratio of 0.81 is found including all three covariates, with a p value of 0.037. In the non-small cell lung cancer/breast cancer population the incorporation of just one covariate in the stratified log-rank shows a hazard ratio of 0.78, with a p value of 0.029.

[Slide]

Let me emphasize the results in the eligible non-small cell lung cancer/breast cancer co-primary population. In this population we saw by unadjusted log-rank a hazard ratio of 0.81 with the corresponding p value of 0.07. The Cox showed a 24 percent reduction in the risk of death with a p value of 0.017. At this point the logical thing to do was to look at the outcome of these two very

distinctive tumor types separately.

That is, indeed what we did. In the eligible non-small cell lung cancer patients the log-rank showed a hazard ratio of 0.97 with the Cox showing a hazard ratio of 0.90. In contrast, a large treatment effect was observed in the eligible breast cancer patients with a hazard ratio of 0.51 by log-rank and a hazard ratio very consistent with log-rank of 0.51 by Cox, both very consistent with each other.

Let me emphasize that the eligible patients with breast cancer do not represent an arbitrary subset. They are the result of a logical analysis of the result that we encountered in a co-primary population of lung cancer, breast cancer patients.

[Slide]

This slide shows the overall Kaplan-Meier survival curve for the eligible breast cancer patients. The median survival in the control arm was 4.5 months and in the RSR13 the survival was doubled, to 9 months. By log-rank, as we recently

reviewed, this shows a hazard ratio of 0.51 and by Cox the same hazard ratio with all 17 covariates included in the analysis. In yellow we see the RSR13-treated patients and in red the control arm. There is an early separation of the curves; clear separation of the curves through the median and a much larger number of long-term survivors in the RSR13 arm.

[Slide]

In fact, we looked at the time of the original analysis of the study for patients with a survival of at least 12 months from randomization and this is what we encountered. Five patients in the control arm had survived these 12 months. Of these, 3 had died at the time of the analysis. In contrast, 11 patients in the RSR13 arm had survived at least 12 months from randomization and of these 9 were still alive at the time of the analysis. I would like to emphasize that all the survivors in the RSR13 arm had from adequate to excellent performance status.

[Slide]

As I mentioned earlier, RT-09 was updated with an additional follow-up of a year. Therefore, we looked at all the breast cancer patients, in this case with a minimum potential follow-up of 18 months by arm, and the results are shown here. Each number represents an individual patient. Those in white are patients that died at the time of the analysis; those in yellow are patients that are still alive. There were 7 patients in the control arm that survived at least 18 months. Two of these had died at the time of the analysis. In contrast, there were 15 patients in the RSR13 arm that were alive a minimum of 18 months from randomization. Of those, all those in yellow were still alive with survivals ranging from 18.5 months to almost 40 months, and there were 7 patients in this column and 2 in this column with survivals in excess of 2 years.

[Slide]

I will now focus on the secondary endpoints. Let me first point out that by statistical analysis planned the secondary

endpoints were to be analyzed in all randomized patients.

[Slide]

Response rate in the brain defined per protocol which is, in our view, the most important secondary endpoint of the study considering that RSR13 focuses on improving local therapy in the brain, is shown here. There was an 8 percent difference in the response rate for all patients in favor of RSR13. There was a 12 percent, and statistically significant improvement in response rate in the lung/breast co-primary population. There was a 23 percent, statistically significant improvement in response rate in the breast cancer patients in the study. Let me emphasize that all those responses were determined by independent radiologists.

[Slide]

RT-09 did not mandate confirmation of response. Advice given at the time the protocol was signed considered this impractical in a population of brain metastases patients.

Therefore, we conducted an analysis that is not planned in the protocol in patients that had a follow-up CAT scan or MRI and minimum of 4 weeks from the initial determination of response. We defined that as confirmed response rate and the results are shown here. There was an 8 percent difference in the rate of confirmed responses in favor of the RSR13-treated arm. There was a 9 percent advantage in the rate of confirmed responses in the RSR13 arm in the lung/breast co-primary population, and there was a 22 percent difference in the confirmed response rate between the RSR13 and the control breast cancer patients.

[Slide]

In addition, we tried to explore the impact of response and survival. We looked at responders and non-responders at 3 months and what their subsequent survival was, and the results are shown here. For patients that had a PR or CR on the 3-month scan, thus survival for those patients, was an additional 7.8 months. For non-responders, progressive disease and stable disease at the

3-month scan, those patients had an additional median survival of 5.2 months.

[Slide]

We then compared the response rate at 3 months between the arms and those results are shown here. In all patients there was a 7 percent difference in favor of the RSR13-treated patients. In the lung/breast co-primary population there was a 10 percent difference in favor of the RSR13-treated patients. In the breast cancer patients there was a 13 percent difference in favor of the RSR13-treated patients.

[Slide]

Additional secondary endpoints for all patients are shown here. There was no difference in quality of life by KPS or Spitzer questionnaire, cause of death, time to clinical or radiologic progression between the two arms.

[Slide]

In the breast cancer patients there was a significantly higher percentage of patients with stable or improved KPS at 3 months or stable or

improved Spitzer questionnaire at 3 months in the RSR13 arm. There was no difference in cause of death, time to clinical or radiologic progression between the arms.

[Slide]

Clearly, we observed in this study a different treatment effect of RSR13 in breast cancer patients and lung cancer patients. This difference could be due to many factors, some of which are summarized here and they include biological differences between these two very different tumor types; different growth rates; and differences in efficacy of they for extracranial disease in these two tumor types. One thing we observed is that there are body weight differences in the distribution of high weight/low weight patients between the arms and this may have influenced the pharmacokinetics of RSR13, specifically maximal concentration in the red cells.

[Slide]

As we see here, when we classify patients

based on body weight, the RSR13-treated patients by primary site and gender, we can see that the majority of lung cancer patients are in the low weight category independent of gender, and less than half of the patients with breast cancer are in the low weight category.

[Slide]

We then studied the pharmacokinetics of RBC by body weight, tumor type and dose, specifically RSR13 RBC concentration which is the key parameter because this is the site of action of RSR13, and we observed that patients in the lung cancer low weight category that received 75 mg/kg has a lower median concentration in the red cell than any of the other groups studied. If you remember from Dr. Kavanaugh's presentation, this median concentration in the red cell will be below what would be expected to generate the desired pharmacodynamic effect through RSR13.

[Slide]

Let me summarize the efficacy data before we review the safety results. We saw significant

reduction in the risk of death in the prespecified co-primary populations by Cox multiple regression. We saw an improvement in response rate and a 38 percent improvement in the median survival time in the eligible lung cancer/breast cancer co-primary population. In the eligible breast cancer patients we saw an improvement in response rate; a clinically meaningful improvement in survival with a doubling of the median survival; and a higher number of long-term survivors in the RSR13 arm.

[Slide]

Let me review the safety profile of RSR13, focusing on the result of RT-09.

[Slide]

First let me say that more than 500 patients to date have received RSR13 as an adjunct to radiation therapy in a series of Phase 1, 2 and 3 studies that are listed in this slide. These patients have received anywhere from 2-32 doses of RSR13 and a dose of RSR13 has been up to 100 mg/kg.

[Slide]

One important point is the issue of

hypoxemia which is the most characteristic adverse event related to the use of RSR13. If you recall, the CTC grading scale defines supplemental oxygen as a grade 3 toxicity. By protocol, all these patients were on supplemental oxygen, therefore, we had to design a hypoxemia grading scale that was adequate for these studies, and that is shown here.

This scale uses the length of oxygen supplementation, the flow of oxygen required, and the presence or absence of symptoms or requirement for hospitalization to grade high hypoxemia. It is important to point out that grade 4 hypoxemia in this grading scale is the use of CPAP or mechanism ventilation and that is identical to the CTC scale. Of note, there were no grade 4 hypoxemic adverse events in RT-09.

[Slide]

This slide shows treatment-emergent adverse events that occurred in at least 20 percent of the patients in RT-09, all patients by arm and the breast cancer patients by arm. The ones highlighted in yellow are those that were

significantly higher in the RSR13-treated patients and they include headache, nausea, hypoxemia, vomiting and infusion symptoms. However, the majority of adverse events were grade 1 and 2.

[Slide]

This table lists the grade 3 adverse events that occurred in more than 5 percent of the patients, once again by arm and in the breast cancer patients by arm. The most frequent grade 3 adverse event in all patients receiving RSR13 was hypoxemia, with 11 percent. Let me emphasize that hypoxemia does not mean hypoxia in this setting. This is either low saturation, longer requirement for oxygen or need for more than 4 L of oxygen to maintain saturation, or one of the other factors defined in the scale. This is not tissue hypoxia. The most common grade 3 adverse event in the breast cancer patients were nausea and vomiting, at 8 percent each.

[Slide]

Grade 4 adverse events were even less common. These are grade 4 AEs that occurred in

more than 2 patients by arm and in the breast cancer patients.

[Slide]

Further emphasizing the role of RSR13 adverse events, we reviewed the drug-related grade 4 adverse events in RT-09 by primary tumor type. There were no grade 4 drug-related adverse events in the breast cancer patients treated in RT-09.

[Slide]

Regarding hypoxemia, only 11 percent of the patients treated in RT-09 had a grade 3 hypoxemia adverse event. Of these, 73 percent were asymptomatic. Hypoxemia was self-limited and easily managed with supplemental oxygen in all patients.

[Slide]

To summarize the safety, we have data from 535 patients that indicate that RSR13 is safe in cancer patients receiving radiation therapy. We saw a very low incidence of grade 3-4 adverse events in a heavily pre-treated population of cancer patients in RT-09. All Adverse events in

RT-09 resolved within the 1-month follow-up period and were easily managed with supportive care. Hypoxemia associated with RSR13 is self-limited; requires only supplemental oxygen and is asymptomatic in the majority of the patients.

[Slide]

At this point, I would like to turn to the microphone over to Dr. Paul Bunn. Dr. Bunn is Professor and Director of the University of Colorado Comprehensive Cancer Center and he will provide some concluding remarks. Dr. Bunn?

Conclusions

DR. BUNN: Thank you, Pablo. ODAC members, FDA staff and guests, as a clinician who sees many patients with brain metastases, I am pleased to share my views on these studies and their results.

[Slide]

Clearly, brain metastases are associated with disabling symptoms and short survival in these patients. This is an unmet need. Having enrolled 538 patients, this study represents the largest

randomized, controlled study of its kind.

[Slide]

As shown in this slide, the survival in the non-small cell lung cancer and breast cancer prespecified co-primary population was superior in the RSR13-treated patients, with a median of 6 months in the treated group compared to 4.4 months in the control group. This survival represents a 19 percent reduction in the hazard ratio of death by log-rank and 23 percent by Cox multiple regression analysis, with corresponding p values of p equals 0.07 and 0.02 respectively.

