This transcript has not been edited or corrected, except where relevant for the deletion of materials not releasable under the Freedom of Information Act. Accordingly, the Food and Drug Administration makes no representation as to its accuracy.

02'50 99 APR 15 A11:14

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE

61st Meeting

(Open Session)

Tuesday,
March 23, 1999

Versailles Ballroom
Holiday Inn Bethesda
8120 Wisconsin Avenue
Bethesda, Maryland

IN ATTENDANCE:

RICHARD L. SCHILSKY, M.D., Acting Chair
Director, University of Chicago
Cancer Research Center
The University of Chicago Medical Center
5841 South Maryland Avenue, MC1140
Chicago, Illinois 60637

KAREN M. TEMPLETON-SOMERS, Ph.D., Executive Secretary
Advisors & Consultants Staff, HFD-21
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

KATHY S. ALBAIN, M.D.
Professor of Medicine
Division of Hematology/Oncology
Loyola University Medical Center
Cancer Center, Room 109
2160 South First Avenue
Maywood, Illinois 60153

DAVID H. JOHNSON, M.D.
Director, Division of Medical Oncology
Department of Medicine
Vanderbilt University Medical School
1956 The Vanderbilt Clinic
Nashville, Tennessee 37232

JAMES E. KROOK, M.D.
Principal Investigator
Duluth CCOP
400 East Third Street
Duluth, Minnesota 55805

STACY R. NERENSTONE, M.D.
Associate Clinical Professor
Oncology Associates, P.C.
Helen & Harry Gray Cancer Center
Hartford Hospital
85 Retreat Avenue
Hartford, Connecticut 06106

IN ATTENDANCE: (Continued)

ROBERT OZOLS, M.D., Ph.D.
Senior Vice President, Med Sciences
Fox Chase Cancer Center
7701 Burholme Avenue
Philadelphia, Pennsylvania 19111

DEREK RAGHAVAN, M.D., Ph.D.
Associate Director
University of Southern California
Norris Comprehensive Cancer Center
Head of Medical Oncology
1441 Eastlake Avenue, Room 3450
Los Angeles, California 90033

VICTOR M. SANTANA, M.D.
Associate Professor
Department of Hematology/Oncology
The University of Tennessee
332 North Lauderdale
Memphis, Tennessee 38101

RICHARD M. SIMON, D.Sc.
Chief, Biometric Research Branch
National Cancer Institute
Executive Plaza North, Room 739
Bethesda, Maryland 20892

GEORGE W. SLEDGE, JR., M.D.
Professor
Departments of Medicine and Pathology
Indiana University School of Medicine
Indiana Cancer Pavilion
535 Barnhill Drive, Room 473
Indianapolis, Indiana 46202

Also Present

KENNETH McDONOUGH, Patient Representative
North Huntingdon, Pennsylvania

C O N T E N T S

	PAGE
Call to Order and Opening Remarks	
Richard Schilsky, M.D.	6
Introduction of Committee	6
Conflict of Interest Statement	
Karen M. Templeton-Somers, Ph.D.	7
Sponsor Presentation of NDA 21-051, Temodal (temozolomide), Schering Corporation	
Introduction	
Colin Turnbull, Ph.D.	9
Disease Background	
John Kirkwood, M.D.	12
Pharmacokinetics/Metabolism	
David Cutler, M.D.	18
Clinical Data	
Robert Spiegel, M.D.	22
Clinical Perspective	
Hilary Calvert, M.D.	38
Summary	
Robert Spiegel, M.D.	43
Questions from the Committee	44

C O N T E N T S

	PAGE
FDA Presentation	
Martin Cohen, M.D.	79
Questions from the Committee	96
Committee Discussion and Vote	108

P R O C E E D I N G S (8:07 a.m.)

DR. TEMPLETON-SOMERS: We're ready to start now.

I'd like to introduce Dr. Richard Schilsky, who will be the acting chair for this meeting. Dr. Dutcher can't be here.

I'd also like to announce that our consumer rep, Carolyn Beaman, became ill yesterday. She's okay now, but could not make it to this meeting. We did attempt to find a last-minute replacement, but were not successful, so we will be going without a consumer rep for this morning's meeting.

Dr. Schilsky?

DR. SCHILSKY: Thank you.

Good morning. I think we should begin with introductions of the committee members, so perhaps we can start with Dr. Johnson.

DR. DAVID JOHNSON: David Johnson, medical oncologist, Vanderbilt University.

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

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

MR. McDONOUGH: Kenneth McDonough, patient

representative, Stage 3 melanoma survivor.

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

DR. OZOLS: Bob Ozols, medical oncologist, Fox Chase Cancer Center, Philadelphia.

DR. SCHILSKY: I'm Rick Schilsky. I'm a medical oncologist from the University of Chicago.

DR. TEMPLETON-SOMERS: Karen Somers, executive secretary to the committee, FDA.

DR. KROOK: Jim Krook, medical oncologist, Duluth CCOP.

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

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

DR. JUSTICE: Bob Justice, acting director, Division of Oncology Drug Products, FDA.

DR. COHEN: Martin Cohen, medical oncologist, FDA.

DR. JOHN JOHNSON: John Johnson, clinical team leader, FDA.

DR. SCHILSKY: Okay. I think Dr. Somers has a conflict of interest statement.

DR. TEMPLETON-SOMERS: The following announcement addresses the issue of conflict of interest

with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting:

Based on the submitted agenda for the meeting and all financial interests reported by the participants, it has been determined that all interests and firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for conflict of interest at this meeting, with the following exceptions:

In accordance with 18 USC, Section 208(b)(3), full waivers have been granted to Dr. Kathy Albain, Dr. Derek Raghavan, Dr. Victor Santana, and Dr. George Sledge. A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A30 of the Parklawn Building.

In addition, we would like to disclose that Dr. George Sledge, Dr. Derek Raghavan, Dr. Robert Ozols, and Dr. Richard Schilsky have reported involvements in Bristol Myers-Squibb, the sponsor of a competing product to Temodal, which do not constitute a financial interest in the particular matter within the meaning of 18 USC, Section 208, but which could create the appearance of a conflict. The agency has determined, notwithstanding these interests, that the interest in the government in their participation

outweighs the concern that the integrity of the agency's programs and operations may be questioned. Therefore, these individuals may participate fully in today's discussion and vote concerning Temodal.

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

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

Thank you.

DR. SCHILSKY: Thank you.

I'm told that no one has requested previously an opportunity to speak before the committee, but are there any members of the audience who wish to make a public statement at this time?

(No response.)

DR. SCHILSKY: If not, I guess we'll proceed directly to the sponsor's presentation.

DR. TURNBULL: Good morning. I'm Colin Turnbull, vice president, oncology clinical research,

Schering-Plough Research Institute. On behalf of Schering-Plough, I would like to thank the FDA for giving us the opportunity to present temozolomide to this ODAC meeting today.

This ODAC is, of course, familiar with temozolomide, having considered the drug 2 months ago for the glioblastoma multiform and anaplastic astrocytoma indications, recommending an accelerated approval for anaplastic astrocytoma.

Can I have the next slide, please.

The indication we are seeking today for temozolomide is for the first-line treatment of metastatic melanoma.

Next slide, please.

At the outset, we would like to acknowledge that we recognize that temozolomide is not a breakthrough in the treatment of metastatic melanoma. Temozolomide is essentially an analog of the standard melanoma treatment, dacarbazine, or DTIC, with which it shares the same active moiety, the monomithialtrizine, MTIC. In contrast to dacarbazine, however, which has to be administered intravenously and which requires hepatic metabolism for its activation to MTIC, temozolomide is orally administered with 100 percent bioavailability, and it forms the active moiety MTIC spontaneously.

Next slide, please.

This common mechanism of action with dacarbazine, together with observations of objective tumor responses with temozolomide in Phase I and II trials in patients with metastatic melanoma and the fact that this is a convenient oral drug, provided the impetus for the pivotal trial comparing temozolomide to dacarbazine, which we will be presenting to you today.

Next slide, please.

We will in particular be addressing three key issues in the presentations that follow. First, in spite of the fact that the trial results did not quite meet the statistical criteria for demonstrating superiority to DTIC on survival, we will make the case for the pivotal trial having convincingly demonstrated effectiveness of temozolomide and at least equivalence to dacarbazine, and we will address the issue of the validity of dacarbazine as a comparator in this disease against the background that even though it is standard palliative treatment for metastatic melanoma, there have been no trials comparing dacarbazine to observation or placebo.

Next slide, please.

Dr. John Kirkwood will now provide a brief overview of metastatic melanoma and its treatment, and will review the available data on the efficacy of dacarbazine in

this disease. Dr. David Cutler will then describe the mechanism of action of temozolomide and dacarbazine, together with the pharmacokinetics of the active moiety MTIC, following their respective administration. Dr. Robert Spiegel will present the pivotal clinical trial, and following a clinical perspective on temozolomide and melanoma from Dr. Hilary Calvert, who was one of the U.K. investigators on this pivotal trial, Dr. Spiegel will lead the discussion.

Dr. Kirkwood?

DR. KIRKWOOD: Good morning. I'm John Kirkwood, vice chairman of medicine and director of the Melanoma Center at the University of Pittsburgh Cancer Institute, as well as the chairman of the Eastern Cooperative Oncology Group's melanoma committee. I've been asked to provide a disease overview today on melanoma for this committee.

The incidence and death rate from melanoma have risen continuously for the time in which we have good statistical evidence in the U.S., as well as many other countries, and the rising death rate from this tumor is particularly seen amongst elderly males over 60, and its continuing role as the leading cause of cancer death among solid tumors in women 25 to 30 adds substantial relevance to discussions we will talk about today.

Next slide, please.

In melanoma the prognostic factors related to disease stage are paramount in guiding us with respect to prognosis. The prognosis for localized Stage 1 and 2 disease is the most favorable for lymph node involvement, Stage 3 disease more ominous, but for Stage 4 disease the monotonous history of all therapies that we have pursued in this disease and the median survival of 6 months has been unchanged for decades in this disease.

Next slide, please.

For Stage 4 melanoma the prognosis is predicted by the site of metastasis, where visceral disease is more ominous than non-visceral disease, and where hepatic disease of all sites outside the brain is the most ominous. Performance status and gender are additional prognostic factors which were used for the stratification of the studies of temozolomide that will be presented today. In addition, the number of metastatic sites and the duration of remission before metastasis are recognized prognostic factors in Stage 4 melanoma.

Next slide, please.

The median survival of melanoma in Stage 4 is 6 months, with a range between 5 and 9 months. There is significant variability for individual patients and between series, dependent upon the prognostic factors for each.

There are long-term survivors ranging between 1.5 and 5 percent in repetitive series in the literature.

Next slide, please.

The goals of treatment for the oncologist and for patients with melanoma are several. For many the goal is palliation of symptoms, because that is all that we can convincingly say with our agents at hand, and preservation of quality of life and toxicity, therefore, are key factors in the decisions for palliatherapy. For some patients an effort to prolong survival is the goal, and for these patients modest potential gains with available agents allow us to consider this in a factored analysis with the quality of life. For a small fraction of patients the goal is cure, and for these patients toxicity may become irrelevant.

Next slide, please.

The treatment options for patients with metastatic Stage 4 melanoma range from observation for patients who are asymptomatic and have indolent disease of a variety of non-visceral sites to surgical resection of solitary disease in single organs or sometimes more than one organ system. For patients with bone and brain metastatic disease, radiation therapy is the standard recourse, and for patients with multiorgan involvement, systemic therapy with immunotherapies, including

interleukin-2, chemotherapy -- dacarbazine in particular, and combinations -- as well as biochemotherapy are considered.

Of all of the agents that we have available for the treatment of melanoma, as I've mentioned, dacarbazine is the one with which we have the greatest experience. For dacarbazine treatment, the overall response rates range between 10 and 20 percent, the complete response rates between 2 and 5 percent, and median duration of response between 3 and 6 months. Approximately one-quarter of responses are complete.

Next slide, please.

In a pooled analysis of 22 randomized studies, 1,095 patients treated with dacarbazine, the cumulative mean response rate was found to be 16.2 percent, the 95 percent confidence intervals between 14 percent and 18 percent, and response rates range between 6 and 25 percent.

Next slide, please.

Unfortunately, in the literature there are no comparisons between dacarbazine and placebo or best supportive care. This is, as we all recognize, the only licensed cytotoxic agent for the treatment of metastatic melanoma, and it is commonly, therefore, used as a single agent for the treatment of this disease. It is also, therefore, commonly included in combinations for treatment

of this disease.

The next slide shows five randomized studies in the literature, the only that we could find in which dacarbazine was compared to a non-dacarbazine combination or single agent. For these five studies, it's notable that for the three in which there was survival data reported, dacarbazine beat the comparator, BCNU/vincristine, BVP in our study from Yale, BCNU/vincristine from the Southwest Oncology Group, and for the largest of these comparative studies between dacarbazine and other agents, that against TIC mustard performed in 1976, the response rate was three-fold that for TIC mustard, 18 percent versus 6 percent, but there are no survival data available.

Next slide, please.

In our own Eastern Cooperative Oncology Group, in a study reported in June of last year, dacarbazine was the pillar drug in a 2x2 factorial design study in which we attempted to show the synergism with either interferon alpha or tamoxifen. For this study, it is notable that no combination was shown to be superior in terms of time to progression or overall survival, but the overall survival values, best in this portrayal here for dacarbazine, are notable.

Next slide, please.

It is notable that for dacarbazine, then, no

single agent has been shown to be superior to this agent in randomized, controlled trials in terms of either response rate or survival, and no combination has been shown to be superior in randomized controlled trials.

At ASCO this year Scott will report our M91/ECOG/Memorial Sloan-Kettering/Hoosier Oncology Group study, in which dacarbazine was compared against the commonplace Dartmouth combination, including tamoxifen, BCNU, cisplatin, and dacarbazine, and will again show no superiority for this combination against dacarbazine.

Our own current cisplatin, vinblastine, dacarbazine, interleukin-2, and interferon alpha combination, so-called biochemotherapy, was actually proposed originally to be compared against dacarbazine, and it was the unanimous vote of the Eastern Cooperative Oncology Group and Southwest Oncology Group melanoma committees to compare this polybiochemotherapy regimen against dacarbazine. CVD was adopted as the reference only for reasons of scientific purity in this final trial.