I would note as a clinician that the log-rank p value in the final analysis with 12 months of additional follow-up is 0.05. In my opinion, not the statistician's, this represents the most important data as it has the most events. I would also note that the magnitude of the hazard rate reductions are comparable to those induced by approved cancer therapies, including cisplatin-based chemotherapy for non-small cell lung cancer. Thus, I consider this study to be

positive in this prespecified co-primary group of patients.

When the data were analyzed in the non-small cell lung cancer and breast cancer populations separately it became evident that the breast cancer patients had the greatest survival benefit, with a median survival of 9 months in RSR13-treated patients compared to 4.5 months in control patients. Breast cancer patients also benefited the most in the secondary analyses, with statistically significant increases in objective response rate, performance status, Spitzer questionnaire and fraction of patients alive at 12, 18 and 24 months. Obviously, breast cancer alone subset was not prespecified other than by stratification but garnered the most benefit.

With a positive survival benefit for the lung/breast cancer co-primary population, but most of the advantage in breast cancer patients, would it be best to approve RSR for both types of patients or for breast cancer patients alone? This is why we have ODAC and this is your decision.

Personally, I would vote for approval of the prespecified lung/breast cancer patient co-primary population.

However, given the fact that the results in the prespecified population were largely driven by breast cancer patients, I would feel comfortable voting for approval in breast cancer patients alone. I say this because of the huge efficacy benefit in breast cancer patients produced by RSR13 combined with an acceptable safety profile in a heavily pre-treated population.

At this time I will turn the podium to Dr. Cagnoni for questions.

DR. PRZEPIORKA: We will hold the questions until after the FDA presentation. Dr. Ridenhour?

FDA Presentation

Clinical Review

DR. RIDENHOUR: Good afternoon.

[Slide]

My name is Kevin Ridenhour and I will present to you the results of the clinical review

for this NDA.

[Slide]

All of these individuals assisted with the review process. The presenters for the FDA are highlight. Following my report on the clinical portion of this NDA, Dr. Sridhara will discuss the statistical issues.

[Slide]

I will briefly cover the regulatory background of RSR13 and describe the two trials submitted to support this NDA. I will then discuss the findings from study RT-008. The remainder of the discussion will focus on the RT-009 study.

[Slide]

The applicant's proposed indication for RSR13 is as adjunctive therapy to whole brain radiation for the treatment of brain metastases originating from breast cancer.

[Slide]

In June, 1995 the IND for RSR13 was first submitted. In June, 2003 we discussed with the applicant our concerns regarding the lack of a

survival benefit in RT-009 and our concerns with their subgroup analysis. In July, 2003 the pharmacology data was submitted as the first component of the NDA. In December, 2003 the clinical and statistical components were received finalizing the NDA submission.

[Slide]

The two clinical trials submitted to support this NDA are RT-009 and RT-008. RT-009 was a randomized, open-label study of standard whole brain radiation therapy and oxygen, with or without RSR13, in patients with brain metastases. There were 267 patients on the control arm and 271 patients on the RSR13 arm.

RT-008 was a single-arm study of RSR13 administered to patients receiving standard whole brain radiation therapy with oxygen for brain metastases. There were 69 patients in this study.

[Slide]

In RT-009 patients on the RSR13 arm received 100 or 75 mg/kg through central intravenous infusion over 30 minutes daily within

30 minutes of whole brain radiation therapy. Whole brain radiation therapy was given as 30 Gy in 10 fractions.

Patients on the control arm received whole brain radiation therapy given as 30 Gy in 10 fractions and at least 4 L/minute of supplemental oxygen was given to both arms 35 minutes prior to, during and for at least 15 minutes after the completion of whole brain radiation therapy.

[Slide]

The primary endpoint in RT-009 was survival in the overall population as described in the original protocol and subsequent versions. With the second protocol amendment the applicant provided the description for an analysis to be done in the non-small cell lung/breast co-population. Dr. Sridhara will also discuss these analyses further in her presentation. Secondary endpoints included time to radiographic and clinical progression in the brain, response rate in the brain, cause of death and quality of life.

[Slide]

The major eligibility criteria were a Karnofsky Performance Status greater than or equal to 70, radiographic studies consistent with brain metastases, resting and exercise SpO-2 greater than 90 percent on room air. Concurrent steroid therapy was allowed, and the presence of a cytologically confirmed primary malignancy. Patients with small cell carcinoma, germ cell tumors and lymphomas were excluded. In addition, patients with leptomeningeal spread were also excluded.

[Slide]

This slide illustrates the even distribution of tumor histology across both treatment arms. Non-small cell lung cancer was the most predominant type, followed by breast and other subgroup, mostly melanoma, colorectal and renal cell carcinoma.

[Slide]

In the overall population the distribution of post-randomization systemic treatment types appear even between both study arms.

[Slide]

But in the breast subgroup subsequent exposure to radiation therapy, chemotherapy and hormonal therapy appeared slightly more frequent on the RSR13 arm.

[Slide]

The number of brain lesions appeared to be fairly well distributed in the overall population between the control arm and the RSR13 arm.

[Slide]

However, within the breast cancer subgroup a higher proportion of patients with 3 or more brain lesions was noted in the control arm. The distribution of patients with only 1 brain lesion was greater on the RSR13 arm. This suggests the presence of a greater tumor burden in breast cancer patients on the control arm which may have influenced outcome.

[Slide]

I will now summarize the efficacy results for RT-009. There was no survival advantage demonstrated in the overall population or in the non-small cell lung/breast co-population. These

were the two prespecified populations for analysis defined in the protocol. After analysis of their data, the applicant is claiming a survival advantage in a non-prespecified breast cancer subgroup which we consider exploratory at this time. Again, Dr. Sridhara will also discuss this further during her presentation.

[Slide]

As previously discussed, one of the secondary endpoints was response rate in the brain. In response to a query from the FDA during the review process, the applicant stated that confirmation of response was not required for RT-009. However, the applicant provided estimates of confirmed responses and this was done by comparing the response of the first scan taken after the dose response to the best response. If the response was the same as best response, the response was considered confirmed. This is demonstrated under the confirmed column on this slide. Whether you look at total versus confirmed responses between treatment groups, there is a

trend in response rate that favors the RSR13 arm but it is not statistically significant. The confidence intervals do overlap.

[Slide]

This slide illustrates distribution of neurologic and non-neurologic causes of death. These findings show that the majority of patients with brain metastases died of non-neurologic causes, causes that were not influenced by RSR13. The results are a large number of indistinguishable causes of death.

[Slide]

As expected, most patients on both treatment arms received steroids. The distribution of steroid use was comparable between both treatment arms.

[Slide]

In addition to the fact that most patients that did not die of neurologic causes, we have the following concerns regarding the relevance of the response assessment.

Given that there is no apparent advantage in

response rate in the brain with RSR13, whole brain radiation and oxygen versus whole brain radiation and oxygen, there does not appear to be a contribution of RSR13 to tumor response. More than 90 percent of patients in both arms received steroids, and response duration cannot be assessed since confirmatory imaging studies were not required. Also, the designation of complete response and partial response was given irrespective of the appearance of a new brain lesion.

[Slide]

As for the other secondary endpoints, the applicant found no statistically significant difference between the control arm and RSR13 arm in time to radiographic tumor progression introduction he brain, time to clinical tumor progression in the brain and quality of life.

[Slide]

RT-008 was a single-arm study with 69 patients given RSR13 and whole brain radiation therapy with oxygen. This included mostly patients

with lung cancer and breast cancer. The median survival was reported as 6.4 months but in a single-arm study it is difficult to interpret time to event points such as survival. Response rate in the brain was 29 percent. However, in a setting where patients received RSR13, oxygen and radiation the relevance of this response rate is difficult to interpret.

[Slide]

Moving on to safety in RT-009, RSR13 exposure was similar between the overall population and non-small cell lung/breast co-population. Radiation exposure was also similar between the overall population and non-small cell lung/breast co-population. The FDA was able to reproduce the applicant's analyses for RSR13 and radiation exposure.

[Slide]

As for oxygen exposure, patients on the RSR13 arm appeared to have received a longer duration of oxygen therapy than patients on the control arm. We should note again that oxygen is

hypothesized to be a modifier of the biologic effect of ionizing radiation and, as noted in the slide for oxygen exposure, some of the extreme values observed for the duration of oxygen delivered beyond 24 hours could be related to hypoxia exacerbated by RSR13, requiring prolonged oxygen delivery.

[Slide]

The treatment-emergent adverse events shown on this slide occurred with more frequency on the RSR13 arm. Of specific interest are hypoxemia, 41 percent RSR versus 4 percent control; hypotension, 13 percent RSR versus 1 percent control; and vomiting, 38 percent RSR versus 17 percent control.

[Slide]

This slide shows the most common grade 3 and 4 adverse events. Again, hypoxemia was more common on the RSR13 arm. There are also more cases of acute renal failure seen on the RSR13 arm.

[Slide]

In conclusion, there was no survival

advantage demonstrated for the RSR13 arm versus the control arm in RT-009. There was no advantage demonstrated for RSR13 versus control in secondary endpoints. The most common adverse events included hypoxemia, hypotension, nausea, vomiting and headache. Severe adverse events also included acute renal failure.

The exploratory analysis demonstrating a survival advantage in the breast cancer subgroup, consisting of 60 patients on the RSR13 arm and 55 patients on the control arm, is being further evaluated by the applicant in a randomized study.

[Slide]

Now Dr. Sridhara will discuss the statistical issues of this NDA. Thank you.

Statistical Review

DR. SRIDHARA: Thank you, Dr. Ridenhour. Good afternoon. I am Rajeshwari Sridhara, statistical reviewer of this application.

[Slide]

In this presentation I will be focusing only on the efficacy results of the confirmatory

registration study, RT-009. There are three major areas of concern in this application. They are overall finding, subgroup findings and multiplicity issues. I will present the concerns in each of these areas in the following slides.

[Slide]

First with respect to overall finding, evidence of efficacy has not been established. Multiple analyses have been conducted and there appears to be a lack of internal consistency in the results.

[Slide]

Regarding the evidence of efficacy as presented by the applicant, the median survival was 4.5 months and 5.3 months respectively in the control whole brain radiation arm and the treatment arm with RSR13 followed by radiation. Of note, the study RT-009 was designed with an estimated median survival of 4.5 7 months in the control arm. The study was adequately powered to detect a difference of 1.6 months in median survival in the overall study population. As presented here, there was no

statistically significant difference between the two treatment arms.

[Slide]

The two sets of results presented in the previous slide correspond to the first one which refers to the data submitted at the time of application to the agency, which had a data cutoff date of January, 2003. Subsequently, the applicant submitted updated survival data in March of 2004 which included updates up to January, 2004. Also, it should be noted that the p values presented here are not adjusted for multiple looks of the data and these p values, as such, should not be compared to 0.05.