Therefore, when we consider dacarbazine, toxicity of this agent is important. It requires 1 to 5 days of intravenous administration, with visits to the clinic for every patient who gets treated. It is associated with a frequency of up to one-third of phlebitis and local pain at the site of administration, which has led

to a whole series of efforts to try to reduce local regional toxicity at the site of infusion with coverage of the I.V. lines. It is associated with nausea and vomiting, which is easily now controlled with antiemetics, but also with neutropenia and veno-occlusive disease in a rare patient.

In summary, dacarbazine provides useful palliation for symptomatic metastatic disease. It has consistent activity against melanoma across a number of trials that I've reviewed. It is the only approved chemotherapeutic agent for Stage 4 melanoma, and it is the standard of care for this disease in the community. It is a component of nearly all combinations for this reason, and I believe it is the only appropriate comparator for new agents such as temozolomide, to be presented today.

Thank you.

The next presentation will be given by Dr. David Cutler on the pharmacokinetics of this agent.

DR. CUTLER: Thank you very much. I'm Dr. David Cutler from the Department of Clinical Pharmacology at Schering-Plough. I would like to spend the next few minutes contrasting aspects of the metabolism of temozolomide and dacarbazine and discussing the implications of the metabolic versus chemical transformation of these two similarly structured agents to

their active species MTIC. And, finally, I would like to briefly review the salient pharmacokinetics of MTIC in patients enrolled in the pivotal study I95-018.

Next slide.

Temozolomide is an orally bioavailable cytotoxic agent of the amidotetrazene class, and it's an analog of the approved agent dacarbazine. Both agents are inactive prodrugs of the active alkylating agent MTIC. MTIC exerts effect primarily by resulting in DNA alkylation and transmethylation of the 06 site of guanine. Temozolomide is unique in that its conversion to MTIC is a non-biologically mediated, pH-dependent chemical reaction which occurs rapidly in vitro and will occur in vivo, with a half-life of 1.8 hours in all tissues in which temozolomide is present. In contrast, dacarbazine, a structurally related agent, has to be converted metabolically in the liver through a saturable process to the agent MTIC, which then can effect its action.

The importance of this difference can be seen if one makes a simplified compartmental picture of the body. This rather busy slide can be broken into two halves, with the upper half describing the compartmentalization of dacarbazine and the bottom half the compartmentalization after administration of temozolomide.

For dacarbazine after I.V. administration, the

dose ends up circulating in the bloodstream. Along its concentration gradient, dacarbazine will diffuse into the liver, where a portion will be converted to the active agent MTIC. MTIC then will diffuse, again, along its concentration gradient from the high concentrations in the liver, into the bloodstream, and from there be transported, again, through the bloodstream and along its concentration gradient into the peripheral tissues and the tumor, where it can have its effect.

Temozolomide, on the other hand, after oral administration is approximately 100 percent orally bioavailable. Temozolomide enters the bloodstream, and some of it will diffuse into the liver along the concentration gradient and be converted in the liver spontaneously to MTIC. This reaction, however, will occur also locally in the blood, where there will be local generation of MTIC, and temozolomide will diffuse into tissues, which will result, again, in the tissues and tumor local generation of MTIC. The net result of this is higher blood level of the active agent MTIC and, by inference, higher tissue and tumor concentrations of MTIC generated locally at the tumor site.

Next slide, please.

In the pivotal study I95-018, which will be presented in detail later today, a subgroup of patients who

were enrolled at sites were able to perform pharmacokinetics at multiple-dose pharmacokinetics of MTIC determined on Day 4 of administration. The doses that were used in the study for temozolomide were 200 mg/m^2 per day by oral administration for 5 days, and for dacarbazine, 250 mg/m^2 per day by I.V. administration for 5 days.

Next slide, please.

This slide is a concentration time curve of the concentrations of MTIC observed after administration of temozolomide, in the open circles in white, and in the closed yellow circles, after I.V. administration of 250 milligrams of dacarbazine. One can see that although one administered lower doses of temozolomide orally, there was a higher MTIC concentration generated in the blood. If one looks in the upper right-hand corner at the AUC, area under the concentration time curve, the exposure to MTIC after temozolomide administration was approximately 90 to 100 percent greater than that observed after administration of 250 mg/m^2 of dacarbazine.

Next slide, please.

In summary, I'd like to conclude that temozolomide and dacarbazine are chemically related prodrugs of the active compound MTIC, and that compared with I.V. dacarbazine, the non-metabolic conversion of temozolomide to the active species MTIC results in

increased concentrations of MTIC in the plasma and, by inference, in the peripheral tissues and in the tumors.

I'd like to now turn over the podium to Dr. Robert Spiegel, who will discuss the safety and efficacy data from the pivotal trial.

DR. SPIEGEL: Thank you, David.

I'm Dr. Robert Spiegel, senior vice president of medical affairs at Schering-Plough, and I'd like to spend the next 20 minutes or so going through the design and the results of the pivotal trial I95-018, a randomized Phase III study of temozolomide versus dacarbazine in patients with first presentation of metastatic melanoma.

Next slide.

The key characteristics of this study include the following. The population was to recruit patients with first presentation of metastatic melanoma. It was a randomized, controlled trial conducted in 34 sites in 14 countries. Notably, we did not utilize sites in the U.S., as at the time in 1995 that this study was being designed, there were three large competing trials either under way or about to start at major centers in the U.S. Enrollment was completed with 305 patients accrued during the period July 1995 to February 1997, and at the end of enrollment 156 patients had been randomized to temozolomide versus 149 to dacarbazine. Components of the trial design included

central randomization and stratification for prognostic factors.

It was noted by the FDA in their briefing book that we did not seek specific consultation on the design of this trial, and at the time, in contrast to the glioma program, we did not feel there were substantial issues, and the trial design was actually quite straightforward, and I'd like to discuss those elements of the trial design in the next few slides.

The primary endpoint selected for this study was overall survival in the intent-to-treat population. The protocol also specified two secondary endpoints, progression-free survival and response rate. The statistical design was premised on a target hazard ratio of 1.5. This was chosen on the assumption that dacarbazine would result in a 6-month median survival, and that an observed 9-month median survival with temozolomide would have 80 percent power to detect a difference, which would involve recruitment of 260 patients and an analysis when 210 deaths had occurred. The protocol also specified two interim analyses and a calculation that a final P value would have to be adjusted to the 0.045 level to show significance.

Next slide.

Key eligibility criteria included the

following: histologically confirmed metastatic melanoma at first presentation, with at least one measurable lesion; no previous systemic treatment for metastatic disease was permitted, although patients were allowed to have had one prior adjuvant regimen; and no CNS metastases were to be present at the time of study entry.

Next slide.

This slide describes the trial schema. As mentioned, stratification was done for three factors prior to randomization: patient gender, performance status, and disease site. Patients were then randomized to one of two treatment regimens. Temozolomide, in the schedule that was just described by Dr. Cutler, was to be administered as a 200 mg/m^2 oral dose for 5 days, to be repeated every 28 days. Patients on that treatment arm had clinical assessment performed every 4 weeks and radiographic assessment every 8 weeks. Patients randomized to dacarbazine received intravenous dacarbazine at its approved dose of 250 mg/m^2 in a 5-day schedule, repeated every 21 days. Patients on that arm of the study had clinical assessment performed every 3 weeks and radiographic assessment every 6 weeks.

Now, the consequences of this difference in the schedule of tumor assessment in the treatment arms will be addressed in my subsequent slides.

Next slide.

I'd like to spend a moment discussing the demographics of the population that was enrolled, using the intent-to-treat population. There are a number of interesting features on this slide that I'd like to point out, beginning with the age. The median age in this study was 58, and of interest, this is about 10 years older than most of the studies in the literature, and it's about 15 years older than the patients who were in the IL-2 pivotal trials. It's also noteworthy that the age of patients enrolled in this study actually went into their 80s, and I'm going to show you some of the responses that occurred even in patients who were in their 70s and 80s. But it does show that this was an older population in general than the reference literature.

Male gender is also known to be a poorer prognostic factor than female gender. In this study about 60 percent of the patients recruited were males. Nine percent more were randomized to temozolomide than dacarbazine, but this was not statistically significant. Also, performance status is a very strong prognostic factor in this disease, and of note about 45 percent of the patients entered into this trial were WHO Grade 1 or 2, simply showing that we did not recruit a particularly good prognosis group in this study.

The next slide shows that somewhat further by looking at the baseline disease characteristics of the recruited population, and almost a third of the patients, evenly distributed, presented for this study with metastatic disease to the liver, which is a poorer prognostic group, and only 8 percent of the patients had subcutaneous or skin-only disease. We also looked at time from initial diagnosis to metastatic disease and time from metastatic disease to randomization, and these were equally balanced between the treatment arms.

Next slide.

This slide shows the pivotal endpoint prescribed in the protocol -- that is, the overall survival in the intent-to-treat population. I would point out that in this result the curves separate early and remain separated, and the median survival estimate from these Kaplan-Meier curves yields a time of median survival of 7.7 months for temozolomide versus 6.4 months for dacarbazine. This has a P value of 0.2, a hazard ratio of 1.18, and a confidence interval around that hazard ratio that ranges from 0.92 to 1.52.

I'd like to spend a moment in the next slide discussing the meaning of this hazard ratio, the P value, and the 95 percent confidence interval around the hazard ratio. If one wants to prove superiority, the hazard ratio

needs to be greater than 1. We were greater than 1 at the 1.18 level, but the P value was 0.2, meaning that this could have happened by chance at the 0.2 level and not at the prespecified 0.045 level, the corrected value for statistical significance.

Now, if one is not excluded by the lower limit of the confidence interval, one cannot prove superiority. However, the question arises in the absence of proof of superiority, what is the threshold for proving a lack of inferiority? In bioequivalence this is conventionally set at the 0.8 level, or a more rigorous standard might be to exclude 0.9. In this study the lower limit of the 95 percent confidence interval is 0.92. This means since this is a two-sided test, there's a 2.5 percent chance that temozolomide could be 8 percent worse than DTIC. This amount of difference, however, amounts to only 14 days.

We, therefore, believe a conclusion can be made of equivalence, justified by the following: that the lower bound of the 95 percent confidence interval was 0.92, which is above the usual convention for equivalence, and that the worst-case scenario of 8 percent inferiority equates to approximately a 14-day difference. The legitimacy of this equivalence test has been challenged in the FDA's review. I should say that we have discussed these results with expert statistical consultants who have advised us that

when the point estimate for superiority is so close, it is not inappropriate to test for equivalence.

Moreover, what I'd like to now review are a few other aspects of this survival outcome that demonstrate a consistency of the effect seen.

Next slide.

This slide depicts a very complete subgroup analysis for the overall survival, looking at hazard ratios. It shows that in both large groups and small groups, in groups that have both favorable and unfavorable prognostic factors, there is a consistent trend on the point estimate showing improvement trending toward temozolomide over dacarbazine in all but a single subgroup, and this single subgroup is very close to unity.

Next slide.

We also thought it would be important, although the intent-to-treat was the primary analysis, to assure ourselves and to assure you that there was no difference when one looked at a legitimate treated eligible population of those patients who met entry criteria and actually received the study drug to which they were randomized. Therefore, before the database was locked, the sponsor made an analysis of what we considered to be logical and significant categories that should be excluded from a treated eligible population.

What we found was that there were seven patients who had the wrong diagnosis at entry or did not have adequate demonstration of metastatic disease in the temozolomide group, and six patients in the dacarbazine group who met the same criteria. There were an additional five patients in temozolomide and seven in dacarbazine who never received study drug after randomization. This, therefore, defined a treated eligible population of 144 patients on temozolomide and 136 on dacarbazine, and in the next slide I'd like to show the results of an analysis of that group.

Before doing that, let me remind you again of the analysis of the intent-to-treat population, which showed median survival rates of 7.7 versus 6.4, significance only at the 0.2 level, and a hazard ratio of 1.18. The next line shows the results of a similar overall survival analysis only in the treated eligible population, and the results widen, with the median survival for temozolomide in this group reaching 7.9 versus 5.7 in the dacarbazine group, a P value of 0.054, which still does not reach the adjusted rate of statistical significance, but a confidence interval that gets closer to the value of 1.

I've also on this slide included for you the FDA's assessment, and we have simulated the FDA evaluation of an eligible population, which would exclude another 25

patients. In the FDA's process, they applied a very strict criteria from the protocol of inclusion and exclusion criteria and included to be excluded those patients whose laboratory values just missed entry criteria. For example, the criteria for entry in the protocol required a hemoglobin of 10. Any patient with hemoglobins of even 9.8 or 9.9 were excluded in this latter analysis by the FDA.

Interestingly, even in this population the results are very similar, 7.9 goes to 7.7 as the median survival for the temozolomide group, and the dacarbazine group from 5.7 to 5.8. The statistical significance is even less, of course, because the denominator is less. However, we believe this analysis also shows a consistency of the results, although we certainly agree that the primary analysis specified in the protocol was the intent-to-treat.

Next slide.

I'd now like to turn to the first of the secondary analyses prespecified in the protocol, which would be progression-free survival. Looking at this curve, the curves begin to separate close to the time of the first evaluation, between the first and second months. It separates at that point, and it stays separated with a 6 to 10 percent range of separation, indicating that more patients in the temozolomide group were still progression-

free throughout the study. As the FDA notes, however, the clinical meaningfulness of this median difference is questionable.

This is also an analysis which is subject to the potential bias of differences in the time of evaluation. In an attempt to analyze whether this bias may in fact have played a strong role, we did look specifically at the 2-month time point, and as you will note, at 2 months both treatment groups had had their first radiographic assessment, and both treatment groups had gone through two clinical assessments, therefore making their evaluation at that point relatively equivalent or, if anything, perhaps biasing against temozolomide. At 2 months the progression-free survival favored temozolomide at a 39 percent rate versus a 30 percent rate for dacarbazine.

Next slide.

The other secondary endpoint in the protocol, and one that the FDA has asked you to evaluate subsequently today, is the objective response rate. On this slide, I've portrayed both the sponsor's analysis and the FDA analysis of objective response rate. On the left-hand side, our results show that we determine there to be four complete responders in the temozolomide group and four complete responders to dacarbazine. We also assess there to be 17

partial responses versus 14, for overall response rates of 13.5 percent versus 12.1 percent.