[Slide]

The applicant has conducted numerous adjusted analyses, adjusting for many covariates using Cox regression models. These adjusted analyses can only be considered as supportive when the overall unadjusted finding is positive. As stated in the ICH-E9 guidelines, in most cases subgroup analyses are exploratory and should be

clearly identified as such. They should explore the uniformity of any treatment effects found overall.

[Slide]

The applicant had clearly stated that the primary analysis would be based on unadjusted log-rank test and, in fact, had identified both in the protocol and subsequent statistical analysis plan that the adjusted analyses would be considered only as exploratory. The quote from the applicant's statistical plan reads as follows, "while designated prospectively, supporting analyses should be considered exploratory in nature, and inferences made based on p values should be done so with caution. Primary reasons for exploratory analyses are for estimation rather than hypothesis testing."

[Slide]

The applicant had stated in the original protocol and its amendments under the section "survival" that, "RPA class of primary cancer and other important covariates, such as primary tumor

control, age, presence of extracranial metastases, baseline KPS and number of metastatic lesions will be included in a multivariate Cox model, along with the treatment to test the relative importance of these factors for survival."

[Slide]

These covariates are listed as protocol covariates in this table. Subsequently, the applicant included the 18 covariates listed in this table under SAP covariates in their final statistical analysis plan under the section of covariates and significance, with a comment that these are exploratory in nature and the primary reason for such analyses were for estimation and not hypothesis testing.

[Slide]

Here I will present results of one such exploratory model. In this exploratory model I have included the protocol-specified exploratory analysis with the evaluating covariates, RPA Class I versus II; site of primary breast and non-small lung cancer; primary control, yes/no; age group

less than 65 versus greater than or equal to 65; presence of extracranial metastases, yes versus no; KPS group more than 90 versus less than 90; and the number of brain lesions, single versus multiple.

It should be recognized that in determining the RPA class for a given patient KPS, age, whether or not primary was controlled and extracranial metastases were present or not were considered and these factors are likely to be correlated.

[Slide]

This table lists the results of analysis of data submitted at the time of the application and analysis of updated survival data. Within each of these data time points two sets of data have been analyzed. One data set consists of all patients as randomized and the second data set consists of only eligible patients.

The applicant, in their statistical plan which was finalized after the completion of enrollment, had stated that these adjusted analyses would be conducted in eligible patients. Hence,

analyses in both data sets are presented here. None of the analyses presented here demonstrated a statistically significant treatment effect, as seen in this table.

The applicant has conducted Cox regression analyses including 17 of the 18 covariates that were added in the final statistical analysis plan. The applicant has submitted 48 Cox regression models with the same 17 covariates, but varying some covariates between a continuous variable and a dichotomous variable. For example, two models are considered, one with age as a continuous variable and another with age as two groups, less than 65 years versus more than 65 years. None of these models were adjusted for multiple analyses.

[Slide]

In summary regarding the overall finding, the single, randomized RT-009 study conducted in patients with brain metastases does not demonstrate substantial evidence of benefit with respect to survival in the overall randomized study population.

[Slide]

The second area of concern is subgroup findings. I will be presenting results from two subgroups, namely, non-small lung cancer/breast primary subgroup which was added on as a co-primary hypothesis during the course of the study, and the second subgroup of patients with breast cancer primary, which was a post hoc data-dependent exploratory subgroup analysis.

The reason given by the applicant to have a co-primary hypothesis in the subgroup of non-small cell lung cancer/breast primary patients was that this subgroup was a large homogenous subgroup. Also, with the addition of this co-primary, the protocol was amended so that the type-1 error rate was adjusted using a modified Bonferroni procedure in order to maintain an overall type-1 error rate of 0.05.

[Slide]

The results of comparison of survival distributions in the subgroup of lung/breast primary patients are presented in this slide.

Again, two sets of analyses were conducted with the data submitted at the time of the application with the updated data. In both analyses the median estimated survival was 4.5 months in the control arm and 5.9 months in the RSR13 arm. There was no statistically significant difference between the control and the RSR13 in both analyses.

The applicant submitted earlier data on eligible patients only. The protocol specified that the primary analysis in the overall population, as well as in the lung/breast primary subgroup would be conducted in all patients but the Cox analysis would be done in eligible patients.

[Slide]

In summary, the single, RT-009 study conducted in patients with brain metastases does not demonstrate substantial evidence of benefit with respect to survival in the subgroup of patients with lung or breast primary cancer. Once gain, the p values listed here should not be compared to 0.05.

[Slide]

The findings of the non-prespecified subgroup with primary breast cancer has three major problems, namely, absence of overall survival benefit; a very small subgroup; and apparent imbalances. I will go over each of these issues.

[Slide]

In the absence of overall survival benefit, any subgroup advantage is questionable. The ICH-E3 guidelines clearly state that these analyses are not intended to salvage an otherwise non-supportive study but may suggest hypotheses worth examining in other studies.

[Slide]

The second issue of concern is that the breast primary subgroup is a very small group with a total of 115 patients representing only 21 percent of the study population, with 55 patients in the control arm and 60 patients in the RSR13 arm. Of these patients, 6 in the control arm and 2 in the RSR13 arm were ineligible according to the protocol entry criteria. There was a total of 7 patients who were misclassified at randomized, 6

patients who died in less than 1 month after randomization, and there were 6 patients in the RSR13 arm who received up to 2 doses only of RSR13. These patients continued further to receive radiation as in the control arm.

[Slide]

Furthermore, some imbalances were observed between the two treatment arms in some baseline factors and post-therapy factors, as presented by Dr. Ridenhour. Of those imbalances in a few important factors are presented here. Although none of these factors were individually statistically significant, it is not plausible to determine the collective influence of these imbalances to the subgroup findings.

[Slide]

Although we considered this as an exploratory analysis only, this slide presents the breast subgroup finding. As presented by the applicant with data as of the NDA submission, the p value in this small subgroup of breast primary patients was 0.006. However, with the updated

survival data submitted by the applicant in March of this year, the p value has diminished to 0.02. Of course, we do have a problem in interpreting these p values.

[Slide]

In summary regarding the subgroup of patients with primary breast cancer, some imbalances were observed and a true finding cannot be isolated. There appears to be no robustness in the subgroup finding. The p values presented in all these analyses are not adjusted for multiplicity and, at best, given the lack of an overall finding, this subgroup finding is exploratory and hypothesis generating.

[Slide]

The third major area of concern in this application is multiplicity. There are three types of multiplicity concerns. First, multiple hypotheses were tested. The type-1 error rate was only allocated for two hypotheses, one in the overall population and the other in the lung/breast subgroup. However, several hypotheses were tested.

Also, multiple analyses of the same hypothesis were conducted at different times and different analyses. Unadjusted and adjusted analyses were conducted. Furthermore, multiple subgroups were also examined. None of these analyses were adjusted for multiplicity.

[Slide]

In this slide I would like to present some important points to be considered when evaluating results from a single study. it is known that inherent variability may produce a positive trial by chance alone. That is, a p or 0.05 implies that 1/40 studies of ineffective drugs will be positive.

The FDA guidance to industry also states that it is critical that the possibility of an incorrect outcome be considered and that all the available data be examined for their potential to either support or undercut reliance on a single multicenter trial. Statistical persuasiveness can only be verified by replication, especially when the results under consideration are from a small subgroup of patients.

[Slide]

Finally, here is a review of results presented. The applicant has submitted results from a randomized, controlled, open-label multicenter single trial. The analyses of these results do not demonstrate efficacy based on the primary endpoint of overall survival both in the overall population and in the subgroup of non-small cell lung or breast primary patients. Also, no significant benefit was observed in any of the secondary efficacy endpoints.

[Slide]

The apparent survival benefit claimed by the applicant in a small subset group of breast cancer primary patients is questionable because of imbalances possibly influencing treatment effect, very small sample size from a single study, and results of a post hoc exploratory analysis. Thank you.

Questions to the FDA and the Sponsor

DR. PRZEPIORKA: We will have questions to the FDA and the sponsor. Dr. George?

DR. GEORGE: I have a question for the sponsor. The trial that was mentioned as ongoing, randomized trial, did I miss something here? Did you address that at all or could somebody tell us what that is about?

DR. CAGNONI: The question is about the ongoing randomized trial. It is a randomized trial in patients with breast cancer and brain metastases.

DR. GEORGE: Is it exactly like this one?

DR. CAGNONI: It is a very similar study, yes. It is focused on patients with breast cancer and is very similar. Patients are randomized to RSR13 and no RSR13. Both arms receive supplemental oxygen and the primary endpoint is survival.

DR. GEORGE: What is the target sample size in that?

DR. CAGNONI: It is 360 patients.

DR. GEORGE: And where is it in its conduct right now?

DR. CAGNONI: Twenty sites have been initiated in the U.S. and Canada and patients are

being enrolled.

DR. PRZEPIORKA: Dr. Mortimer?

DR. MORTIMER: I am just curious, in the new study have you stratified for estrogen receptor and HER2 status, and do we happen to know that in this present study at all?

DR. CAGNONI: The ongoing study stratifies by liver metastasis and KPS which were the two strongest prognostic factors in RT-09, in addition to resection which is not allowed in the current study.

DR. MORTIMER: Was HER2 known in RT-09?

DR. CAGNONI: No, it was not.

DR. MORTIMER: So, you don't know that it is not a prognostic factor.

DR. CAGNONI: There isn't a lot of literature on the subject. The very little there is out there doesn't seem to indicate that there is a difference in survival in HER2-neu versus HER2 positive versus negative patients once they develop brain metastases. What we do have from RT-09 is the percentage of patients that received

trastuzumab after randomization, and those numbers are roughly similar between the arms.

DR. PRZEPIORKA: Ms. Portis?

MS. COMPAGNI-PORTIS: Yes, considering that that study is recruiting and accruing at this time, why aren't we waiting for those results? Why are we looking at this now?

DR. CAGNONI: We fully believe that the data that we have presented today is sufficient for approval of RSR13 in patients with breast cancer and brain metastases. That study is in the process of being initiated. It could take a very long period of time to accrue 360 breast cancer patients.

MS. COMPAGNI-PORTIS: How long do you think that will be?

DR. CAGNONI: I can't speculate. I can tell you that it took 29 months to enroll 115 breast cancer patients in the study we are reviewing today.

MS. COMPAGNI-PORTIS: Thank you.

DR. PRZEPIORKA: Dr. D'Agostino?

DR. D'AGOSTINO: I don't want to stop the discussion on the new study but I have a different question. I am just a simple statistician from Boston so maybe I am off but it seems to me like the sponsor keeps claiming that they have significant results, especially with the addition of data, and the FDA does not. Could we have an agreement? Is this significance on the overall in the subset or is there not significance, statistical significance?

DR. PRZEPIORKA: If I can just rephrase the question, is it true you have shown both in 008 and 009 that the median survival for the breast cancer subgroup is doubled and significant?