The FDA did an independent assessment of patient eligibility and of tumor measurements. They confirmed that there were four complete responders in the temozolomide and the dacarbazine group; however, they determined that there were 15 and 10 partial responses, leading to comparative response rates overall of 12.2 percent versus 9.4 percent. This is a relatively low rate compared to the medical literature on dacarbazine, but it is consistent with the poorer prognostic indicators that I mentioned in the demographics of the population recruited to the study.

Now, I've shown here the 95 percent confidence intervals around each of these response rates, and in the sponsor's analysis the 13.5 percent could range from 8.1 to 18.9, and the 12.1 could range from 6.9 to 17.3. These rates can be manipulated to calculate odds ratios of 1.377, and as noted in the FDA's briefing book, this means that temozolomide could, in truth, have anywhere from 60 percent of the activity of dacarbazine to up to 2.7 times the activity of dacarbazine.

I must say as a clinical oncologist, this is not the conventional way that I've been trained to look at what I consider to be relatively equal response rates in a

relatively large patient population, and I interpret these response rates, together with survival and the quality of the responses, to mean that there is real activity here, and as I think you will appreciate, I'd like to show you a little more detail about why I believe this activity is real.

Next slide.

We've looked specifically at the duration of the response. This slide shows the median objective response duration for the responders. I'm presenting here the FDA analysis of this result. Among the 19 temozolomide patients, the median response duration was 5.5 months. Among the 14 dacarbazine responders, the median response was 3.22 months. These, of course, are small numbers, but they seem to indicate that a longer duration of response was obtained in those patients who were randomized to temozolomide, and the FDA has used a log rank test to calculate a P value of 0.003 around this statistic.

Next slide.

Perhaps more meaningfully to the oncologists on the committee today would be to look at some of the specifics of the complete and partial responders, and on this and the following slide, I've given somewhat more detail, and I realize this is a little busy, but I hope it's helpful for you. I should say that this represents

data that was updated in March of 1999, but there are a few interesting features. One is the age of the patients. There are a number of elderly patients here in their 70s and 80s who became complete responders, and I think it's notable that these patients would be very unlikely candidates for IL-2 treatment and probably unlikely candidates for combination chemotherapy, which would be more toxic than single-agent therapy. In the temozolomide group, three of the four complete responders are alive at greater than 3 years after randomization, and also of note, two of the four complete responders on temozolomide had visceral disease at study entry, and two of them had skin or subcutaneous disease only.

The next slide is even busier. It shows the 17 partial responders determined by the sponsor. Again, many of these patients had visceral disease at entry. It's notable that three of these patients have ongoing partial responses of greater than 2.5 years duration. And, again, my personal assessment is that this type of response pattern would not happen by chance alone, but reflects an active drug.

Next slide.

We also looked at the survival of responders at fixed endpoints which are of usual clinical interest, 12, 18, and 24 months. This gives a snapshot of the survival

benefit at fixed endpoints. Again, this was not prespecified in the protocol, but we thought it was worthwhile to show that the responses appeared to be meaningful in those patients who became responders: at 12 months 90 percent of the 19 temozolomide objective responders versus 72 percent of those in dacarbazine, at 18 months the statistic was 71 percent versus 56 percent, and at 24 months 62 percent versus 36 percent.

If one calculates the overall median survival for all the responders, this figure, which is estimated because median survival has not been reached yet, but takes a worst-case analysis, shows 26.1 months for the temozolomide group versus 20.9 months, again suggesting that responders to temozolomide might have longer duration response and perhaps longer survival.

I would now like to turn briefly to the safety observed in this indication and in this study.

Next slide.

One measure of safety is the number of patients who require dose reduction. This slide shows that among the temozolomide patients, 85 percent were able to complete their treatment at full dose, and an additional 12 percent required a one-dose level of reduction, for a total accounting for 97 percent of all the patients. Only 3 percent required a dose reduction two levels down. This is

similar to the dacarbazine outcome, which, of course, the clinicians have more experience administering. Ninety-three percent were able to complete the study at their full dose, 3 percent required a one-dose level of reduction, and 4 percent a two-dose level of reduction. Overall only a handful of patients dropped out due to treatment-related adverse events, five on the temozolomide arm versus seven in dacarbazine.

Next slide.

Another traditional assessment of tolerability would be the number of adverse events of Grade 3 or 4 that occurred at any time during treatment, and I want to point out that this slide and the briefing book that we have prepared does show adverse events at any time. With that in mind, we actually think it's noteworthy that although the incidence of nausea and vomiting appears similar in the analysis that was performed, most of the vomiting with temozolomide occurred during the first cycle, which was a period when fewer patients on the temozolomide arm were receiving prophylactic antiemetics than were those patients who were treated with dacarbazine, where it was permitted in the protocol.

Next slide.

As Dr. Kirkwood mentioned in his review, myelotoxicity is a well-known consequence of dacarbazine.

This slide shows the number of patients who change from a Grade 0 or 2 baseline hematologic value to a Grade 3 or 4 during treatment, and we show a relatively similar pattern of myelotoxicity, with neutropenia occurring in 22 percent of the patients on temozolomide versus 15 percent on dacarbazine. There was no difference in the incidence of neutropenia-related infections or in the use of growth factors, which occurred in about nine patients on each arm of the study. The thrombocytopenia was similar in its quality and in the number of patients who were noted to have decreases in their platelets throughout the treatment cycles.

Next slide.

In summary, we believe the melanoma trial shows an acceptable safety profile for temozolomide and comparable safety to dacarbazine in the rate of overall adverse events, in a similar character and number of Grade 3/4 adverse events, the myelotoxicity profile, and in a similar low dropout rate. Also of note, this is a similar safety profile to the overall experience which we have accrued with temozolomide in over 1,017 patients, which was reviewed with this committee in the context of glioma at our last meeting.

Next slide.

We believe one can conclude from my summary of

effectiveness that there's a consistent evidence here that this drug is effective. Temozolomide and dacarbazine are both active, as indicated by the objective responses. Temozolomide response durations were longer than dacarbazine. Progression-free survival favored temozolomide. The overall survival estimate demonstrates that temozolomide is at least equivalent to dacarbazine and not meaningfully worse. And, finally, further speaking to the consistency of the result, the overall survival results are consistently better in almost all of the subgroups that were analyzed.

I'd now like to ask Dr. Hilary Calvert to provide a clinical perspective on these results and how they fit into the current treatment of melanoma.

DR. CALVERT: Thank you very much.

Perhaps I'd better introduce myself. I'm the professor of medical oncology and the head of the Cancer Research Unit in the Northern Centre for Cancer Treatment, which is in Newcastle in the United Kingdom. There we have an oncology practice and also do a number of Phase I and Phase II trials. In addition to that, I'm the chairman of the Cancer Research Campaign's Phase I/II committee, which is the national U.K. charity that organizes Phase I and II trials throughout the U.K.

Could I have the next slide, please.

As was mentioned, I was an investigator not just on the 018 pivotal study that we've had described, but also on two Phase II studies prior to that, which were conducted by the CRC. I'd just like to give you some of the results of those.

Both of these studies had a population which accepted patients with CNS metastases, which potentially made the patients at slightly worse risk than those on the pivotal study. The regimen was the same, 200 mg/m^2 per day, and the first study was a straight Phase II to look for activity, and in the study the overall response rate was 21 percent. Now, in fact, as the person supervising the study as the chairman of the committee, the investigator-reported response rate that we got here was something over 30 percent, but it dropped to 21 percent when the responses were externally reviewed, and, of course, the reason for that was that there were quite a lot of patients who had a tumor reduction which didn't meet the criteria for partial response. The median response duration was 5 months, which was very similar to the response durations seen in the randomized trial.

In Study 028, this study was essentially done as a biopsy study to look for biochemical parameters to response to temozolomide, but the clinical results are just shown here, and they provided a response rate of 13

percent, median response duration of 6 months, and were consistent with the other studies.

Could I have the next slide?

Now, just to put you in the perspective for our own practice in the Northern Centre for Cancer Treatment, which would probably be quite typical for many other practices around Europe, we see 30 to 40 patients with metastatic malignant melanoma a year, and our normal first-line treatment would either be dacarbazine or an investigational drug, and, of course, the reason for the interest in investigational drugs is because we wish to find something better than existing therapy. Unfortunately, of all the many Phase II studies of investigational drugs that I've done over the years, the only one that's ever come out with substantial activity was the temozolomide Phase II.

Significant responses are undoubtedly seen to temozolomide, and although the percentage is low, I think it's important to remember that for the patient who gets them, this is a significant event, and you can obviously see clinical benefit to the patients who do respond. And in my experience, although there's a lot of discussion of spontaneous remissions in melanoma, in the last 18 years of this type of practice, I've actually only personally observed three spontaneous remissions.

Could I have the next slide, please.

I'd like to comment on whether this trial design was appropriate, and my feeling in retrospect is that in fact the trial design of Study 018 was somewhat overambitious looking for 50 percent improvement in survival time, and the reason I believe this is because we can expect a response rate in the region of 15 to 20 percent, and if you look at other areas of oncology, where survival-based trials have been done with drugs that only produce a 15 to 20 percent response rate, it's extremely rare to be able to detect an improvement in survival on that kind of basis. That would be the first reason why you wouldn't expect to see a lot of difference in survival.

The second is that, of course, temozolomide is a more efficient way of delivering MTIC, so it's a more efficient prodrug for MTIC than DTIC. But it isn't qualitatively a different agent, so you wouldn't expect a quantum difference in the activity between the two.

So perhaps equivalence would have been a more realistic goal for this study. Bearing that in mind, I personally felt it was quite noteworthy that every sort of measure of activity that you looked at in this randomized study did show an advantage for temozolomide, even though they failed to match statistical significance.

Could I have the next slide?

So the main advantage that I would see with temozolomide is that it has an increased level of patient convenience. The actual incidence of adverse events was very similar for both drugs, but, of course, dacarbazine requires venous access, which requires attending the hospital and the administration of potent antiemetics, while temozolomide is an oral agent and the patient only needs to attend the hospital for assessment. And, in fact, one of my patients on temozolomide was able to receive two courses while on a climbing holiday in the New Zealand Alps.

Could I have the next slide?

So, in conclusion, I feel that the benefits available by using temozolomide for treating metastatic melanoma are clinically meaningful. The patient convenience is much enhanced, and the information we've got is suggestive that the drug is at least as good or could be better than DTIC. It's very convenient for the physician and the patient, and in particular I see it as a stepping stone to future treatments that could further improve on this, and, of course, I'm sure you'll all be familiar with the work that's going on with 06AT inhibitors to potentiate agents of this type, and there's also evidence that some new drugs acting by inhibiting polyADP ribose polymerase will potentiate drugs that induce this lesion, and these

will be available within the next year or so.

Thank you very much indeed. I'd now like to reintroduce Dr. Robert Spiegel, who will lead the discussion on this compound.

DR. SPIEGEL: I'll start my introduction of the discussion staying close to my experts, and I should state that we do have with us today the project physician for the pivotal trial, as well as biostatisticians who have been involved in the analysis.

Next slide.

I have a single conclusion slide, and I simply want to introduce the discussion period by stating that the ODAC is going today to be asked shortly to look at response rate as evidence of effectiveness. We would ask you to look at response rate, but also look beyond response rate and consider that every endpoint and every analysis, without exception, was in the right direction. We believe this shows consistent evidence of effectiveness.

I would summarize that all the point estimates demonstrate effectiveness through the objective responses, the longer response duration, more responders being alive at 12, 18, and 24 months, the progression-free survival analysis favors temozolomide, and the overall survival favors temozolomide, allowing and supporting a demonstration of equivalence to dacarbazine. Temozolomide

delivers higher MTIC concentrations at equitoxic doses to dacarbazine, and as just summarized by Dr. Calvert, temozolomide is a convenient, well-tolerated oral drug.

At this time we'd be pleased to entertain the questions of the committee.

DR. SCHILSKY: Thank you.

Questions from the committee members? Dr. Johnson?

DR. DAVID JOHNSON: It would be helpful to me to ask the sponsors to tell me what level of difference they would have sought had they chosen to do an equivalence trial in survival.

DR. SPIEGEL: Well, that's obviously a key question, and we would have been in a better position to be here today if we had prescribed an equivalence level. I think in conversations with the agency in 1998 and 1999, this is a new trend, and some of our newer development programs, which we have thought about testing first for equivalence and then testing for superiority as a statistical approach, had set a 0.9 level as a level where the agency would feel comfortable that not meaningfully worse outcomes were being demonstrated, in terms of the statistical answer to your question.

Obviously, there have been other examples where the agency has said if you can show equivalence in

efficacy, then a sponsor can choose, so to speak, what other advantages they think a compound might bring, either through a specific outcome like better response duration or something like convenience or some safety advantage.

I should also say, Dr. Johnson, the sizing to do an equivalence trial of that type would be about three times as large, so if we had prospectively set that as our goal, we would have needed about 900 patients to have statistical power to show the equivalence level that was achieved in this study.

DR. DAVID JOHNSON: Let me ask the question again. What level of survival difference would you have sought? Put it to me in time, not in terms of hazard ratio. I'm very familiar with how one prospectively designs trials, and I know that generally speaking one can give us a time frame. Is 3 months difference in survival tantamount to equivalency, in your mind? Six weeks difference in survival tantamount to equivalency?

DR. SPIEGEL: Well, as I understand your question, I'm going to play amateur statistician, but maybe professional oncologist. I think we normally seek a 1.2 hazard ratio. In this study I'm told the 1.18 outcome translates into about 1 month of improvement. If we would have accepted on the other side of 1 a decrement -- that's why I said when we were at 0.92, it was about a 14-day

potential decrease in survival, and to me personally, I would say that would be an acceptable tradeoff if there's an advantage to a new compound.

DR. DAVID JOHNSON: The study was nicely designed for superiority, which, unfortunately, you did not demonstrate. I'm curious as to you've spent a fair amount of time telling us about the pharmacokinetics of the drug and gave us a nice theoretical reason why the drug might be superior in some ways, and yet the trial failed to demonstrate that. Might it be that the dosing of this drug was in fact inappropriate after all is said and done?