DR. D'AGOSTINO: Well, even in the overall--there is a slide on page 28 and the p values are 0.05 for overall survival in breast, and I think somewhere there are also sheets that have significance or other survival. My understanding from what the FDA is saying and reading is that there is not statistical significance with the overall survival. Is that agreed upon?

DR. CAGNONI: If we could have the slide up, it summarizes the analyses we conducted following the SAP.

[Slide]

The SAP specified eligible patients, two co-primary populations, and this shows the lung/breast co-primary population median survival. The original analysis is in white, 4.4 months for the controls, 6 months for the RSR13. The hazard ratio is 0.81, the p value is 0.07. By the prespecified Cox multiple regression that was conducted as the SAP described, the p value is 0.02.

DR. D'AGOSTINO: But I thought the prespecified analysis was an unadjusted log-rank test.

DR. CAGNONI: The primary analysis was unadjusted log-rank, correct.

DR. D'AGOSTINO: So, it is not the 0.02.

DR. TEMPLE: But it says eligible up there. That is where the difference comes I believe.

DR. CAGNONI: That is the difference.

DR. TEMPLE: It would be good if everybody addressed that.

DR. D'AGOSTINO: That is what I was going to get to, are we dealing with different analyses or are we dealing with different groups of individuals?

DR. TEMPLE: Different analyses, at least in part.

DR. PRZEPIORKA: Go ahead, Dr. Sridhara.

DR. SRIDHARA: The analysis that I presented was in the ITT population. Those were the p values that I was presenting both in the overall population as well as in the non-small cell/breast cancer population. The results that you are seeing, both 0.07 and 0.05 in the non-small cell lung/breast subgroup are based on eligible patients only. Even so, we wouldn't consider that as significant since we are not comparing with 0.05 since there are multiple hypotheses.

DR. D'AGOSTINO: So, in either sets of data it is not significant.

DR. SRIDHARA: Correct.

DR. TEMPLE: But the reasons are multiple. It is important to tease them out. I think, Raji, you are saying with two co-primary endpoints you don't test at 0.05, you test at something smaller but nobody is quite willing to say at what, I gather. So, that is one issue.

The other issue is the intent-to-treat, the all patients, or the eligible and that needs to be discussed too. Does everyone agree that ITT was the prespecified endpoint? Because, if that is so, then that matters.

DR. D'AGOSTINO: I was assuming somebody else would pick it up but if nobody does, I would like to.

DR. TEMPLE: No, everybody needs to pick it up.

DR. D'AGOSTINO: I mean, it is usual that you have an ITT sample as the sample that you are analyzing as opposed to some definition of eligible.

DR. PRZEPIORKA: Dr. Cagnoni?

DR. CAGNONI: Yes, if I may have Dr. Scott address the issue, please.

DR. SCOTT: Actually, this takes a very standard design that we, within the RTOG, have used for quite some time and most of the cooperative groups as well. That is, with a multicenter clinical trial such as this, we are going to have retrospective ineligibilities that are going to occur. The design of this study, as specified in the protocol, adjusted the sample size by 5 percent to account for the ineligibility that was expected to occur. So, the definition that we have always used is that eligible patients as randomized will be analyzed.

DR. D'AGOSTINO: Is that unusual for the FDA, to get that type of description?

DR. TEMPLE: Well, as a general matter an after the fact exclusion raises potential problems. You know, if you know exactly how it is done and whether it is all blind, and stuff, that is one thing. But if you don't know exactly how it is done there is always a concern whether someone is

eligible or not has something to do with the outcome. So, I don't think that is usual but other people who know more about it can tell me. It wouldn't be usual in other clinical disciplines; it would be quite unusual.

DR. PAZDUR: I would also like to point out that if one takes a look at the ineligible patients there are almost three times as many in the control arm as they are on the RSR arm. I don't know if these were prospectively suggested or stipulated in the protocol about leptomeningeal disease, no measurable brain lesions, dural disease due to bone, small-cell carcinoma--I know the small cell carcinoma was at least one patient but are the other ones prospectively stipulated in the protocol?

DR. CAGNONI: That is correct, these are all exclusions based on the protocol. The SAP provided additional level of detail. In following ICH guidelines, all these ineligibilities were determined on pre-randomization factors. The specific eligibility criteria in the protocol that

would be used to define ineligibility were also specified in the SAP and that was the analysis that was conducted. The reviews for ineligibility were conducted blindly by the same team of radiologists that conducted the response assessment.

DR. PRZEPIORKA: Dr. Buckner?

DR. BUCKNER: Just a question for the FDA statistics group, if you analyze just the eligible patients do you agree that even with the primary or the co-primary, in either set, there is a statistically significant difference in survival?

DR. SRIDHARA: The p values that the sponsor presented, we agree with those p values but, again as I said, in the non-small cell/breast subgroup the p value of 0.07 and 0.05, with the multiple hypotheses that we are testing, will not be considered as significant.

DR. PRZEPIORKA: Dr. Pazdur, do you have additional comments? No? Dr. Redman?

DR. REDMAN: Just for clarification purposes, to the sponsor, confirmed responses are defined how?

DR. CAGNONI: Yes, the protocol did not mandate confirmation of response.

DR. REDMAN: Right.

DR. CAGNONI: So, what we did was in the responders, we looked at those responders that had a CAT scan or MRI at a minimum of 4 weeks from the response to termination. We looked at those patients and there was a certain number of patients that did have CAT scans confirmed in those responses. But I want to make it clear that that was not an analysis per protocol.

DR. REDMAN: Then back to the FDA, there is a statement on your slide 19, looking at the exact same numbers that the sponsor provided for confirmed responses--you state that there is no apparent advantage in response rate but you don't give a p value. Not that I am big on p values but the sponsor gives a p value which is significant, using the exact same numbers.

DR. SRIDHARA: The p value is 0.06.

DR. REDMAN: The sponsor has the same numbers and has a p value of 0.02--exact same

numbers on their slide on page 33.

DR. CAGNONI: If we can have the slide up?

[Slide]

Are you talking about confirmed responses?

DR. REDMAN: Yes.

DR. CAGNONI: In all patients these are the confirmed response rates for the two arms, non-small cell/breast co-primary and breast cancer patients.

DR. REDMAN: I was looking at all patients.

DR. CAGNONI: All patients is the top row.

DR. PRZEPIORKA: Any FDA response?

DR. SRIDHARA: I think there were some slight number differences there. Let me get to that.

DR. PRZEPIORKA: While she is doing that, Dr. Martino, did you have a question?

DR. MARTINO: Two questions, both to the sponsor. I need to understand more clearly what the causes of death were in the two populations of breast cancer patients. Can someone answer that

one first? Did they die of systemic disease? Did they die of brain-related issues? And, was there a difference between them?

DR. CAGNONI: Yes, the specific cause of death, results were collected. We asked the investigators to define cause of death as neurologic, non-neurologic or indistinguishable. The problem with evaluating cause of death in these patients, this is very complicated in this population. Can I have the slide up, please?

[Slide]

Let me show the results. The protocol defined cause of death was neurologic, non-neurologic, indistinguishable or alive. RTOG combines indistinguishable and neurologic and those results are shown here. Using this classification, for the control patients there were 49 percent neurologic versus 39 percent in RSR13; 51 and 62. However, what I am showing you is not the analysis by protocol. The protocol included a category of indistinguishable that had a high number of patients.

Let me also add that at the time of this analysis 21 of the 60 patients in the RSR13 arm were still alive, making the interpretation unclear at this point. I would also like to ask, if I may, Dr. Friedman who has experience in treating patients with brain metastases, for his opinion on cause of death as an endpoint in this population and the ability to discriminate cause of death.

DR. FRIEDMAN: To be blunt, I don't think we can do it. I think that is such a challenging proposition that in trying to discern why a patient with brain metastasis died--from neurological complications, from systemic disease in at least a third to 40 percent we simply can't tell.

DR. MARTINO: But I think those of us who treat this disease, and there are those of us in this room besides the present speaker, oftentimes can tell a brain-related death from a liver- or a pulmonary-related death. It is not such an impossible task although, I will grant you, there are patients where it is not so obvious. But you have answered my question reasonably well enough

that I am happy with that.

I have one more, please. In these patients, I am assuming that this was, in fact, first therapy for their brain metastases but what was allowed subsequently, because I am sure many of these relapsed and other things were done? Were there restrictions imposed on that?

DR. CAGNONI: Regarding the first part of the question, prior therapy for brain metastases was not allowed, with the exception of resection as long as the patient had measurable disease after that resection, in other words, they were partial.

Regarding subsequent therapy, I will ask Dr. Elias, who is Director of the Breast Cancer Program at the University of Colorado, to comment on that since he conducted the review.

DR. ELIAS: Slide up, please.

[Slide]

Just also to discuss the previous question briefly, sometimes patients may die of systemic disease but if they have uncontrolled brain metastasis you are much less likely to offer them

further therapy. That is one of the reasons for the imbalance in the subsequent treatment for the RSR versus control groups.

In any case, this is subsequent treatment and, as you see, there is comparable amount of systemic or subsequent brain metastasis therapy. Clearly, our options after primary treatment are quite limited.

[Slide]

This analyzes the percent of patients who received different types of subsequent therapy. Again, there is a slight predominance of more chemotherapy being given, although this is not statistically significant but this also may relate to the somewhat better Karnofsky performance status of those patients. Very few patients got brain surgery or stereotactic radiation.

[Slide]

This is the percent of patients who received further therapy in terms of number.

[Slide]

This is the balance between the control

and RSR13 group in terms of the specific agents that we have seen.

DR. PRZEPIORKA: Before we go back to the FDA, I just want outcome re-ask the question that was posed before. If I recall correctly, you have now shown from 008 and 009, two studies, that the median survival is doubled with RSR?

DR. CAGNONI: That is correct, 008 did not quite double the survival.

[Slide]

It was 5.4 versus 9.7 in 008 and 4.5 versus 7.0. This is Class II patients. There were very few Class I breast patients in 008. This compares the Class II patients.

DR. PRZEPIORKA: Dr. Sridhara, did you find the information you were looking for?

DR. SRIDHARA: I believe the applicant presented that in all patients unconfirmed responses were 37 versus 45 and we agree with that. The p value is 0.067. However, in the confirmed responses--I don't have the percentages but I can tell you that in the control arm there were 43 of

the 267 who had responses, and 61 of the 271, and the p value that we got was 0.06 versus what the applicant has given here which is 0.02.

DR. PRZEPIORKA: Dr. Redman, does that answer your question?

DR. REDMAN: Was that because you couldn't confirm some of the responses they confirmed?