DR. SPIEGEL: When you say the dosing may have been inappropriate, we have been considering for future development looking at alternative schedules, looking at higher doses to see if we could push the tolerance, and as Dr. Calvert said, there are some very interesting questions to be asked about biochemical modulation. But at the time we chose this dose, it was the dose that had been developed through fairly extensive Phase I development in both melanoma and non-melanoma patients that appeared to be well tolerated.

The pharmacokinetics that Dr. Cutler described showed that we indeed, with 200 milligrams of temozolomide per day orally, had considerably higher AUCs than 250 milligrams of DTIC I.V., so we had the hope that that might

translate into something that could be detected clinically. But as you state, the reality at the end of the day is that it's very difficult to show the clinical benefit for the full population that was entered.

DR. DAVID JOHNSON: The last question I have had to do with one of the points made in your briefing book, and that had to do with there was a fair amount made about the survival difference at 6 months, which seemed to be something of an artificial point, and also there was a lot made about the time to detection of metastatic disease, and you chose this figure of 1 month, which I'm curious as to why those two points were chosen for analysis.

DR. SPIEGEL: The 6-month snapshot is admittedly a post hoc point that was chosen, and although it was mentioned in the briefing book, we have not felt it was important to try and stress that in the presentation today, and I think we would agree with the critique that it's both post hoc and arbitrary about whether that's the most important time point to look at.

As you know, however, most patients do progress quite rapidly. In our study, within 1 to 2 months we had over 50 percent of the patients demonstrating progression, and the median survival in most of the literature is about 6 months, and for that reason, we thought it was of interest to say at 6 months how are we doing in this study.

But I don't want to overstate that we believe that's a legitimate or critical analysis to assess the effectiveness today.

DR. DAVID JOHNSON: And the 1 month?

DR. SPIEGEL: Could you say that again? I'm not sure I understood the --

DR. DAVID JOHNSON: Well, in your analysis where you have shown us that the trends, according to your analyses, "all favor temozolomide," one of the points you use is the time to detection of metastatic disease, and you use a cutoff point of 1 month.

DR. SPIEGEL: I'm told that that was an analysis of time to detection of metastatic disease at entry.

DR. DAVID JOHNSON: Right.

DR. SPIEGEL: Dr. Frost is the project physician.

DR. FROST: The question that was brought up, if I understand it correctly, is the cutoff of 1 month, and that refers from the time of the diagnosis of metastatic disease to the randomization, and there was distribution done according to the median patients with more than a month and with less than a month. That is the subgroup parameter. It's cut off at the median.

DR. TURNBULL: All we did was take the cutoff

at the median to be able to look at the consistency of results. So 1 month happened to be about --

DR. SPIEGEL: Can you use the microphone, please?

DR. TURNBULL: I'm sorry. One month is -- on the subgroup, all we did was take the median time, and that happened to be at 1 month in the distribution, so you could get an equal number of patients below 1 month and greater than 1 month, just to show the consistency of the results, and that was why it was chosen. Nothing else.

DR. DAVID JOHNSON: And that's the median time to --

DR. TURNBULL: It's the median time from metastatic to randomization, and it just happened to be that half the patients fall below 1 month and half fall over 1 month, equally distributed within the groups, and we were just looking at subgroups here to show consistency of results, and that's why that was chosen. Nothing else.

DR. SCHILSKY: Dr. Krook?

DR. KROOK: A couple of questions. One, in the book which we received, as the site of metastatic disease, the study listed hepatic disease, subcutaneous, and then the other. Can you tell me what was in the other? Was it mainly lung metastases or lymph nodes? There was a large group which was there, if I remember right --

DR. SPIEGEL: You're correct that the other meant any other visceral sites or bone other than liver, but Dr. Frost might have more details.

DR. FROST: Yes, the answer is correct. The stratification was set up that patients who had hepatic lesions plus other metastases were defaulted to the hepatic group, patients that had subcutaneous and skin only were grouped to this, and any other metastases -- primarily visceral, lung, soft tissue -- were defaulted to the other group.

DR. KROOK: So basically the hepatic was the poor prognosis, the subcutaneous only, I take for granted, were the good prognosis, and the other were kind of the medium.

DR. FROST: Correct.

DR. KROOK: My second question is that the slide which you showed in complete responders, you showed the complete responders -- these were you had individual patients -- you showed the four complete responders in both groups, and then in the Temodal only did you show the partial responders. In a previous drug which came before this committee, one of the points which was made was that there was a significant 5-year duration of response. Realizing this study closed in 1997, some of that information, you said, was March of 1999. Is there a 2-

year survival that you can compare the two groups? You must have some data, because you mentioned that this data was from March of 1999.

At least this group looked at the previous drug as a long-term 5-year, and all patients were entered. The number of people alive yet in terms of survival at 2 years from entry to the study, I guess that's the point I'm trying to ask.

DR. SPIEGEL: In response to your specific question, we do have an analysis of overall survival of the entire intent-to-treat population, which shows that at the end of 2 years there were 13 percent -- Slide 92 -- there were 13 percent of the intent-to-treat population alive in both of the treatment arms, if you took the entire population. I had been previously during the presentation showing the outcome in the responders only.

We also, if you wish, have thought long and hard about the IL-2 precedent. It is notable that those responses were achieved in probably a considerably better population than the population we think entered our trial, and if we wish to, we could talk a little bit more about how we see this type of drug contrasting with what's been demonstrated for IL-2.

DR. KROOK: If I take that one step further, you have 13 survivors --

DR. SPIEGEL: Thirteen percent.

DR. KROOK: Thirteen percent. Pardon me. Thirteen percent are -- and this may be difficult to answer -- are these all the PS-0 subcutaneous nodules only, or are there some poor prognostic in that group? I mean, that may be difficult to sort out. Are these all the good-risk patients?

DR. SPIEGEL: The answer is no. I don't have it all on my fingertips. I know there are some patients who had significant disease, some of which were resected, I have to say, at the time CRs were achieved, and then they continued to be either disease-free or go for long periods before recurrence.

DR. DAVID JOHNSON: Could you just clarify that last statement? When you said some of them were resected, what do you mean?

DR. SPIEGEL: I'm sorry?

DR. DAVID JOHNSON: You just made a comment that some of these patients were resected. Did you mean after they received the therapy they were resected?

DR. SPIEGEL: There is one of the partial responders I'm aware of who is one of the long-term partial responders who had residual disease, was resected surgically, and remains a long-term survivor.

DR. DAVID JOHNSON: Do we know how many of

those patients -- I mean, is it just one?

DR. FROST: In the group of the partial responders, there are two patients who had undergone surgery. They responded, and then after a certain time frame they had relapsed, and then surgically the disease was removed, and then the patients had survived.

DR. DAVID JOHNSON: Without relapse.

DR. FROST: Right.

Can we go to the slide with the partial responders?

And coming back to the previously asked question that was the question of only patients with good performance status and limited disease burden survived, for example, as we can see, Patient 12-001, the patient had lymph node disease, liver metastases, bone metastases, and a spleen lesion measuring 5x7 centimeters, and that patient is still alive. It also can be seen that there are at least five or six patients with lung metastases and three with liver disease who responded and survived for at least 16 or 18 months.

DR. KROOK: If you could go to the previous slide to this one, there is a patient here, age 74, performance status of 2, whose response duration was 3.7 months, and yet he's alive at 29. Is this one of the resected patients? I mean, I don't mean to ask specific --

but something else had to happen. The gentleman is alive 2 years after the response duration is over. Is that the explanation? This, and then there's a second patient, age 43, on the experimental arm, who is alive, again, 2 years later. Is this an example of the -- are these both --

DR. FROST: Patient 14-014 is an example of a resection. That's correct.

DR. KROOK: Okay. So he progressed and then was resected or -- okay.

DR. SCHILSKY: Dr. Simon?

DR. SIMON: Has DTIC been compared to anything, either palliative support or any other chemotherapy regimen, in which it's shown a superiority with regard to survival?

DR. SPIEGEL: I think Dr. Kirkwood might want to review the literature that he brought to bear before. I think the answer is probably no, there is no large study with sufficient power to say that it beat either another single agent or combination with statistical significance. He did show that in our review we found five studies in which DTIC as a single agent was compared to either combination therapies or, in one case, TIC mustard, a single agent, that did not contain DTIC, and in three of the five there was a trend where there was survival data available that DTIC did show better survival. But,

unfortunately, we were not able to find a study large enough -- single study -- to demonstrate that.

DR. SCHILSKY: I wonder if I could follow up on that question and ask John a question. On your Slide 21, you made what I thought was a rather striking conclusion. You said that DTIC provides useful palliation for symptomatic disease. That's your first conclusion. It wasn't clear to me that any of the data that you reviewed prior to making that statement would actually support that statement. So what information is available to suggest that DTIC provides useful palliation for symptomatic disease?

DR. KIRKWOOD: Simply that there are responses, and that the mean in the literature is 16 percent, and that for those patients this is the agent of recourse, the standard that the field has. It was not to indicate that this is --

DR. SCHILSKY: Is there any data to suggest that a response constitutes useful palliation?

DR. KIRKWOOD: Oh, I think anecdotally all of us who have treated patients with melanoma have seen patients who have responded and had benefit as a consequence of --

DR. SCHILSKY: So an asymptomatic patient with PS-0 who has a response that lasts for 3 months is

effectively palliated by the treatment?

DR. KIRKWOOD: No, symptomatic metastatic disease, and I think that's really the guidepost. I think that this is, for patients with asymptomatic disease, as Hilary mentioned already, often a prompter to pursue investigational therapy.

DR. SCHILSKY: Dr. Albain?

DR. ALBAIN: Following up a little more on that, it was striking that the ECOG trial data, I believe, that you showed had a 9.9-month median survival for dacarbazine alone. Is there any data that you could cull from the literature, knowing that prognostic factors really strongly impact the survival duration in metastatic melanoma historical data, untreated, granted historical data, but with the similar prognostic profile as this pivotal trial? Is there anything in the literature you could use to compared untreated historical data with the prognostic factor profile like this study?

DR. KIRKWOOD: I think it is so hazardous because of the selection bias that can drive accrual. I should mention again that the older age, the more visceral distribution of disease in this particular trial made the outcome expectedly worse than in multiple series. In particular our studies of E3690 and the trials of biologics, like the trials of interferon gamma, have

selected patients with less-than-3-centimeter disease, with non-visceral disease, have had hugely larger proportions of patients without liver, lung, bone involvement.

DR. ALBAIN: Is there a survival statistic you could quote, untreated metastatic melanoma, from the historical database?

DR. KIRKWOOD: I think it is entirely dependent upon selection of the patients, and I wouldn't really think that is a valid thing to pull out of thin air.

DR. SCHILSKY: John, one other question, if I might, just again to follow up on your definitions that you just gave us. So if I look at the slide that shows the temozolomide partial responses, there are 17 partial responses that are depicted there. Eleven of those patients were PS-0 at the time of entry on study, meaning that they were asymptomatic. Would you conclude that those 11 patients had the opportunity to benefit from temozolomide treatment?

DR. KIRKWOOD: I think so.

DR. SCHILSKY: Based on what?

DR. KIRKWOOD: The temozolomide-treated patients that had visceral and had other sites -- I actually don't know the symptomatic status of these patients --

DR. SCHILSKY: Well, they're listed as being

PS-0, so that by definition means they were asymptomatic.

DR. KIRKWOOD: If it was PS-0, I think it would be very difficult to suggest that one could alter their course or their outcome through therapy. We don't in general consider therapy for patients with asymptomatic and especially non-visceral disease.

DR. SCHILSKY: So you would conclude, then, that 11 of the 17 responders didn't really have much of a potential to be able to benefit from the treatment?

DR. KIRKWOOD: Yes. I think the difficulty here is if they had regression of disease, would that have altered the outcome of disease that one would have expected down the road. We don't really know.

DR. CALVERT: Just a small point that performance status 0, the first performance state, is not to symptoms.

DR. SCHILSKY: But isn't the definition that the patient is asymptomatic? To be a PS-0 by definition, don't you have to be asymptomatic?

DR. CALVERT: Well, a patient who had controlled symptoms with analgesics, I think, would still be PS-0.

DR. SCHILSKY: Well, I guess it's a debatable point. But while you're at the microphone, Hilary, I had one question I wanted to ask you. Put on your

pharmacologist hat.

It's of some interest to note that the temozolomide effectively delivers MTIC into the circulation, and that from the data we were shown, the AUCs are about twice what was obtainable in the patients receiving the dacarbazine. It's, therefore, I guess, a little bit confusing to me to see that in fact there were roughly equivalent toxicity rates in the two arms of the study, because if we were dosing to an AUC, for example, something you're familiar with, we would be delivering twice the dose, twice the concentration of drug into the circulation with temozolomide, and yet we're not seeing any real difference in biological effect. What are your thoughts about why that might be the case?

DR. CALVERT: I think, first of all, the level of myelotoxicity in both arms is quite low, so that you wouldn't -- we're not seeing very many Grade 3 or 4 toxicities. Now, I think if you looked at the data carefully, although statistically there's not much significance, there are a little more on the temozolomide side. But if you look for lower degrees of toxicity that you'd expect from what is basically a mild treatment, I think you'd probably see the difference coming in there. So we're basically dealing with two treatments, neither of which is particularly myelotoxic.

DR. SCHILSKY: Dr. Santana?

DR. SANTANA: I want to follow up on that, because I think a lot of importance has been put on this difference in pharmacokinetics and pharmacodynamics of the way the two drugs are administered. So if you could refer to page 16, Table 3, of your booklet, it seems to me when I read this data that there's a lot of interpatient variability in the temozolomide AUCs as compared to the DTIC. So I would want somebody to comment on that.

Secondly, this issue of pharmacodynamics and whether the patients that were studied pharmacokinetically had any difference in their degree of neutropenia. I'm trying to get at this issue that you were trying to address. Obviously, we can't talk about the other 200 patients who didn't get pharmacokinetic studies, but the ones that got pharmacokinetic studies, did you look at some pharmacodynamic parameters in those subgroups?

DR. CUTLER: As far as I know, the pharmacodynamics have not been looked at in those 17 patients. Those 17 patients were selected because they were enrolled at sites that had the facilities to obtain pharmacokinetic samples for a drug that required special handling to make sure that it was properly collected and preserved.

DR. SANTANA: And getting back to the issue of

interpatient variability, that it seems to be higher in the temozolomide AUCs, did you look at quartiles rather than looking at means and see what the overlap was?

DR. CUTLER: No, we did not.

DR. SANTANA: Thank you.

DR. SCHILSKY: Dr. Ozols?

DR. OZOLS: I'd like to ask Dr. Kirkwood and Dr. Calvert, if this drug were approved, would this alter any way that you approach patients with metastatic melanoma? I mean, with the response rates and the survival, would you still offer experimental treatment to the majority of these patients?

DR. KIRKWOOD: Well, it's certainly more facile, and so for the patients that we would use dacarbazine to treat, it would be a far easier therapy to deliver. It is more flexible as well, and as was mentioned before, we can't give dacarbazine daily for 30 days, we can't give it twice a day, because patients can't come back to the clinic twice a day or thrice a day, and I think that is the option, that is the hope that we've had for future developmental studies of this agent, that it really would be possible to give it far more flexibly, far more easily to patients, and to consider combinations and other formulations that would be potentially more efficacious.

DR. CALVERT: I think Schering-Plough has a

considerable file of requests from me for compassionate release of temozolomide subsequent to the closure of this trial, and certainly for me personally it would be the treatment of first choice, unless there were a more interesting investigative regimen.

DR. SCHILSKY: Dr. Sledge?

DR. SLEDGE: A question for either John or Hilary. It strikes me that the argument that we're hearing here is that this new drug is at least no worse than the old drug, and the old drug represents the standard of care. Does it truly represent the standard of care, or is it just simply American oncologists' reluctance to be involved in placebo-controlled trials, I guess would be question number one.

And, number two, realizing that we have no placebo comparator in overt metastatic disease, do we have trials with DTIC in the adjuvant setting where DTIC has either been used as a single agent or as part of a combination, where we have either a relapse-free or overall survival advantage for the DTIC-containing arm?

DR. CUTLER: The personal basis upon which private oncologists do or don't use dacarbazine, I'm really not able to say. I guess I suspect it is because it is easy, and this would be easier. It certainly would be the recourse of choice.

The World Health Organization has conducted large randomized trials of BCG, dacarbazine, and the combination, and although there are trends and there are late analyses of this trial, there are no statistically significant differences between the arms now at a follow-up, I think, of past 15 years median.

DR. SCHILSKY: Dr. Krook?

DR. CUTLER: I guess one would not really ever have expected, with a 20 percent, 16 percent, or 13 percent response rate in trials even of hundreds and hundreds of patients, to have seen meaningful differences in survival on that basis of activity.

DR. SLEDGE: How about relapse-free survival?

DR. CUTLER: There were not differences in relapse-free survival. Whether one would expect it with dacarbazine as it was tested, I don't know.

DR. KROOK: A comment first on Dr. Sledge's. There was an ECOG study that I remember -- this is back 20 years ago -- where an adjuvant -- it was DTIC versus observation. I do not --

PARTICIPANT: SWOG.

DR. KROOK: It was a SWOG study that ECOG did, but I don't know the answer to your question.

But I want to comment on the community oncology, since I guess I represent that or I am. Most of

us out there don't like to use DTIC. It's 5 days, it's I.V., there are lots of side effects, and we'll look for something else, particularly in performance status 0. That's just my bias, and part of that is the response rates which you see here, there are a lot of other things you can -- and I'll use the word "dabble in" -- before you get to I.V. DTIC.

DR. SCHILSKY: Dr. Temple?

DR. TEMPLE: I have two areas of questions. One is about the argument that equivalence has been shown or is pertinent, so this sort of follows up on what Rick Simon was suggesting. If two therapies had no effect at all, you could probably show that they're equivalent if you make your study large enough. To do a proper equivalence study, you have to make the case that the effect of the control was known and has a defined side, like the survival benefit is a month, 2 months, whatever you think it is. You then carry out a study that shows you haven't lost that effect. This has all been written up by Bill Blackwelder, and Tom Fleming wrote it up after an experience with this committee, actually.

Nothing you've said explains why an equivalence outcome should be considered informative at all in this setting, because as you've said repeatedly, there isn't any clear evidence that DTIC has a survival benefit. So can

you explain that a little further? That's the first question.

DR. SPIEGEL: I'm glad to explain it. Obviously, this is an area that you personally, a number of biostatisticians, and this and other advisory committees have talked about. We structured our presentation today to not hopefully overstate the results we have and to show some fair balance about where we did have statistical significance versus trends that were not statistically significant. It should have been clear from my statement of the design of this study that it was designed to show superiority, and if we had shown superiority, we'd be having a different conversation today.

Having not shown superiority statistically, but having a trend, we consulted with Dr. Fleming and with some other biostatisticians to say what's the legitimacy of testing for equivalence, knowing that the agency has been very clear throughout in saying that we would have a burden of proof to say that dacarbazine does something, if we did say we were equivalent to that. What I think we can say fairly today, we are not worse than dacarbazine. If the confidence interval had been less good, if it had gone down to 0.8 or below, I'm sure we would be here defending much more severe questions about how could we consider putting a drug potentially on the market that could have a worse

outcome than dacarbazine. I think what we're able to say today is that there's a trend in a study that was underpowered to show superiority that suggested that the hazard ratio, the survival benefit, might be slight.

I think Dr. Calvert appropriately, when he was asked by us to put together a critique-type presentation, said the goals of this strategy for drug development were too ambitious, that if we had even achieved a 20 percent response rate -- and we have a 12 percent through this strict criteria we used -- it would be very hard to show that the median survival for everybody moves.

So I think -- it's a long answer to your question. I think we're backing away from trying to claim -- certainly, we can't claim superiority. The equivalence statement, I think, is a valid statement; equivalent to what is something that -- although we were asked on numerous occasions by the FDA division to scout the medical literature and find any evidence that would demonstrate survival benefit, progression-free survival benefit, clinical benefit of dacarbazine, the best we've been able to do is the review that Dr. Kirkwood summarized, saying that there's a general sense that oncologists are doing something, but we can't prove that with dacarbazine.

DR. TEMPLE: Okay. It's just worth saying that equivalence here is to be considered -- I mean, the hope

would be that equivalence would be considered evidence of effectiveness, not just evidence that you're not worse than something that may have little or no effect.

DR. SPIEGEL: That would be our hope.

DR. TEMPLE: So that places a special burden, and just to repeat it, you really have to have some idea of what the effectiveness of the control is before you can use that design, and that's pretty well established.

DR. SPIEGEL: Having said that, Dr. Temple, I think if we had had extensive consultations with the FDA in 1995, I think we probably still would have walked out saying DTIC is the right comparator, and if we came in today with a new drug, I think DTIC would still be an appropriate comparator.

DR. TEMPLE: Oh, and everybody thinks your study design was fine. It's the outcome that's the problem.

DR. SPIEGEL: Okay.

DR. TEMPLE: The second question is, you described a reduced data set, an efficacy subset or an eligible patient subset. Can you describe a little further the process by which you went through the various patients and decided which ones were eligible and which ones weren't?

DR. SPIEGEL: Well, unfortunately, this study

was never truly blinded, so the drugs were I.V. or --

DR. TEMPLE: This review could have been blinded, though.

DR. SPIEGEL: Yes, that's right. I'll take a quick shot, and then I'll ask my statisticians who were doing it.

As I understand it, we followed what would be our normal standard operating procedure in our biostatistics and clinical group. That is, before the database was locked, the clinician and the biostatistician sat down to go through the entry criteria with a list, without unblinding formally what violations there were. We made a decision that certain violations were very obvious and important if we wanted to do an appropriate analysis of patients who had the right diagnosis of malignant melanoma and demonstration of metastatic disease and had not received prior therapy within a window that was prescribed in the protocol, and those patients were flagged and were eliminated from the eligible population.

Then we subsequently looked at patients who also did not receive treatment after randomization, and this is an important area of potential bias in this study, because patients knew after randomization that they got dacarbazine, and some of them bailed out and said, "We don't want to be in the trial anymore. I want my

dacarbazine even as a non-experimental drug from their physician. There were five of those, I think.

That was the basis, and I'll let someone expand on the nature of the blinding of the company when we did that.

I know that Dr. Cohen has prepared a careful analysis to show quite a discrepancy between what the FDA found using strict criteria of all the eligibility inclusion and exclusion criteria. We think some of that is accounted for by a very strict adherence to the laboratory parameters, not all of them, but normally when we review a study, at the study end if we think there are trivial -- and it's a judgment call -- violations of the protocol, if someone was not supposed to have received previous chemotherapy within 30 days and they got it at 29 days, we sometimes make that allowance.

I'll let some other people expand on it.

DR. TURNBULL: Before we close the database at Schering, we have what's known as a validity meeting. The meeting is done with a whole set of listings. Listings do not have treatment code on them. We review the listings, we determine -- obviously, we're doing an intent-to-treat analysis. We would also determine, so we can see the consistency of data, those that we consider to be major protocol violations and outside or have some type of a

subgroup.

In this case, when we did the analysis, these patients were prospectively determined before we locked the database, and like I said, until we lock the database, treatment codes are not put in. Even though they may be known to the physicians or individual patients, we do not know them. They're not on the case report, they're not on the listings that we review. So the analysis that was done and the elimination was done without any treatment codes and in a totally blinded fashion during this validity meeting.

DR. SCHILSKY: Dr. Raghavan?

DR. RAGHAVAN: One of the difficulties in listening to the presentation is that we're starting from the point that, as George Kinellas is fond of saying, melanoma is the disease that gives cancer a bad name. So it's not easy to make progress unless you have a breakthrough drug, and it's clear that this isn't a major breakthrough drug.

One of the problems that I've had listening to the presentation is that I think everybody agrees that this wasn't the ideal execution of trial, and we're trying to get something useful out of it. It's always troubling when you have patients where you haven't defined whether they actually needed symptomatic palliation, because it's hard

to palliate symptoms that aren't there.

My question is to Hilary Calvert. Hilary, you made the statement that coming off the trial, you had flooded the company, the sponsor, with requests for compassionate use of the drug, and the one thing that really hasn't come out, I don't think, today is the issue of patient benefit. I understand fully that the trial really wasn't very well designed to look at those issues, but can you give us, as someone who treats a lot of melanoma, an understanding of why you use the drug off trial? What does it do for patients that you would identify, as an experienced oncologist, as being of benefit to the patients? Not talking about asymptomatic lesions that are being followed. What's good about this drug, in your experience?

John Kirkwood, the same, if you've got experience.

DR. CALVERT: Well, I'm afraid the answer to that will be in the form of clinical anecdotes really. I think, first of all, the request would be for patients who had symptomatic disease, and, secondly, the reason for wanting temozolomide was because you don't wish to interfere with the patient's lifestyle more than you can help. And, of course, many of us are subject to seeing results, and maybe we have a belief that temozolomide

probably is better than DTIC, even if we can't prove it today with the statistics.

The sorts of symptomatic benefits that were seen are, for example, a lady who went climbing in the New Zealand Alps, who's now 4 years out from having had hepatic, bronchial, and uterine metastases; a patient who was performance status 2 with an enlarged liver, lost a lot of weight, who regained normal weight and went back to being a tennis instructor. These are sort of clinical anecdotes that make you keen on giving the drug to somebody else when you find them.

DR. RAGHAVAN: Can I follow up?

Hilary, you were involved in the Phase II trials, as you said. I'm still struggling -- it sort of reminds me of my first date, stumbling uncertainty. What in fact is going to be the patient benefit in the symptomatic population? In this population, as was said, it sounds as if a lot of the patients didn't have symptoms. It's well known, I think, that in the U.K. symptomatic patients tend to be entered into Phase II trials. You've described the mountain climber and the long distance runner and so on, and I understand that they were unwell.

What proportion from your Phase II trials of patients do you anticipate, have you documented to have had benefit that you can quantify? Symptom reduction. It's

impossible to assess prolongation of life here, where you have a cohort of patients who are asymptomatic and where we do know that they will sometimes run a long course. It's not common for symptomatic patients with melanoma to survive a long period of time. So in and amongst the anecdotes and the information that you and the sponsor have, what is the proportion of patients that is likely to get benefit from getting exposure?

Because the obvious question is, do you request this drug because you just don't want to say to a patient, "I have nothing to offer you," or are you requesting the drug because it actually does something in a significant number of patients? And if it does something in a significant number of patients, give me a number. Twenty percent, 15 percent, 5 percent? Where does this fit into the marketplace?

DR. CALVERT: Well, I mean, I'm making guesses here. First of all, I think the majority of the patients that we have referred are symptomatic. The primary gatekeeper for the patients is normally the plastic surgeon, and like many British physicians, they're quite conservative and often quite nihilistic, so patients don't always get referred to medical oncologists very early.

Secondly, if I feel I need to give a patient some treatment, we're a big Phase I center, we normally

have five Phase Is ongoing at a given time. I'm never short of something to pull out of my back pocket and say to the patient, "How's this?" But quite frequently I feel inclined to try to get temozolomide for the patient when I might, from a publication point of view, prefer to put that patient onto a Phase I trial and complete it, and that's because of the perception that it works.

I think the best estimate that we could have of those patients who the investigators felt had improved would actually be the investigator-reported response rate from the CRC Phase IIs, which is about 30 percent, or somewhat more than the number who get formally categorized partial response.

DR. KIRKWOOD: Because we've only really participated in the Phase I studies of temozolomide, I don't think the percentage estimates that I can make are very relevant, but I can tell you that we've had a couple of objective responses, one which was complete regression in malignant ascites. I've never seen that happen with any drug or any biologic in patients with metastatic melanoma. This is turgid malignant ascites, and a response of 5 months in a 29-year-old mountain biker who came in, had eluded diagnosis outside. I don't think we see that spontaneously, and I think that that kind of palliation for symptomatic -- and certainly turgid ascites is a

symptomatic presentation. In our patients with malignant serosal involvement, the median survival is measured in weeks.