DR. DAGHER: Another point that may be attributed to a slight difference in numbers, and we can discuss this, is that when we queried the sponsor on this issue of confirmation they actually gave us three sets of possibilities for patients who may be considered "confirmed." The first was if some scan after the baseline and then a subsequent scan--if you had the sequence of a CR and then a CR, they called that a confirmed CR. If you had at some point a PR and subsequently another PR confirmed, that was a PR. But they also had this middle category where if you were PR and then CR--or I think it was CR and then PR, that is right, so if you had a CR on one scan and then the scan you got right afterwards was a PR, they

considered that I think a complete response. I don't know that we would agree with that assessment. So, there may be a slight difference in the interpretation of that middle group.

DR. PRZEPIORKA: Go ahead.

DR. CAGNONI: May I make a comment?

[Slide]

This is the response rate in the brain per protocol. All these analyses we are discussing were not per protocol. The protocol specified that they had to be done a certain way and it was done the same way in both arms, was reviewed independently and is statistically significantly higher in the lung/breast co-primary population. I would like to emphasize that.

DR. DAGHER: Also, I would like to emphasize that the main point we were trying to make is that, yes, the issue of do you have a difference between the two arms is a significant issue but also with this endpoint of response rate in the brain, what are the factors that would give you certainty or uncertainty regarding the

findings? So, the main points were this issue of confirmation, which is only one of several; the fact that you had steroids on board with most patients, which was appropriate but is certainly an element that causes uncertainty when you are looking at scans, edema, etc.

The other two that Kevin mentioned, one of which was the fact that the protocol-specified criteria did not require absence of any new lesions when response, either CR or PR, was called. For that last one that I mentioned, and the sponsor will probably comment as well, in terms of this issue of not requiring absence of any new lesions--that was a small number of patients. But we are just showing that there are several points here that make us uncertain about the contribution of RSR to the response in this particular trial and in the particular subgroup for which benefit is claimed.

DR. PRZEPIORKA: Dr. D'Agostino?

DR. D'AGOSTINO: My point is probably lost now but I just wanted to make sure that it was

understood that when you ask about the two studies in the breast cancer results, in fact, we have to remember that the first study was a registry comparison but, more important, the second study was not a planned group that was actually looked at. So, the statistical significance, be it double in terms of magnitude, could be questioned or should be questioned, and also the sample size--we are dealing with only 20 percent of the original sample so we are getting down to a smaller subset.

DR. PRZEPIORKA: And I think I asked that question because it was significant and it was reproducible. So, even though it is not statistically valid it is certainly striking.

DR. D'AGOSTINO: I don't know the history but why didn't they focus the second study on that group, given that they had something with the registry? Did they go back later on and find out it was in the registry as opposed to designing the study? It doesn't look like they designed the next study with that result. If you give me enough time, I probably will find a subgroup that is

significant in both samples also.

DR. PRZEPIORKA: Dr. Buckner?

DR. BUCKNER: I have three questions related to the response endpoint. First of all, there was a statement that looks like 13 of the 115 patients were not assessable for response and that, in fact, the median survival of those with missing data was 0.99 months in the RSR arm and 2.7 in the control arm. Is that correct? More than 10 percent of your cases had missing data?

DR. CAGNONI: Yes.

DR. BUCKNER: The second regards scans. Were patients required to have identical type of scans for comparison? For example, response assessed, CT compared with CT scan?

DR. CAGNONI: Correct.

DR. BUCKNER: And that was prespecified in the protocol, that they must have the same type of scan for comparison?

DR. CAGNONI: That is correct.

DR. BUCKNER: The third question, were patients required to be on a stable dose of

corticosteroids prior too the baseline scan for a certain period of time before they were assessed for response?

DR. CAGNONI: No. However, number of patients on steroids, mean median dose, dose adjustments, increases, tapers and length of steroids in days was comparable between the two arms. There were no differences, as the FDA I think implied in one of their slides.

DR. BUCKNER: Were there in fact patients that were called responders that had a new lesion on a subsequent scan?

DR. CAGNONI: A small percentage of responders had new lesions.

DR. BUCKNER: What percentage was that?

DR. CAGNONI: Four percent and six percent. Cam we have the slide up, please?

[Slide]

Six percent of patients in the control had new brain lesions and four percent in the RSR13 arm.

DR. BUCKNER: And those were still

considered responders?

DR. CAGNONI: That is correct. Dr. Dagher explained that the way the protocol was written, response could be determined as a PR or CR even in the presence of new lesions. When the study was designed the sponsor was advised that reseeding could occur from extracranial systemic disease and, therefore, to assess truly their response in the brain new lesions should not be accounted for. The percentage of new brain lesions was very small and there were no new brain lesions in the breast cancer patients that received RSR13.

DR. BUCKNER: Thank you.

DR. PRZEPIORKA: What percentage of the patients had hemoglobinopathies such as sickle cell anemia?

DR. CAGNONI: We did not screen for hemoglobinopathies. Hemoglobin electrophoresis was not done.

DR. PRZEPIORKA: And is there any information from the clinical studies to suggest that the abnormal hemoglobins might react

differently or confer additional toxicities?

DR. CAGNONI: I will have Dr. Steffen, head of pharmacology/toxicology, answer that question.

DR. STEFFEN: In laboratory studies using human sickle cells, fetal cells and adult normal hemoglobins, red blood cells RSR13 has no effect on rheologic activity and the p50 effect is similar across all hemoglobin types studied.

DR. PRZEPIORKA: Dr. Buckner?

DR. BUCKNER: I am sorry, on the response criteria one other question, if I may, what proportion of your patients were followed by CT scan and what portion by MRI?

DR. CAGNONI: The majority were MRIs. I can't give you the exact number. We can try to get it for you in a few minutes but the majority were MRIs.

DR. PRZEPIORKA: Other questions? Dr. Temple?

DR. TEMPLE: I am sorry to be dense about this, it is really a question for both groups, when

you modified the study to give yourself co-primary endpoints you must have identified a critical alpha for each of the endpoints. It wouldn't be the usual 0.05 ones; you had two of them. So, what was it? That is one question.

The second is, was your primary endpoint for the primary analysis the intent-to-treat population or the eligible patients population? It must be in the protocol or the statistical analysis, it must be somewhere. If Raji disagrees with that, I want to hear what the disagreement is because I have the same problem Ralph does. We are sort of talking beside each other.

DR. CAGNONI: We will have Dr. Scott comment on that.

DR. SCOTT: Sure. The analysis was specified as eligible patients as randomized--in the protocol.

DR. TEMPLE: In the protocol?

DR. SCOTT: In the protocol. Beyond that, the appropriate adjustment here that we used in the protocol basically states that we will take the p

values, order them and then compare the highest p value to 0.05. If that is not significant, then the next highest p value to 0.25, and so on until you get down to statistical significance. In other words, if we have 3 p values and they may be ordered as 0.13, 0.08 and then 0.05 or 0.02 or 0.017, somewhere around there, then we would adjust the p value because the first one was not significant, the second one was not significant and then the third one would be adjusted at 0.05 divided by 3, which would be 0.0167. Does that help?

DR. TEMPLE: I think so but by that standard--you only had two co-primaries. It sounds like that procedure would not leave, say, 0.05 for the small cell plus breast as significant.

DR. SCOTT: Right.

DR. TEMPLE: Would that be true?

DR. SCOTT: That is correct. Right, as long as the overall one was not significant it did not leave 0.05 and we didn't make the connection that the unadjusted log-rank at 0.05 for the

updated data analysis--we did not say that that was statistically significant.

DR. TEMPLE: Let me be sure I get this, for the total population that is not significant. That is clear, even in the new adjusted one.

DR. SCOTT: Right.

DR. TEMPLE: And when you make whatever the right correction is for the second co-primary, the lung/breast, that wouldn't be either. Right?

DR. D'AGOSTINO: That is what I was asking before and I thought I got the answer that neither would be significant.

DR. SCOTT: Right, and then the contention that we had, which was that we needed to make an adjustment for the heterogeneity by using an adjusted p value, an adjusted test such as either a stratified log-rank or Cox analysis. So a Cox analysis, as defined in the protocol, was performed and that reaches statistical significance.

DR. TEMPLE: Without dismissing it, that wasn't identified as the primary analysis. I mean, sometimes you do things that aren't specified, I

understand, but it was not the primary analysis.

DR. SCOTT: It was specified in the protocol though as a confirmatory type of analysis.

DR. TEMPLE: As exploratory, but if you fail on the others you don't usually do exploratory. Wouldn't that be true?

DR. SCOTT: Not necessarily. I don't agree with that and I will explain why. That is, when we design these studies and we design the trial with the log-rank and also a Cox analysis with the intent to use that analysis, we know through simulation analyses and in the statistical literature that you lose power if there is a heterogeneity in the data set. Thus, the only way that you can retain that power as designed through the parameters of the study is to do a Cox analysis or stratified log-rank.

DR. TEMPLE: But nothing stops you from having specified that as the primary analysis in case there was heterogeneity. I mean, it is not commonly done but you could do that.

DR. SCOTT: Right. We could have done

that. When I was part of the team that designed this study, back in the late '90s and early 2000, we didn't have the heterogeneity simulations performed. So, at that time what we did was the unadjusted log-rank. So, I really believe that the statistical literature has helped us along that way in showing that aside from stratification the way to adjust for the heterogeneity is also in a stratified log-rank.

DR. TEMPLE: I am not sure anybody would disagree with you but when it is done after the fact the implications are somewhat different.

DR. SCOTT: But it was specified that we would do that. I mean, it is not like we looked at it and we saw, oh gee whiz, we missed and we are going to go back and do something different. We actually did what we specified in the protocol.

DR. TEMPLE: But you do wish it had been the primary analysis now, of course.

DR. SCOTT: No, but it was part of the primary analysis.

DR. TEMPLE: Not exactly.

DR. PRZEPIORKA: Dr. D'Agostino?

DR. D'AGOSTINO: It wasn't the primary analysis. It says "exploratory" and you did make protocol amendments along the way that were accepted. If the statistical literature informed you that that would have been a better analysis or analysis to tie into the primary you had plenty of opportunity to do it before the data set was locked. So, I am really not following the statement that the decision was made years ago. To me, it is not the primary analysis.

Open Public Hearing

DR. PRZEPIORKA: Any other questions from the committee? Hearing none, we are going to move on to the open public hearing. We have one speaker and I need to inform the group that both the 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, the FDA believes that it is important to understand the context of an individual's presentation. For this reason, the

FDA encourages 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 the sponsor's payment for your travel, lodging or other expenses in connection with your attendance at this meeting. Likewise, the FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships at all. If you choose not to address the issue of financial relationships at the beginning of your statement it will not preclude you from speaking. Our first speaker is Peggy Wesselski.

MS. WESSELSKI: Good afternoon. My name is Peggy Wesselski and I am a cancer survivor. I have been happily married for 28 years to my husband, Fred. We have three wonderful daughters, one of which is with me today, my oldest daughter, Amanda.