DR. MYERS: I'm Michael Myers. I'm a clinical oncologist with Schering. Up until about 8 months ago, I was a clinical oncologist treating melanoma patients at Memorial Sloan-Kettering, and during my time at Memorial Sloan-Kettering treated probably somewhere between 50 and 100 patients each year with metastatic melanoma. So I want to lend a clinical perspective and a humanistic perspective on this issue of symptomatology.

As you all well know, melanoma is a disease in which a vast majority of patients with Stage 4 disease have cutaneous and subcutaneous metastases, which they are very aware of, often the only site of disease, and I can tell you that these patients every day are looking at their metastases, looking to see if there are more metastases popping up, looking to see if there's growth or shrinkage, and that clearly affects their quality of life strictly from an emotional point of view, if nothing else. Maybe it's not a symptom that can easily be measured, but when you're looking at your skin every day and noticing new lesions or noticing that a lesion is getting larger, that affects the way you go about your life.

Clearly, both dacarbazine and temozolomide do

cause regressions in lesions, cutaneous/subcutaneous lesions, and the effect on the patient is a significant effect of seeing that their disease, their visible disease, the disease that they can see, that their loved ones can see, is actually shrinking or at least stabilizing, and I think that is a very significant fact that should not be overlooked.

Thank you.

DR. SCHILSKY: Any other questions from the committee? Yes, sir?

MR. McDONOUGH: As a potential Stage 4, my question -- I'm looking at the vomiting, the pain, and the headache. Having taken Intron, I was able to experience all three. I'd like to get some idea as to how severe.

DR. SPIEGEL: Well, as the people who brought you Intron, we're familiar with that, too. I could probably give you a statistical answer, but, again, I think I'll turn to Hilary and John, who have treated a lot of patients personally with temozolomide and could give you that perspective.

From our analysis, we -- again, in answer to Dr. Temple's challenge, we had hoped to show a more clear safety benefit when we looked at all the numbers. We think that some of the reason we don't is that we capture any adverse events at any time, and during a few months of

treatment, any adverse event that is recorded in a patient's case report form gets checked off as an adverse event that might be related to the drug itself. For example, the headaches that we record, although the ones I showed were Grade 3 or 4, could have been for any cause. They could have been trivial due to reasons that people without melanoma get severe headaches, but they could also be because of CNS metastases starting.

We think the profile of the drug looks similar to dacarbazine. We think that as doctors get more experienced using temozolomide, they'll be able to control the nausea and vomiting as well as they control it with dacarbazine, and they might require less use of more serious 5HT heavy-duty antiemetics.

I think the headache and the pain that we recorded, we didn't take to mean that there was something seriously related to the mechanism of the drug that was causing that. Dacarbazine, as we've heard from the clinicians, is a pretty nasty chemotherapy. It's one that doctors would like to avoid or like to have something better. We consider temozolomide convenient and oral, but it probably would best be administered with an antiemetic regimen. It doesn't have the risk of intravenous phlebitis or access issues. Otherwise, the side effects that were popping up were pretty consistent with what you would

expect in that population when you follow them for 3 or 4 months.

But I'll let the clinicians who have treated these patients comment further.

DR. CALVERT: To start with the pain, I don't think there is any pain associated with temozolomide treatment. When the pain was recorded, it would have been from some other cause. Of course, in contrast, there is quite often pain on injection with dacarbazine, which is the alternative.

With regard to vomiting, most patients do feel nauseated or vomit if they take temozolomide without antiemetics. However, with adequate antiemetics, in the vast majority of patients, there's no nausea, and I think none will vomit. So it's actually fairly mild, providing it's guarded with antiemetics.

From the point of view of headache, I also was a little surprised to see it coming up on the adverse event chart, because I haven't had it reported in person, and I think the most likely explanation is that the HT3 antagonists that are frequently used to control nausea and vomiting do occasionally cause a mild headache.

DR. CUTLER: I have nothing to add, except to say that by comparison with interferon, this is child's play.

DR. SCHILSKY: Okay. Any remaining questions?

(No response.)

DR. SCHILSKY: If not, we'll take about a 15-minute break and resume at about 10:05.

(Recess.)

DR. SCHILSKY: At this point we'll go ahead with the FDA presentation by Dr. Cohen.

DR. COHEN: Good morning. I'm Martin Cohen, and I'm going to be presenting the FDA review of temozolomide, and listed on the first slide is the FDA team that was involved in the evaluation of temozolomide. For today's medical review, the primary individuals involved were Dr. John Johnson, Dr. Ning Li, and myself.

To go through the administrative history of this NDA, over the years the FDA and Schering-Plough have had several meetings to discuss temozolomide clinical development. In the November 1994 meeting, the October 1996 meeting, and the August 1997 meeting, discussions primarily involved the glioma protocol. There was no discussion of the melanoma protocol. The first we really heard about the melanoma protocol was in June of 1998 at the pre-NDA meeting, in which trial results were presented. The NDA was submitted in August of 1998 and is being presented today to ODAC.

Before we get started, just to quickly review

the regulatory history of DTIC in advanced metastatic melanoma, the drug was evaluated probably in the late 1960s/early 1970s in 450 patients who were enrolled in an NCI-sponsored cooperative group trial. FDA approval was given in May of 1975. The approval was based solely on response rate, and the response rate was 23 percent overall and 6 percent CRs. Neither at that time nor at any time subsequent to that time has any data come along to indicate that DTIC prolongs either overall or progression-free survival.

Turning now to the NDA under discussion this morning, the pivotal trial was I95-018. It was a Phase III randomized study. Patients were randomized to receive either temozolomide or dacarbazine. Thirty-four sites participated, none in the United States.

As we've heard earlier today, among the pertinent design features was the fact that the treatment schedules differed. Temozolomide was given daily for 5 days orally every 4 weeks, dacarbazine was given daily for 5 days intravenously every 3 weeks, and as we've heard today, the significance of this is that tumor evaluation was scheduled to be done at the beginning of each cycle for lesions that could be palpated on physical exam, and was to be done at the beginning of every even-numbered cycle for lesions that required radiologic documentation, so that

over time patients on dacarbazine received more tumor evaluation than the patients on temozolomide. Also as we've heard this morning, the study was not blinded.

In terms of study analysis, the FDA got actual tumor measurements from the site, so we were able to do our own calculations and determine response rates and times to progression. All the other information, at least in the electronic database, came from tables that were compiled by the sponsor.

In the FDA study analysis, our analysis differed in principally two ways from the sponsor's. The first was how we handled delayed evaluations indicating progression. As I said, lesions detectable on physical examination were supposed to be examined at every cycle. Well, say a skin lesion was measured at cycle 2, then the patient came back for cycle 3 and the lesion was not measured, and then the patient came back for cycle 4 and the lesion had progressed. The sponsor recorded the day of progression as the day of examination at cycle 4, whereas we didn't really know when the patient progressed. It could have been at cycle 3, it could have been at cycle 4. So we censored the patient at the time of last evaluation.

A second area concerns deaths occurring without documented progression or clinical deterioration. The sponsor coded the date of death as the date of progression,

whereas we, again, did not know actually when the patient did die, and so we censored the individual at the last evaluation for progression.

Now, generally speaking, these factors applied only to a few patients, and so it didn't really alter analysis of treatment results that much. What it did, though, was add precision to evaluation of progression-free survival, in that we think we eliminated a lot of noise that might have resulted from an inaccurate coding of date of progression, and I will show you data and the actual curves for progression-free survival to indicate in fact that we got better P values for these parameters than did the sponsor.

The data set, as you heard earlier from Dr. Spiegel, consisted primarily of the intent-to-treat population, which included a total of 305 patients, 156 patients on the temozolomide arm, 149 patients on the DTIC arm. The sponsor then further defined an eligible population, and then further defined a treated eligible population, and as you've heard from the sponsor's presentation, the FDA objected somewhat to these two subclassifications of patients, and I'll show you the data as to why we don't put much weight on either the eligible or the treated eligible population.

Also as was stated by Dr. Spiegel this morning,

the primary endpoint of the study was overall survival, and the study was designed as a superiority study. The statistical section of the protocol stated that with 210 deaths, a 3-month median survival difference -- that is, 6 months for DTIC versus 9 months for temozolomide -- would be detectable with 80 percent power at an overall 5 percent level of significance. At the time the data was submitted to FDA, 244 deaths had occurred, 124 temozolomide and 120 DTIC.

Secondary endpoints for the study were progression-free survival, objective response rate, quality of life, and pharmacokinetics. The principal regulatory issue that's been alluded to several times already this morning is that DTIC is not known to prolong either overall or progression-free survival in advanced melanoma patients, and thus temozolomide must be shown to be superior to DTIC. Equivalence is not sufficient, because equivalence may mean being equivalent to placebo.

Turning now to the study itself, the randomization process accomplished its goals, and patients in the two arms of the study were comparable for all the factors listed on this slide. My impression of the patient characteristics in this study differs a little bit from Dr. Kirkwood's. I think this is a relatively good study population. The median performance status of patients in

this study was 0, and less than a third of patients on either arm had liver metastases.

For overall survival, this is the intent-to-treat population, and both the sponsor and the FDA came out with exactly the same results, as you would expect. This is mature survival data. Out of 156 temozolomide patients, 124 are dead. Out of 149 DTIC patients, 120 are dead. The median survivals are listed, 7.7 months versus 6.4 months, and the P value is 0.2, and, again, we don't believe that the equivalence argument is really pertinent here.

For those of you who like to look at actual survival curves, this is the survival curve. The dark line is temozolomide, the lighter line is DTIC, and as you can see, the two curves pretty much parallel each other through the course of the curve, with temozolomide always being slightly superior.

Now, the sponsor has also done survival analyses for the eligible patient population and the treated eligible population, and as you can see, the P values start to come tantalizingly close to 0.05, being 0.06 for the eligible and 0.054 for the treated eligible, but as I've said before and as I will show you later, the FDA does not give much weight to either the eligible or the treated eligible population.

The sponsor also did a 6-month survival rate.

I guess we're the only one presenting the sponsor's data on this point. It was 61 percent 6-month survival for temozolomide, 51 percent for DTIC, and the sponsor's P value was 0.063. FDA did the same analysis and got a P value of 0.066. So it's basically the same, but, again, for the reasons the sponsor indicated this morning, we don't put much weight on this 6-month survival data either, and we'll come back to that as we go on in the results.

Turning now to progression-free survival -- and this is the FDA analysis of the intent-to-treat population -- again, this is a mature analysis. Most patients had progressed at the time of analysis. In the temozolomide arm, 140 of 156 patients had progressed. In the DTIC arm, 128 of 149 patients had progressed. The median progression-free survival in the temozolomide group was 1.74 months versus 1.38 months, and this difference, which was 0.36 months, or about 11 days, turned out to be highly statistically significant. In the FDA analysis, the P value was 0.002, the sponsor's P value was 0.012.

The first question you might ask when you look at this data is, how can a survival difference of 0.36 months generate a P value of 0.002? So I've shown the curve here, and as you can see, this is temozolomide, the darker curve, this is DTIC, the lighter curve, and as you can see, at about the median point there's not much

divergence in the curves, and the curves really start diverging when you get down to about the 30 percent point, and then they come together around 14 months. So that most of the divergence of the curves takes place after the median was reached.

And to show you why I think our method of analysis was somewhat more sensitive than the sponsor's method of analysis for progression-free survival, I've included our curve, on the left, and the sponsor's curve, on the right, and you can see at this point down here there's much more variability in the sponsor's curve than there is in our curve, and I think this probably represents more noise than anything else.

We've heard about the sponsor's response rate before. In the intent-to-treat 156 temozolomide patients, there were four CRs, 17 PRs, for a total of 21 patients responding, or 13.5 percent. In the DTIC arm, again, there were four complete responders, 14 partial responders, for a total of 18 patients responding, or a response rate of 12.1 percent, and the P value for that was 0.7.

In the FDA analysis, again, we saw four complete responders in both arms of the study. We found two fewer PRs in the temozolomide arm than the sponsor did. The sponsor had 17, we had 15. So overall for temozolomide, we had 19 patients responding, or a 12.2

percent response rate. In the DTIC arm, we found four fewer partial responses than did the sponsor, so we have a total of 14 overall responses, or 9.4 percent, and our P value is 0.43.

In terms of sites of disease in responders, as Dr. Kirkwood pointed out earlier today, the cutaneous lesions tend to be most responsive -- cutaneous and nodal disease appears to be most responsive in melanoma, lung metastases have intermediate responsiveness, liver metastases are the worst, along with other visceral metastases, and as you can see here, the most responses occurred in patients with cutaneous disease or nodal disease or both. There were seven temozolomide responders, seven DTIC responders, for a total of 14 responses. Patients with lung involvement, with or without cutaneous involvement or lymph nodes, constituted the second-largest group of responses. There were six in temozolomide, four in DTIC, or 10. But even with liver, there were five responses overall, three temozolomide, two DTIC, and a total of four responders for other visceral sites.

For complete responders, of the four temozolomide complete responses, two had disease confined to skin lesions and/or lymph nodes, one had bone lesions, and one had liver lesions. All four DTIC complete responders had disease confined to cutaneous sites and

lymph nodes.

Generally speaking, the mean tumor area in responders was smaller than it was in all patients. The mean tumor area was 3.7 centimeters squared in the responders versus a mean tumor area of 10.8 square centimeters in all patients, and you can see from the range that we were frequently dealing with very small lesions. These were millimeter-size lesions, and they could be present primarily in the skin, but they were also present in lung and even in liver.

As was pointed out by the sponsor, median response duration was longer for temozolomide-treated patients than for dacarbazine-treated patients, 5.53 months versus 3.22 months. Originally when we prepared this slide, we had a P value attached to it. We subsequently removed that P value when our statisticians told us it was improper to do a statistical test on these two groups of responders. But there is median response duration prolongation with temozolomide.

Since we observed a lack of effect of temozolomide treatment on survival, we thought that possibly this could be explained by post-progression factors, and so we looked at what happened to patients after they had progression of disease. As you can see here, this slide indicates a number of chemotherapy cycles

that were received after progression, and as you can see, the majority of patients in the study, or 217, received at least one cycle of chemotherapy, and that almost exactly equivalent numbers of temozolomide and DTIC patients received that one cycle of therapy. Then over time the numbers of patients receiving subsequent therapy cycles decreased, but in all time periods equal numbers of temozolomide and DTIC patients received chemotherapy after disease progression.

This slide indicates the drugs that were used in these patients. The four drugs predominantly used were, again, dacarbazine, cisplatin, nitrosourea, and vinblastine or vindesine. For example, for DTIC, 28 patients who had initially received temozolomide received DTIC either as a single agent or as part of a combination after progression, and 29 patients who initially received DTIC received the drug again at the time of progression, and you can see data for the other drugs on the slide, but you can see, again, it's remarkably consistent that the number of temozolomide-treated patients and the number of dacarbazine-treated patients received almost the identical chemotherapy drugs post-progression.

In terms of survival after progression of disease, median survival for temozolomide patients was 4.7 months, median survival for DTIC-treated patients was 3.8

months, and the P value was 0.27, and we conclude based on these three slides that post-progression factors were not responsible for the failure to see a survival difference between temozolomide- and dacarbazine-treated patients.

Health-related quality of life was a secondary endpoint of the study. The protocol called for a longitudinal analysis and a QTwiST analysis to be done. The longitudinal analysis was not performed because of severe patient censoring. The analyses that were performed were the QTwiST analysis and three other analyses that had not been specified in the protocol. All of these analyses, though, were subject to heavy censoring. Generally speaking, no formal statistical analysis was done, and no statistically significant differences were observed.

In terms of pharmacokinetics, I'd like you to pay attention just to the bottom line of this slide, and this gives data on area under the curve. The two panels on the left deal with the parent drug. The two panels on the right deal with the active metabolite MTIC, the first panel, MTIC generated from temozolomide; the second panel, MTIC generated for dacarbazine. As you can see at the bottom, for both the parent drug and for the MTIC metabolite, the AUC was approximately two times greater for temozolomide than it was for dacarbazine, and this obviously raised the question about whether equivalent

amounts of drug were given to the two arms.

To try and answer this question, we decided we would look at toxicity profiles. Assuming that more active drug was given in the temozolomide arm, one might expect to see more toxicity in the temozolomide arm. And this slide, with slightly different denominators, is a slide you've seen earlier today, but this looks at the development of Grade 3 or 4 hematologic toxicity for the 156 temozolomide patients versus the 149 dacarbazine patients. You can see here that 6 percent of temozolomide patients developed Grade 3/4 anemia versus 7 percent for dacarbazine; for granulocytopenia, slightly more temozolomide patients developed this toxicity, 16 versus 13; and for thrombocytopenia, 20 percent versus 13 percent had a Grade 3/4 toxicity. So one might say here that there's a suggestion that maybe there's more toxicity in the temozolomide arm.

However, we also then went on to look at duration of nadir toxicity, and we approached this in two ways. This is the first, somewhat indirect way, but we looked at the percentage of all CBCs that were done in patients that demonstrated Grade 3/4 toxicity, and for neutrophils in temozolomide treatment, 17 percent of all the CBCs in temozolomide-treated patients had Grade 3/4 toxicity versus 25 percent for DTIC, and for platelets it

was 23 percent versus 25 percent. This suggests that the nadir of leukopenia was -- or the duration of Grade 3/4 toxicity was greater for DTIC than it was for temozolomide, which is a little bit opposite of the results in the last slide, and the sponsor's data on time from nadir to recovery is also in the exact same direction. Median time to recovery is longer for DTIC than it is for temozolomide for both neutrophil and for platelet. So we conclude from this that despite what we see in the AUC, equitoxic doses of both drugs were given.

When I presented the glioma data in January, there was a suggestion at that time that temozolomide treatment might be associated with hypercoagulability -- that is, there was a relatively high incidence of thrombosis, phlebitis, and pulmonary emboli in temozolomide-treated patients -- so we looked at the same data again for this melanoma population, and we don't see that tendency toward hypercoagulability. There were only two temozolomide patients with thrombosis, no phlebitis, and no suspected pulmonary emboli.

Now to get into interpretation of the data in this study, FDA has no problems with the intent-to-treat population and does have a problem with the sponsor's eligible patient population, because in the FDA analysis there was a minimum of 53 patients who either did not meet

protocol inclusion criteria or who did meet protocol exclusion criteria. Further, there was another group of 25 patients who were non-evaluable as far as response or progression-free survival goals, and we'll go into the reasons for this in the next couple of slides.

These are the FDA's reasons for study ineligibility, and as you can see, there were many, but basically as the sponsor suggested, what I did was go through the inclusion criteria and the exclusion criteria and see who didn't meet those criteria, and you can see the wide variety of reasons for ineligibility: abnormal brain scan, no measurable tumor, inclusion criteria not met, exclusion criteria met, the protocol said you couldn't have biologic treatment within 28 days and these people were outside those limits, couldn't have radiation therapy within 14 days. The baseline hemoglobin was addressed before. I happen to think baseline hemoglobin is an important test, in that it may well be a surrogate for performance status.

But the category that I have the most trouble with is that the protocol said the patients had to go on study within 3 months of the time of detection of metastases. I included the Stage 4 patients in here, because if a patient was Stage 4, they should have gotten into the study by 3 months, according to the protocol

criteria. But I didn't know about patients who were Stage 1, 2, or 3 before. It's a little ambiguous as to whether they were more or less than 3 months at the time they finally entered into study when they had progressed. But be that as it may, there were a significant number of ineligible patients.

Reasons for non-evaluability are six patients had no baseline tumor measurements, and another 19 patients had no tumor measurements after baseline, so that we couldn't use these individuals to look at either response or progression.

Turning now to a summary, this is the sponsor's survival data. As you know, the P value for the intent-to-treat population was 0.2, and as you go to the eligible population and the treated eligible population, the P value approaches 0.05, and the P value for the 6-month survival in the intent-to-treat population was 0.6.

FDA concerns with the survival analysis are, as we mentioned before, equivalence of survival is insufficient, since DTIC has never been shown to prolong survival. You've heard that the FDA disagrees with the eligible patient population. The sponsor has downplayed the 6-month survival analysis, so I won't say too much about that, except to note it wasn't prespecified in the protocol, and the FDA really doesn't use it as a basis for

marketing approval.

FDA concerns with progression-free survival are, as I pointed out, the P value was 0.002. The median progression-free survival difference was only about 11 days, but as you've seen in the progression-free survival curves, most of the important events occurred after the median had been attained. Another problem with it was that the DTIC patients were evaluated more frequently, and the final area was the possibility for bias, in that the study was not blinded.

FDA concerns with the response rate, you see on top in blue. The response rates by FDA analysis were 12.2 percent versus 9.4 percent. If you look at the odds ratio for tumor response, the lower bound of the 95 percent confidence limit is 0.66, so that the temozolomide response rate could be 34 percent less than the DTIC response rate, and if you look at difference in response rates, that difference was 0.028, with lower bound of the 95 percent confidence limit at -0.056 percent, so that if the DTIC response rate was actually 9.4 percent, the temozolomide response rate could be as low as 3.8 percent.

Response duration, I pointed out before that the response duration was 2.3 months longer in temozolomide-treated patients than in dacarbazine-treated patients.

FDA concerns with other secondary endpoints, quality of life. We know that all analyses were subject to heavy censoring and that no statistically significant conclusions could be drawn. The pharmacokinetic analysis, we have not yet explained the fact that the mean AUC for parent drug and MTIC was twice as high in the temozolomide-treated group, but as far as we can tell, equitoxic doses of both drugs were used.

In terms of safety, FDA agrees with the sponsor that temozolomide has an acceptable safety profile, most of the adverse effects are mild to moderate in severity, and that Grade 4 adverse effects were primarily thrombocytopenia or neutropenia.

That concludes my presentation, and I'll be happy to take questions.

DR. SCHILSKY: Thank you very much.

Are there questions from the committee? Dr. Johnson?

DR. DAVID JOHNSON: Dr. Cohen, I was very interested in the analysis done about the chemotherapy after progressive disease. Presumably none of the patients who were on temozolomide responded to DTIC?

DR. COHEN: I don't know the answer to that. That I was not able to get out of the data. I just know that they were treated, but I don't know what their

response was.

DR. DAVID JOHNSON: And do you have knowledge about whether any of the patients who progressed with DTIC received temozolomide?

DR. COHEN: There were none listed.

DR. DAVID JOHNSON: And, lastly, did any of the patients re-treated with DTIC respond?

DR. COHEN: As I said, there was no response data reported, so I don't know.

DR. SCHILSKY: Maybe I could just follow up on one aspect regarding the post-progression treatment, because we heard a comment earlier that some patients at the time of progression underwent resection of metastatic lesions. So could you identify those patients in your analysis? You didn't say anything about resected patients.

DR. COHEN: I didn't know about the resections at the time I did the analysis, so I didn't look for it.

DR. SCHILSKY: Questions? Dr. Krook?

DR. KROOK: We heard from one of our fellow clinicians for the sponsor that his impressions -- and I realize you did not see the patients, you only saw the data, but you did see the quality of life data, and at least the sponsor did not discuss that greatly. Did you get a feeling -- and I realize the problem with this is that people who took temozolomide had less problems, and,

again, we're into this touchy feeling thing, as one of my partners says -- had a better tolerance to the drug?

DR. COHEN: The sponsor measured quality of life on a 100-point scale. There were a variety of functional and symptomatic measures on a 100-point scale, with a higher value indicating better quality of life, and what happened in both groups after the initial treatment, quality of life declined slightly, uniformly, in the two groups. Subsequent to that, for at least the second and third cycles of treatment, quality of life in both groups improved slightly, and I'm talking about changes in the order of five to seven points on a 100-point scale, and after that there was such severe data censoring that you couldn't get anything more.

DR. SCHILSKY: If I could ask a similar question to you, having seen all the data, including quality of life data and so on, which, interestingly, were not presented by the sponsor, can you conclude or can you draw any inferences as to whether any patients on either arm of this study actually obtained any benefit from having been treated for their melanoma?

DR. COHEN: Based on the data as I saw them, my answer to that would be no, and I base that on looking at, for example, performance status at the time of progression. In the majority of patients, performance status did not

change at the time of progression, and when I say "majority," I'm talking about something between 50 and 60 percent, there was no change in performance status. In the remaining 40 to 50 percent, there was a decline in performance status at progression.

I guess in the patients who had a decline in performance status, you might say that the drug treatment prolonged baseline performance status. But people whose performance status didn't change, I don't think you could say the drug did anything.

DR. SCHILSKY: Dr. Johnson?

DR. DAVID JOHNSON: Along those same lines, I'm going to revisit the point just one more time, not to berate you specifically, but in the briefing book from the sponsor, they went to great lengths to quote Dr. Temple on numerous occasions regarding the FDA's position, and then stated from a publication put out by the FDA regarding this committee's charge with respect to approval of new products, and in one of the comments, a direct quote from the publication that states, "The primary aim of cancer treatment is to prolong life, but the demonstration that a new agent causes tumor regression and improves patients' clinical condition also supports approval of a new agent, even in the absence of improved survival."

From your review of the totality of data, can

you give me any information or any indication that in your judgment this product improves the patients' clinical condition sufficient for an approval by this committee?

DR. COHEN: Well, you're going to have to take the data as it exists. For response rate, there clearly was prolongation of response duration associated with temozolomide treatment. If we believe in the psychological advantage of progression-free survival in patients with advanced disease, then a delay in progression-free survival would be meaningful clinically, in that the lesions took longer to progress in some patients. I think those are the only two data points that I know of that would support an indication for temozolomide.

DR. SCHILSKY: Dr. Spiegel?

DR. SPIEGEL: If I may add some comments, we've learned two things about quality of life analyses. One is that it's almost impossible to describe them at advisory committees in a way that everybody understands it, or for our own statisticians to explain it to us in a clear way, and, secondly, that this is probably not the right setting to try and get meaningful quality of life summary statistics. It might be well suited for arthritis when everybody's alive who started your study, but as you mention and as we pointed out in our briefing book, the censoring that occurs with so many patients dropping either

because of progression or death who aren't available for the type of full quality of life to compare their endpoint to their baseline makes the best intentions go awry whenever we've tried.

Nonetheless, I don't want the committee to be left with the impression that we've held back information or that we had a poor outcome, and if you would wish, I'd ask our statistician to show among those patients who had quality of life or among the responders, there were scales where we did show improvement, but we felt that if we had presented that proactively today, it would be stretching the censoring that only allowed certain patients to be evaluable.

If you'd like, I'd like to let Dr. Sagano just tell you what data we do have on that.

DR. SCHILSKY: Before you show the data, perhaps I could ask if there are any members of the committee who wish to see the data.

DR. RAGHAVAN: Sure.

DR. SCHILSKY: Dr. Raghavan would like to see the data.

DR. SAGANO: Okay. As Dr. Spiegel pointed out and I think the FDA rightly pointed out, the censoring was very severe on all the study patients. We have a different situation, though, with responders, where they're in the

study long enough to begin to look at them longitudinally to see if there might be a difference between dacarbazine-treated versus temozolomide-treated responders.

The EORTC instrument that we use has six major functioning scales that are a part of the instrument. These are physical, role, cognitive, and we'll get into global and emotional later, but these first three illustrate a change from baseline over time for the responders, CR/PR patients, very small numbers for the two groups. The green line shows you in the physical functioning, on the top left, the temozolomide responders over time and their change from baseline, which essentially stays the same or actually goes up a little bit over time. The red line is the DTIC patients who are responders through the analysis. We have to be real careful, because at 24 months, which is the end of the curve there basically, most of the DTIC patients have already dropped out. But the responder analysis, I think, if you take it through 12 to 16 weeks, pretty much shows you what's happening to the responders on these two drugs.

So if you look at physical functioning, you can see the green line is always on top. Role functioning is always on top. The same goes for cognitive functioning, emotional functioning, social, and global quality of life. The green line is always on top. Again, I think as has

been pointed out, these patients, many of them came in with high functioning at baseline, so the change from baseline you wouldn't expect to be huge in terms of a positive effect. What you're trying to, I think, achieve in comparison perhaps with the dacarbazine patients who are going to be on trial or on study for a while is a maintenance of that quality of life, and I think you see that with the green line on all six scales.

DR. SCHILSKY: Now that you've seen the data, are there questions? Dr. Nerenstone?