I was first diagnosed with stage 4 inflammatory breast cancer. At that time, my youngest daughter was in the first grade. I never asked God why me but I did say Lord, my girls need me. And, after much prayer I realized that my girls would be fine with their daddy and with God's help. After all, He could be with them 24/7. He would be a better caregiver than I could be. I surrendered my illness to the Lord for His will to be done, not mine. He has been blessing me ever since.

I have a lot of stories I could tell you but we are here to talk about RSR13. It was January, 2002 when it was discovered that the cancer had spread to my brain. There were five tumors, one of which had fluid around it. Dr. Gabriel Hardabaji is my breast oncologist. He was out that day and I received the results--I am sorry, he was out that day and I received the results from the MRI from Dr. Therialt who gave me the news. I had already survived a lung met. but this sounded more serious to me. Dr. Therialt said

that I would qualify for a study which he highly recommended.

Arrangements were quickly made for me to see Dr. Eric Chang. First the research nurse came up and sat beside me. Her name was Chris. She told me all about the study and explained that originally she was allowed only ten patients. She already had those ten patients but she had just found out that she could have another ten. Chris smiled at me and she said, "you'll be mu number eleven." That said to me that God had gone before me and made provisions so that I could take part in this study.

Chris went on and told me that all patients in this study would have whole brain radiation and receive oxygen but that some patients would receive a 30-minute drip which was RSR13. She informed me that the computer would randomly pick who would receive the drip. At that moment I thought if this is a good drug I know I am going to get it. I could already see God's hand on it.

Everything happened so quickly that day

while I was being set up for the study, I lay still on the table having my helmet made for radiation. It sounded like a dozen people were in the next room discussing my case. I heard my name a few times. I lay there thinking how blessed I was. They were scurrying around as if I were a celebrity.

Later Chris came back and let me know that I would, indeed, be receiving RSR13. The treatments went well. It didn't seem to cause any side effects that I can remember. I did have a lot of fatigue which my doctor told me that I would experience. After treatment I remember being warned that my first MRI, which would be one month later, would probably not show improvement because radiation works down the road. But one month after the treatment with RSR13 and radiation my first MRI did show improvement. Each MRI showed more improvement until there was only slight evidence that something was there.

It has been almost two and a half years now and I am doing well. I am going about my

normal activities, doing anything and everything with my family, enjoying my life to the fullest. My youngest daughter, who is a freshman in high school now, keeps me on the run. I am so thankful for M.D. Anderson, for Dr. Chang and for the clinical trial that God allowed me to be a part of. I am thankful that I was number eleven and that I did, indeed, receive RSR13.

Through my experience in fighting cancer for eight and a half years, I have made friends with many other breast cancer patients. It is my hope that if they develop brain mets. they will be guarantied this same opportunity to receive RSR13 that I had. I truly hope that you will recommend to the FDA that they approve RSR13 to make it available for all my friends and for other patients with brain mets. as well. Thank you.

DR. PRZEPIORKA: Thank you. We appreciate your comments. Lenny Matthews has asked to speak. Is Lenny Matthews here? No? Okay, we will continue on and the next presentation is by Dr. Stephen George.

DR. GEORGE: Well, I am doing something a little different. I am not speaking directly to this application but giving a little, brief primer on some generally accepted methodologic principles in clinical trials as they relate to subgroup analyses. It is, of course, relevant to this discussion today but also to other discussion we have on this committee.

[Slide]

First, what do we mean by subgroup analysis? I think it has been clear that it is an analysis of treatment effects within subgroups of patients on a clinical trial. The first question that arises is why would you want to do this? If you designed it to do an overall test, why don't I just do that and go home? Well, the answer is we all have a suspicion that maybe there is something going on that the treatment effects are not the same in all patients on the study so it is a natural kind of thing and humans want to search around and find these kinds of things.

[Slide]

How often are these done? Well, this first paper I found said that approximately 50 percent of reports of randomized clinical trials contain at least one subgroup analysis. Actually, Pocock has done a more recent analysis where the answer is more like 70 percent. I am actually surprised it is that low. When I read the literature I thought it was 100 percent.

The second quote came for I.J. Good, back in the '80s, who said that deciding on analysis after looking at the data is dangerous, useful and often done.

[Slide]

Now, what are the basic problems with subgroup analysis? Well, the first one you have already heard a lot about. I will go into this a little more and explain what this means but the first is increased probability of type-1 error (the null hypothesis) when there is really nothing going on. If we look around, we have an increased chance of spotting something and that would be erroneous

in that setting.

The second is a problem sort of in the other direction. It is decreased power or what is called an increased type-2 error in the individual subgroups when, in fact, the alternative hypothesis is true, say, for example if the overall truth is, unbeknownst to us, that there is an effect overall and it is the same in all subgroups and if we start looking at subgroup and we are going to find a lot of them that aren't significant and maybe make the wrong conclusion in the other direction.

The last is what we have seen already, that all of these kinds of things create great difficulty in interpretation.

[Slide]

What I would like to do first is point out what are some general assumptions behind doing clinical trials in the first place. Well, the hypotheses that we are testing usually address an overall or what might be called an average treatment effect in the study population.

The second point about that is that there

is no assumption in this of homogeneity of effect across subgroups. We are not assuming that the treatment effect is the same in all subgroups just because we are doing an overall test. But what we are generally assuming to be the case is that the direction of that effect, not necessarily the magnitude but the direction of the treatment effect is the same in all the subgroups. That is, we would be very surprised, because of the way we determine eligibility criteria and set up the trial in the first place, if we saw a result that showed that treatment A worked in this subgroup and treatment B worked in that subgroup. More likely, we would see that if there is an overall effect treatment A might work better in some groups than others, but it is all sort of in the same general direction.

[Slide]

The implications of these kinds of assumptions that are behind most clinical trials are that the overall treatment comparisons are of primary interest, and that is really what we did

the trial for. We can use stratification or regression techniques to adjust the overall comparison for subgroups or covariates if we wish but, again, those should be specified clearly in advance. Subgroup analyses themselves are generally of secondary interest as hypothesis generating techniques for future studies.

[Slide]

I think the key point about these subgroup analyses is whether they were planned or not. So, I have mentioned something here, the pre-planned analyses or hypothesis-driven kinds of analyses--the subgroup hypotheses are specified in advance and supposedly, because we have done that, we can control the error rates or the error rates can in principle be addressed but, as I will show you in just a second, that is not always so easy. It is a tricky business even when it is pre-planned. By the way, pre-planned does not mean you just said ahead of time that we were going to look something. That is not the same as actually pre-planning the analysis.

The second type of subgroup analyses are unplanned analyses or what would be exploratory analyses. These are either analyses suggested by the data or an exhaustive search for differential treatment effects by subgroups. This is often called by the pejorative term as data dredging, although that is perfectly reasonable, again, if you realize that what you are doing is generating hypotheses.

The problem with the unplanned analyses is that you have inflated error rates and, in fact, you don't know what those error rates are because you really haven't specified what you were going to do.

[Slide]

There are a couple of things in the ICH guidelines that address subgroup analyses directly. Here is one from the guideline E3, which is on publication results, and it says it is essential to consider the extent to which the analyses were planned prior to the availability of data. This is particularly important in the case of any subgroup

analyses because if such analyses are not pre-planned they will ordinarily not provide an adequate basis for definitive conclusions.

[Slide]

In guideline E9, which is on statistical considerations, says clearly that in most cases subgroup or interaction analyses are exploratory and should be clearly identified as such. These analyses should be interpreted cautiously. Any conclusion of treatment efficacy or lack thereof or safety based solely on exploratory subgroup analyses are unlikely to be accepted.

[Slide]

What about these error rates? What are we talking about here? If you looked at k independent subgroups and there is really no difference in the treatments, the probability of finding at least one is represented by this formula, here. For example, if you used the 0.05 level and looked at 10 different subgroups your chance of finding at least one is 0.4; it is not longer 0.05.

[Slide]

Here is just a graph of that, showing that this increases quite rapidly as a function of the number of subgroups. This is when you know the number of subgroups.

[Slide]

So, what can we do about it? Well, of course, one way is to control error rates. Well, for planned subgroup analyses you can control the overall type-1 error rate. One conservative way is to use this thing that is often called a Bonferroni correction, which is to simply divide the overall error rate by the number of analyses you are going to do. Of course, that gives you a much smaller alpha level on each particular test.

In this case, the power or the probability of detecting real differences when they are present is sharply reduced in individual subgroups. Of course, for unplanned analyses we don't know k and the error rates are really unknown, as I have already mentioned.

[Slide]

Here is a hypothetical example and I will

show you a real example of where this happened and I think caused some problems. Let's suppose we have two groups, experimental and control. Outcome is overall survival. The null median is 12 months, meaning if there is really no difference in these treatments and all we are doing when we are randomly assigning them is sort of randomly assigning people to the same thing, we would expect about 12 months.

Alternatively, if the experimental treatment is working, let's suppose the median would be 16 months long. That is a 25 percent reduction, 0.75 hazard ratio. Let's suppose we do this trial with 36 months accrual, 12-month follow-up, 500 patients on this study. We want a 0.05 overall alpha level and suppose the power is 0.8. Now, we have a couple of subgroups here. There are males and females. Let's suppose that 70 percent of them are males in this study, about 350 males and 150 females.

[Slide]

What could we do? Well, you could do

subgroup tests with no adjustment--not a good idea but we could do it, and we use 0.05 in each of the two subgroups. The overall type-1 error rate has, of course, jumped up. It is no longer 0.05; it is closer to 0.1. But also the power, the ability to pick up the difference in the males is only 0.64 and in females it is only 0.33. In fact, the probability that the correct conclusion is reached in both subgroups, males and females, if in fact it is true that there is this difference in both subgroups is only about 20 percent, 0.21.

[Slide]

Let's say, okay, that is not too god but at least we want to control the type-1 error rate so we could do this sort of conservative thing I suggested before and divide by 2. So, we use 0.25 in each subgroup and, therefore, the overall type-1 error rate is controlled. It is less than 0.05. But now, because we have made it harder to reject the hypothesis in the subgroups, the power is about half in the males and only about a quarter in the females and the probability that the correct

conclusion will be reached when, in fact, there is something going on is very poor. So that is not good. By the way, the only way to fix this is to have a very large sample size.

[Slide]

Now let me give you a real example where I think this occurred in almost exactly that kind of scenario. This is what I call the aspirin example. I am not going to go into great detail here but in 1978 there was a publication by the Canadian Cooperative Study Group of an excellently done and well run clinical trial of aspirin and another drug. I am just going to focus on the aspirin. This was published in 1978 in the New England Journal of Medicine. Their conclusion in the abstract, and emphasized in the discussion, was among men--among men, remember--men and women were on this study, the risk reduction for stroke or death was 48 percent, whereas no significant trend was observed among women. We conclude that aspirin is an efficacious drug for men with threatened stroke.

[Slide]

Here is what this was based on. The first row here gives males and the columns give aspirin and no aspirin. Among the males there were 85 events, strokes or deaths, 29 on the aspiring group and 56 on the no aspirin group out of the total number of subjects of around 406. So, it is about 70 percent and a great predominance of events were in the no aspirin group, indicating an advantage for aspirin. In females, in fact, the advantage seemed to go in the other direction. If anything, there were more strokes or deaths in the aspirin group among females, only 29 events total and the total number of subjects was only 179. The total number of events, if you just look at that, which is what the trial was designed to do, still favors the aspirin group.

[Slide]

If you translate that into things that we like to look at on these trials, which is the risk reduction in stroke or death, if you just look at that first row again for males, the risk reduction

was about 48 percent. That first column, by the way, is observed over the expected number of events in the categories. But the risk reduction was about 48 percent. That is a very dramatic risk for males, chi square value 8.2, p value 0.004, nominal p value. For females it actually increased by 42 percent, a chi square, but not a significant result. Overall the risk reduction was about 30 percent and a barely significant result by the usual criteria.

[Slide]

Now, ten years later a large meta-analysis of all results of various types of antiplatelet treatments was published in which they concluded, among other things, that overall allocation to antiplatelet treatment reduced vascular mortality by 15 percent and non-fatal vascular events, stroke or myocardial infarction, by 30 percent. I don't have time to go into the details but basically they found there is no difference in males and females. Aspirin worked, and it worked to reduce the mortality approximately by what the Canadians got

in their first study ten years earlier. During those ten years, what was the advice given to women in this situation? So, it can happen. There can be some real mistakes made in looking at subgroup analyses.

[Slide]

What can we do about this? How do we interpret subgroup analyses? We know they are going to be done. Here are some guidelines that were presented several years ago--or some of them, and I didn't put all of them on here--to look for when you are reading about subgroup analyses that are done. First, were there a priori hypotheses stated? As I mentioned, I think that is the most important one. Second, what is the clinical importance of the difference if it is really real? Third, did they assess the statistical significance properly? In some cases, if it wasn't planned, of course, this may be almost impossible. Is there consistency across studies? This is important but it implies there is more than one study. And, is there any indirect supporting evidence either from

preclinical studies of other theoretical reasons why you expect that subgroup to be different? That one is probably a weak one. Humans are remarkably adapt at coming up with reasons for anything they find.

[Slide]

One thing I wanted to mention briefly is the idea of a treatment-covariate interaction because nobody has talked about that today. This is sort of a generalization of subgroup concepts. Basically, the idea is you don't have to be really talking about subgroups, identified groups of people. You can use so-called covariates that are continuous. For example, if you have age you don't have to say age above 65/below 65 you can use it as just a continuous variable. Then you can use this for testing for what are known as treatment-covariate interactions. Basically, it means does the treatment differ in the sense of having an interaction with this covariate. There are quantitative interactions, which is what is the most common kind of thing, where the treatment

effects are in the same direction but of different magnitude, and qualitative interactions where the treatment effects are actually in opposite directions, which would be rare.

[Slide]

This simply indicates the kind of thing that I am talking about. If you have a control treatment and a covariate, males and females again, and an outcome depending on which treatment group you are in, whether you are male or female, and an interaction term, this beta-3, XZ. So, if you look across the rows here, female and male, the treatment effect in females is beta-1; the treatment effect in males is beta-1 plus beta-3. So the statistical test becomes one of simply testing for beta-3. The reason I am pointing this out at all is whether beta-3 is zero. If it is not zero then there is something going on.

[Slide]

So, what are some strategies we could use when we are interested in subgroup analyses? First of all, we could design for the overall hypotheses

but test within predefined subgroups. As I have already noted, that has a high overall error rates, low power in the subgroups and biased estimates. I haven't emphasized biased estimates but what happens in these subgroups when you find a difference is that it is known to be biased. That is, it is going to be larger on average than what the truth is because you searched and haven't found it. This is not a good thing. In other words, in the aspirin example you could have guessed that that effect in the males was too high. It was just sort of implausible, and that is what happens when you look in these subgroups.

Second, we could design for the overall hypotheses but test for prespecified treatment-covariate interactions, which is what I just mentioned in the last slide. That I think is a good strategy but it has low power to detect even modest interactions. The only way around this is to get much larger studies, which is a depressing point. So, there is nothing easy there.

[Slide]

Third, we could design for the overall hypotheses as before and conduct unplanned, exploratory analyses of subgroup differences. This, of course, gives us unknown error rates. That is why we really say this is a hypothesis-generating exercise for future study. It doesn't mean it is wrong to do this. There isn't anything wrong with it, it is just that you have to recognize it for what it is.

Last, we could actually design for prespecified subgroups or interactions. That allows us to control for the error rates but produces depressingly large studies that are often almost impossible to do.

[Slide]

So, what is the conclusion from all this? One is that I think pre-planning is key. It is very important to think very clearly about what you are doing and how you are going to do it, particularly in a regulatory setting. You can get away with this more if you are just trying to publish a scientific paper, as people obviously do,

but it is a lot more difficult in a regulatory setting.

Second, we do need larger studies if we are really going to do proper subgroup analyses. There is actually no way around that, I don't think.

Third, exploratory analyses are good for hypothesis generating but really are not convincing by themselves. The last point is more than one study is very important for validation. It would make results much more believable if you find two studies with a strong subgroup interaction. That is it.

Committee Discussion

DR. PRZEPIORKA: Thank you, Dr. George. I do wish you had given your presentation earlier. It would have assisted in our discussion but if we have any questions for him, now would be the time to do so. Hearing none, we will take a 10-minute break. If we can return here at 3:25, we can get started with the questions.

[Brief recess]

DR. PRZEPIORKA: We are going to get started. We are now into the question portion. Thank you for the brief and unbiased questions for the afternoon. The committee has received a copy of the questions and the data that is felt to be germane.

When the primary analysis in the overall study population is negative, subgroup analyses are considered to be exploratory, i.e., not capable of providing a conclusive finding. Although there could be exceptional cases, these analyses still pose multiplicity and potential bias problems.

So, question number one is, in fact, the survival analysis in the overall population of the randomized trial is negative. Do the observed survival results from the single study in the subgroup of patients with metastatic to the brain represent substantial evidence of RSR13 efficacy in this subgroup?

We will first open the question up to comments and at the end of the comments call the vote. Any comments from the committee? Dr.

Martino?

DR. MARTINO: Well, first of all, I want to thank the sponsors for realizing that this is a fairly serious set of circumstances that they are dealing with and, you know, for all of those of us who take care of breast cancer patients as well as all the other people with brain metastases, that someone is directing attention at this is laudable, and for that I am grateful to them.

This data is very meaningful to me because it is an area that I deal with a great deal so I appreciate its importance, and I do have the sense that there probably is something going on here which is of value. The issue for me is, is it of sufficient value for us to change the way that we practice oncology?

Because if an agent is approved several things follow that. One of the things is that the agent is then used for the population for which an application is sought and given. But more than that occurs, and that is that clinicians who have other patients for whom they mean to do the very

best start to then ask the question, well, if it works in population A, surely it must work in B, C, D etc. So, then a generalization of a behavior occurs.

So, for all of those things to be allowed one has to assume a great deal of responsibility and thinking through not only the simple decision of this drug in this population but the consequences that follow. I think I simply want to remind all of you that that is, in fact, what we do when we make these decisions. It isn't simply that we approve something for a patient population. Medical behavior expands beyond that and we have to take all of that into consideration here.

The other issue that is of great concern to me is that I realize this company has another study that they have started in the population of interest. If we decide today to proceed with this, what will happen to that trial? Well, you all know the answer to that. You have seen it over and over and over. The answer is that that trial will not accrue. We will never know an answer which is

based on more substance than what we see today, and so that is the other responsibility that we have to take on our shoulders.

DR. PRZEPIORKA: Dr. D'Agostino?

DR. D'AGOSTINO: I was embarrassed to raise my hand and said let somebody else raise the first issue, but she stole my thunder. This is an unspecified subgroup. I realize that you look back at the registry and see results but it is based on 18 breast cancer patients. We have this study with the subgroup showing some real interest, unfortunately not specified. Then we have an ongoing study which will be doomed if we make a mistake by over-interpreting the results that we have before us, and I think it really is an over-interpretation even if there wasn't that other study out there, and I am very excited that there is. Reading too much into this data I think is a real problem. I think this really is unspecified and is very problematic in how to interpret it.

DR. PRZEPIORKA: Ms. Portis?

MS. COMPAGNI-PORTIS: Yes, I would just

like to say as a person living with breast cancer and also as a patient representative and someone who has an opportunity to work a lot with people with metastatic disease that I know that even small results can be significant to a patient or a few patients and that that is important. Yet, I think that these results are too preliminary and I really think it is important that this other trial goes forward. I know that recruitment for the trial has already slowed down because this was brought before the FDA, and I think it is really important that that study goes forward. So, I think we always need to let the science lead and I don't think we have the data yet that we need. Thank you.

DR. PRZEPIORKA: Dr. Buckner?

DR. BUCKNER: Looking at the data we have and one of the problems that we have with subsets plus the statistical issues is are we really comparing apples with apples? And, looking for sources of real imbalance between the arms has been alluded to generally but not quite specifically, not in a summary fashion. So, when I was looking

at this I basically went through what are the factors that I thought favored the RSR arm and balance in favor of RSR with nothing to do with treatment efficacy; what favored the control; what seemed to be balanced and what were the unknown factors. All of these have been alluded to but just to list them briefly, there were several that actually favored RSR13, specifically fewer brain metastases in each patient and also less of the bidimensional products, so basically less disease in the brain; less disease in extracranial sites and normal number of metastatic sites; more systemic therapy really, more chemotherapy and more hormonal therapy in the patients on the RSR13 arm. Is that because they had better outcomes going into the radiation treatment or better outcomes coming out? That is hard to sort out. In fact, a slightly better performance score in the RSR.

There was at least one meaningful variable that I think favored the control, which is that a better baseline mental status generally portends a better outcome in patients with brain metastases.

Then there were a number balanced, as we know, RPA class, post-RSR treatment of brain metastases, age, distal metastases and, as Joanne pointed out, several important unknowns--the ER and PR status, the HER2 status, the prior number and types of chemotherapy.

But putting it all together, even if there weren't the statistical issues of subgroup analyses, it seems that there are some fairly substantial imbalances that one a priori might expect that the patients receiving RSR13 would have a better outcome regardless of whether the treatment were effective or not.

DR. PRZEPIORKA: Dr. Redman?

DR. REDMAN: Just for my clarification because, no offense, Dr. George, I thought I understood this and now I am not so sure. The study pre-identified a group of breast cancer patients and it was a stratification factor. Is that correct? Or, was that done after the trial was started? Breast and lung.

DR. CAGNONI: It was in the original

protocol, stratification criteria, that is correct. Breast cancer was a stratification criteria.

DR. REDMAN: The prespecified subgroup was the combination of breast and lung as a co-primary endpoint. So, you know, that carries considerably more weight than something you look at afterward.

DR. REDMAN: Right, but the study was not powered to see a difference between them.

DR. TEMPLE: Well, you can stratify a lot of things--

DR. REDMAN: Right.

DR. TEMPLE: You may or may not choose to analyze your strata as a separate group. That is a decision you make in plotting out your analysis plan. Of course, the groups get smaller and smaller, as Dr. George said, so at some point you don't expect to win because, you know, if your group is only--what?--one-sixth of the total you would have to have a really huge effect to win so you don't usually expect to. But you may want to be sure they are equally distributed in the two groups so you could stratify and not analyze. But

then you might put it in a covariate analysis if you claim the covariate analysis as your primary analysis, which you have heard some debate about.

DR. PRZEPIORKA: Dr. George, do you have comments?

DR. GEORGE: Yes, just a couple of comments on that point. The purpose of the stratification is to get slightly more homogeneous groups on the theory that in those groups they will have sort of responses about the same, but still you are sort of doing an overall test as the primary thing unless you have specified something else ahead of time, which in this case was the combination of two of those groups, I guess. Anyway, you do that presumably to get a little more precision in your result.

With respect to the other issue of imbalances among groups, presumably part of this was addressed with the sponsor's analysis of doing covariate adjustments of various kinds. The issue though for us has to do with that prespecification of whether it was primary or not because that also

becomes after a while fairly exploratory if it wasn't pretty well laid out ahead of time.

DR. PRZEPIORKA: Dr. Cheson?

DR. CHESON: We are in a bit of a conundrum here. Whereas I completely agree with Dr. Martino's analysis that if we do approve this drug that trial is dead, if we don't then it also sends another message that perhaps, you know, we were not in favor of this drug and the trial may be dead as a result of that decision.

So, if the latter is the decision of this committee, then I strongly recommend that the wording be exquisitely careful to encourage participation and not to suggest that it was because we didn't think there was something there but that it required additional support for the approval.

DR. PRZEPIORKA: I am going to take the chair's prerogative and perhaps put some words into Dr. Temple's mouth. I remember the days when the question used to come out as do you recommend approval? And I was very happy to see today's

questions not even come close to that sort of working. So, in fact, the question actually asks only does this provide evidence of efficacy in this subgroup, meaning it could be used for approval, or it could be used for supportive data perhaps if the company came back with preliminary response rates in the current ongoing study as opposed to not approval or approval. So, I don't want anyone on this committee to think that we are going to kill the drug. Whether we say one thing or another, it is simply to provide our opinion about whether or not the evidence provided today actually shows there is any efficacy.

DR. PAZDUR: Donna, the way we wrote the question specifically--obviously, everything is a risk-benefit decision here. The efficacy question is first and, obviously, if that is answered in the affirmative then to go down to look at the toxicity issue.

DR. TEMPLE: Actually, you were putting words in my mouth. I just do want to say something, I realize people who live in the world

can't help but think about the implications and what happens if we do this and what happens if we don't. But we are really supposed to think mostly about whether the therapy shows evidence of effectiveness and not so much about whether people will apply it more broadly than they should and use it off-label. It is not that we don't ever worry about that but we are really asking you to focus mostly on whether there is evidence of effectiveness. You know, the survival of companies is obviously of interest and whether people become depressed is also of interest but the main thing we need to do and we need your help with is figuring out whether there is actual evidence of effectiveness for this drug for what they claim.

DR. PRZEPIORKA: And having said that, I would just throw my two cents back in again and indicate that I was impressed with the fact that there are two trials, albeit not perfectly well designed but two trials with very similar results in terms of the magnitude and the direction of the effect, and most strikingly, similar results with

regard to outcome. It is very rare to see two trials, one right after the other, to have the same median survival in both the control group and the experimental group. I thought that was remarkable. Dr. D'Agostino?

DR. D'AGOSTINO: Again, the first study had 18 breast cancer patients in it. Really as a direction it didn't seem to inform the second study. So, retrospectively it is kind of interesting but prospectively it didn't inform the study at all, and I think it is saying that the third study they are running is exciting. What I tried to say at the end of my earlier spiel is forget the new trial--I have sympathy and am excited about it, but based on the data I think that there are too many questions with the post hoc aspect of this in the subset that wasn't prespecified for us to give a positive to this first question.

DR. PRZEPIORKA: Dr. Buckner?

DR. BUCKNER: I also have some questions about the efficacy issue per se from the data as

presented as far as response goes. There were some problems with the methodology in that there was not a control for dexamethasone. More than 10 percent of the scans were missing and, of the missing scans, the survival went in favor of the control arm rather than the experimental arm. The issue of no requirement for confirmed response perhaps could be argued but it doesn't strengthen the data on response. Furthermore, if we are really looking at the effect in the brain it would have been very reassuring to have some signal that people were living better with their brain disease in terms of progression either on clinical basis or radiologic basis, and we didn't see that, or some sense that the death rate from brain metastases was reduced. We didn't see that either. And, depending on how you interpret the quality of life data, the patient-reported data didn't necessarily seem to indicate strong evidence of benefit in the brain either. So, it is always a little unsettling when endpoints go in opposite directions and that is what I think we have here--I shouldn't say in

opposite directions but when one endpoint is not supported by multiple other endpoints.

DR. PRZEPIORKA: Other comments from the committee before we call the question? Dr. Grillo-Lopez?

DR. GRILLO-LOPEZ: I have a general comment about statistics and clinical research, a comment that applies not only to this particular discussion but perhaps to this morning's discussion and other discussions. As I look at the membership of this committee, I see that most of us are clinicians and most of us have been or are currently involved in the care of cancer patients. If the FDA had been interested exclusively in the statistics behind a clinical trial they would have only statisticians around this table but, in fact, the majority are clinicians.

I think the message the FDA is giving us is that they are interested in clinical input, in the input of those who are actually taking care of these patients and who can, yes, consider the statistics but perhaps consider those statistics as

a tool in the decision-making process, a process that also involves making clinical decisions based not necessarily on numerical or mathematical computations.

I think that today, particularly this morning, we have seen the extreme, very eloquently presented, that statistics can go to. Yes, it is not that we should ignore statistics but I think there is a limit to how much statistical analysis we can do and how complex that analysis can become because statistics is a science; it is based on numbers, it is based on mathematics. Clinical research is an art. It is based on patients and what happens to patients. And the more complex the statistical analysis, the more distant you get from the reality of clinical research, from the reality of what is happening to patients.

So, again, in making our decisions, in making or recommendations to the FDA on these issues we put the statistical analysis on the balance, the results of that analysis on one side of the balance but we also have to put our own

clinical opinion of the data and weigh that equally or perhaps even more strongly than what the numbers alone may say.

DR. PRZEPIORKA: Dr. D'Agostino?

DR. D'AGOSTINO: I thought this was a case where the statistical issues were quite simple actually. If they had declared that subgroup breast cancer as the primary group and had given the right allocation of p values, I think all our votes would be positive. They didn't do it so it is not really a complex statistics issue; it is a very simple statistics issue. It is an unfortunate thing. It may be a real result but because it was unspecified and because it was found only in a post hoc manner we have no way of judging it statistically and I am impressed that you feel you can judge it clinically without some sort of numerical basis, but that is your prerogative.

DR. PRZEPIORKA: Dr. Williams?

DR. GRILLO-LOPEZ: I said I was speaking in general.

DR. WILLIAMS: Donna, I just wanted to

clarify. You mentioned that the question was asking for evidence of efficacy. Substantial evidence I think is an important term. It doesn't just mean some evidence, it means enough evidence to approve it really. That is the term that is used in the regulation for approval, given that it is safe enough.

DR. PRZEPIORKA: Dr. Pazdur?

DR. PAZDUR: I wanted to address the decision-making process here because I have spent some time on this in my introductory comments. Here, again, we do have statisticians here, we do have clinicians, we have patients and everybody's voice is important. But there is an underlying process that is unifying decision-making process that all of you must come to.

Number one, is there an effect and is it adequately characterized? Number two, and you can only answer this question if number one is answered, and that is the clinical relevance. But you cannot make an inference of clinical relevance if you don't know what you are talking about or if

it is poorly characterized. It has to be there and that is how statisticians help us in making these decisions, especially in a randomized study.

Again, remember, this was a randomized study with a primary endpoint of survival with a population that was defined and basically we are looking at subpopulations that were not prespecified.

DR. PRZEPIORKA: Any other comments from the committee? Dr. Bukowski?

DR. BUKOWSKI: I would like to echo those comments. I think this was a well-designed and conducted study with predetermined endpoints that, unfortunately, were not met. I got a little bit confused between eligible and intent-to-treat populations but, notwithstanding, I think the results pretty much hold up. When you start to try to define clinical effect and forget the analyses that were presented I think it becomes an issue. Yes, there were two positive studies showing an effect in breast cancer but the way the data was obtained is less than optimal. So, I am concerned

by the findings and their importance. I think we certainly have to agree that r may well be an effect here but the data speak for themselves.

DR. PRZEPIORKA: Further comments before I call the question? Dr. Reaman?

DR. REAMAN: I just want to respond to Dr. Grillo-Lopez's statement since he characterized the committee as predominantly clinicians and that we are to sanction clinical research as an art rather than a science, and I, as a member of the committee, don't believe that we are here judging the arm of clinical research; it is science.

DR. PRZEPIORKA: I think everyone on the committee would agree with you but thank you for saying that. Other comments? If not, let's go to the first question, the survival analysis in the overall population was negative. Do the observed survival results from this single study in the subgroup of patients with breast cancer metastatic to the brain represent substantial evidence of RSR13 efficacy in this subgroup?

Let's start with Dr. Carpenter, please.

DR. CARPENTER: No.

MS. HAYLOCK: No.

DR. GEORGE: No.

DR. CHESON: No.

DR. DOROSHOW: No.

DR. RODRIGUEZ: No.

DR. PRZEPIORKA: Yes.

DR. REDMAN: No.

DR. REAMAN: No.

DR. TAYLOR: No.

DR. MARTINO: No.

DR. BUCKNER: No.

DR. BUKOWSKI: No.

DR. D'AGOSTINO: No.

DR. HUSSAIN: No.

DR. MORTIMER: No.

MS. COMPAGNI-PORTIS: No.

DR. PRZEPIORKA: One yes, 16 no. You have your answer and you don't want us to discuss the second question. Any other information that you want from us?

DR. PAZDUR: No.

DR. PRZEPIORKA: Thank you very much. I call this meeting adjourned and thank you to all the committee members.

[Whereupon, the proceedings were adjourned.]

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