DR. NERENSTONE: One of the things that concerns me about the quality of life analysis is that -- my concern is that the differences may not have anything to do with the medications, but in fact the way that they're given, just by bringing somebody into the office 5 days in a row versus giving pills that they only get at Day 1. And since this is a very subjective analysis, could you just please comment on that?

DR. SAGANO: We had no specific questions on that issue, and I think that's a very important one. In fact, these six sort of general functioning scales are sort of just measures of different aspects of quality of life. They really don't get at the reasons why.

The only thing that we looked at when we looked at other kinds of questions as to why we might be seeing

this sort of effect over time would be, in one of the symptom scales for the EORTC is a thing that goes into an issue that may relate to perhaps cumulative issues taking place on one treatment arm. But of all the other things that we looked at that were part of the QLQC-30, it was the only thing that sort of gave us some information about what may be happening to these patients over time. There was nothing else we could look at.

DR. SCHILSKY: Dr. Raghavan?

DR. RAGHAVAN: One of the things -- I guess I've missed the point. The denominator that you show there at starting point is very small, and I understand that there weren't that many responders, but I presume you measured quality of life in everyone. I understand the very laudable goal that you had of downplaying this information and recognizing the numbers are small, but did you not have data that related to the whole patient set that might give us a better sense?

We've established repeatedly today that there is a discrepancy when you've got small lesions between what constitutes "response" and patient benefit. Looking at the global set of patients treated in both arms, do you have quality of life outcomes that are independent of response category that show differences of any type that might enlighten us in any way?

DR. SAGANO: The only place where we had sufficient data from all the patients was at Cycle 1, before you started getting this churning, this dropping out very fast. Again, by Cycle 3 the majority of patients were already out of the trial. So at each of the first couple of cycles all the way through Cycle 5 and 6, you just saw lots of people turning over, and as they progressed, their quality of life actually did go down.

But what you see from Cycle 1 is what we would anticipate to be sort of the toxicity burden up front initially for all patients. So if you're looking at all patients and you want to look at as many as we can, this is the best data we have, which is the Cycle 1, which I think just basically talks about a little bit of the toxicity burden, which was fairly similar between the two drugs at Cycle 1, and after that point in time and after you get people dropping out, the early dropouts, then all you have pretty much to look at are the responders who remain on the study for long periods of time.

DR. SCHILSKY: Dr. Krook?

DR. KROOK: If you look at -- I'm looking at the slide again. It would be nice to say which of these are disease-related and which are drug, but you can't do -- we don't have that. Going back to what a lot of us did a long time ago, as physicians -- at least some of us are

here -- we used to use performance score as kind of a catchall before all these high scores, and so perhaps Dr. Cohen could comment on in the responders -- I mean, I realize that a lot of these people started with a PS of 0, but were there people who improved their PS from, let's say, 2 to 1 or from 1 to 0? You mentioned that they went the other way, but did we see an improvement of that physician-derived number as we looked at these in the responders?

DR. COHEN: I'm sorry, I really can't answer that. I don't have the data. I could get it, but I don't have it with me right now.

DR. KROOK: Would the sponsor? I mean, did we see an improvement in performance score in some of those responders?

DR. FROST: As mentioned, the majority of patients were performance 0 and 1. I think remarkable is that these patients maintained their good performance. For the patients with 0, there was not much room for improvement. While the patients were in response, none of them who had a 1 had decreased.

Again, we do not have detailed data, because some of the patients -- I mean, basically the treatment length was 12 months, and responders were ongoing, as you'll see by 36 months, 24 months, and so on. We have

only limited data for performance status after that, but we didn't see any decreases.

DR. SCHILSKY: Other questions? Dr. Simon?

DR. SIMON: Dr. Cohen, were you able to verify the duration of response data for the responders, or did you --

DR. COHEN: Yes.

DR. SIMON: So what kind of information do you have?

DR. COHEN: The data I presented actually was the FDA analysis of duration of response.

DR. SIMON: I'm not just saying that you redo the statistical analysis, but you verified the accuracy of the durations of response --

DR. COHEN: Yes, that's correct.

DR. SCHILSKY: Dr. Johnson?

DR. JOHN JOHNSON: I just wanted to comment about this quality of life material. We're looking at a certain number of points, and you might see on the scale that there seemed to be a difference of 10 points or 15 points. We have no idea whether 10 points is important, and we don't know how many points difference we would need in order to have something clinically significant. There's no definition.

For example, if you were doing a Kronofsky

performance scale, each 10-point interval along that scale is defined in clinical terms, and you can look at 50 and 80 and make a judgment as to whether you think there is any important change between 50 and 80. But between 50 and 80 on these scales, there's no way you can make such a judgment.

DR. SCHILSKY: Yes?

DR. SAGANO: If I can comment on that, one of the reasons we use the EORTC instrument is because there's been a lot of validation on what the clinical meaning of different score shifts looks like. Previous studies and publications on this instrument have shown that 10-point shifts in any of those six functioning scales appear to be meaningful to patients in terms of things they can detect when you look at the validations against their ability to show differences in those scales.

DR. SCHILSKY: Thank you.

Any other questions from the committee for the FDA?

(No response.)

DR. SCHILSKY: If not, thank you very much, Dr. Cohen.

Now, I guess I should ask whether the committee wishes to have any general discussion before we consider the specific questions.

(No response.)

DR. SCHILSKY: Okay. No one is taking the bait, so why don't we go on to the questions. We have what is perhaps the longest preamble to a set of questions that I've ever seen.

(Laughter.)

DR. SCHILSKY: I'll just give the committee members a few minutes to glance through this again, and it's largely a summary of both the efficacy and safety data that has already been presented this morning.

The first question, then, which appears to be at least two questions in one: "Do the results of this study, particularly the objective tumor response rates and response durations for temozolomide versus dacarbazine, and the effect on progression-free survival, even in the absence of any effect on survival, provide substantial evidence of effectiveness? In considering this, note that MTIC is thought to be the active metabolite for both drugs." We're asked to consider whether this information on the mechanism of action and the PK data for MTIC affect the conclusion, even in the absence of evidence of an effect on survival.

Perhaps we should deal with the first question here, the first half of this question: Do the results of the study, in the absence of any effect on survival,

provide substantial evidence of effectiveness of temozolomide? Open for discussion.

DR. KROOK: Well, for discussion purposes, you could turn the drug to dacarbazine the same. That's one of the issues, so you -- I mean, does it provide effect of this disease on either drug? I realize the question, but I think it goes back to that question.

DR. SCHILSKY: Well, does anyone care to address the issue of whether dacarbazine is a drug that is known to have any efficacy in treating melanoma, since that's the comparator here? It seems in a sense that's the crux of the matter, as has been pointed out. I think most everyone around the table is likely to agree that temozolomide has not been shown to be superior to dacarbazine. The sponsor has made the case that the two drugs are equivalent. The question, though, is whether the comparator, the dacarbazine, is a drug that has any effectiveness, so is it, therefore, meaningful for temozolomide to in fact be equivalent to that drug?

Comments on that?

DR. DAVID JOHNSON: I'll make a comment. I actually think that confuses the issue of what we're being asked to do. If we're separately being asked to give our opinion about dacarbazine, I'm happy to do that, and I think most of us have stated that we don't believe that

dacarbazine is a particularly effective drug. Although it occasionally makes the tumor shrink, we're not convinced that it does much else for the patient. Certainly, the asymptomatic patient.

I would prefer to not get off on a sideline about the validity of the comparator, because I happen to agree with Dr. Spiegel when he made the comment earlier that even though no conversation was held with FDA, I suspect that had such a conversation been held, a decision very well might have been made to use DTIC as the comparator. And that's okay, because they came in looking for superiority, not comparability, and that's a wholly different issue, in my opinion.

The point that is being asked of us in this question is, do we believe, based on the response rate, durations of response, et cetera, that this is an effective drug? And in a sense that takes us back to 1975. I mean, we saw the data on which the FDA approved DTIC, and I don't personally subscribe -- and have said so many times before in this forum -- that simply seeing a tumor shrink is sufficient to compel me to personally vote for approval. I would like to see something else in concert with that response rate that seems beneficial, and in many instances that's judgmental. I would have certainly liked to have seen in the symptomatic patient some evidence that they had

improved, even if it was a symptom assessment score on a card that the patient ticked off 1 through 10, "I'm better, I'm worse." That would have made me feel a little better about how I feel about it.

So based on the way the question is phrased, my personal view would be, no, I don't think that the results of this study convince me that temozolomide -- I'm not particularly interested in DTIC, I'm interested in temozolomide -- has been shown to be an effective drug in this disease.

DR. KROOK: Except for purposes of comparison.

DR. DAVID JOHNSON: Well, again --

DR. KROOK: I mean, if you go back to that --

DR. DAVID JOHNSON: Yes, if the question were asked of me --

DR. KROOK: It's equal.

DR. DAVID JOHNSON: Well, you know, if something is equal to nothing, it's still nothing.

DR. KROOK: Well, that's part of the problem.

DR. DAVID JOHNSON: That's true. But, again, the study designed by the sponsor was a superiority study, so we could all agree that DTIC is at worst a bad placebo, and so I think it was reasonable to construct a study that looked for superiority.

Now, candidly, had I been the advisor to the

FDA, had they come back and asked the question about an equivalence trial, I would have warned them against doing such. I would have said that the question will be raised by a number of people, not the least of whom would be myself, of the validity of using DTIC at all as a useful drug for comparative purposes. In this country, I'll grant you that it's likely that the study could only be done with DTIC as a comparator. But I see the question as different, and if I'm interpreting it incorrectly, I certainly can be instructed differently by the FDA, but to my way of looking at this, the comparator issue only confuses the issue further, makes it an emotional one.

I think the issue is did temozolomide show something that allows me to think that it's an effective drug, and merely shrinking the tumor has not convinced me that it's an effective agent.

DR. SCHILSKY: So, David, if this were a single-arm trial that's presenting data that we've seen on temozolomide, a large Phase II trial, just to ask it again, would you conclude based on those data that temozolomide had any effectiveness?

DR. DAVID JOHNSON: No. This question has been asked of us before in accelerated approval settings, and I've been troubled personally -- and I think many of us have -- about that particular situation in which we're

often asked to make a conclusion based on Phase II data. The times when we've come down in favor of approval, I think we've been shown, in some instances in a very convoluted way, patient benefit. Here even the sponsor, I think appropriately, did not present data that they felt were adequate to address those issues, and have really asked us to simply look at a response rate, even though it's a randomized trial, and then hope that emotionally we will respond by saying, "Well, DTIC is an appropriate comparator. It doesn't look worse than, even though it's not an equivalency trial."

I personally think that that's carrying it a little too far for us to go and approve the drug.

DR. SCHILSKY: Comments? Dr. Temple?

DR. TEMPLE: Let me ask that you comment specifically on one of the endpoints, which was the time to progression. By both their analysis and our analysis, time to progression was improved compared to the active control. As Dr. Cohen pointed out, the median difference was tiny, but the tail showed something. Always a problem when you have a very low response rate.

DR. DAVID JOHNSON: And I'm sensitive to that, very much so. Remember, I do lung cancer work, so we're very interested in the tails in curves, and medians don't mean too much. I might have been willing to accept that

had it been linked to something that I could have construed as a patient benefit in a clinical sense, and I don't see that linkage. I personally don't see that linkage.

DR. SCHILSKY: Again, I think the time to progression is a little bit confounded by the differences in the frequency of evaluation, which is going to bias things in favor of temozolomide. Those patients were evaluated slightly less often with respect to progression, so it's likely that progression is going to be identified a little bit later in those patients.

DR. TEMPLE: We actually discussed that a little bit, and I'm sure someone who knows how to do this sort of thing could model the effect of having one group measured every 4 weeks and the other group measured every 3. My guess is that it could certainly account for a few days difference easily, but it probably can't easily account for the difference in the tail, where it looks larger. But we haven't done that modeling. We perhaps could sometime. I think it is an interesting question.

DR. DAVID JOHNSON: Well, actually, I did have my statistician do that modeling, and if the patient were to get out to three and certainly if they were to get out to four assessments, you can come up with a 14-day difference, is the model that they constructed, which I think 11 days is what in fact was observed. And then

according to, again, my statisticians, when one gets out to the tail with the numbers that one's dealing with out there, then those differences become less -- I mean, the overlap in terms of the confidence intervals is there, so then it becomes less relevant in terms of what that really represents.

DR. SCHILSKY: Other comments? Jim?

DR. KROOK: My only other comment is the word "substantial." My own feeling, as one of the reviewers, the word "substantial" leans me to answer that question as no.

DR. SCHILSKY: Does anyone have any comment to make regarding the second half of this question? Does the pharmacokinetic data we've seen in any way -- how do you take that data into account, if at all, in rendering any judgment here?

Are you going to answer the question?

DR. TEMPLE: No, I just wanted to comment on the word "substantial." This may not make much difference to you, but that word is taken directly from the law, and believe it or not, it was meant to describe a modest standard. In law when you want to say "really convincing," you say "beyond a reasonable doubt." In some civil actions you say "preponderance of evidence," that means more than half. When you say "substantial," you actually mean less

than that. The way the law comes out, it says "substantial evidence from well-controlled studies," and the gestalt is one of a reasonably high standard.

I don't know if that helps at all, but I had to say it.

(Laughter.)

DR. SCHILSKY: Okay. Thank you for that clarification.

(Laughter.)

DR. SCHILSKY: Well, perhaps we're prepared to vote on the first question, since no one is interested in commenting about the pharmacokinetics. I suppose we can just contract the question to be, do the results of this study provide evidence for effectiveness of temozolomide?

All who would say yes, raise your hands.

(Show of hands.)

DR. SCHILSKY: All who would say no?

(Show of hands.)

DR. SCHILSKY: Ten no.

Any abstentions?

(Show of hands.)

DR. SCHILSKY: One abstention.

Okay. I guess we don't have to answer the second question, in view of our answer to the first question. So perhaps we can go on to Question 3: Does the

committee recommend approval of temozolomide for treatment of advanced metastatic melanoma?

Any discussion of that before we vote?

(No response.)

DR. SCHILSKY: All who would vote yes?

DR. KROOK: One comment, if I can, before we vote. My thought to myself is that if I am a community oncologist, which I am, and I have the opportunity to make the decision whether to use a chemotherapy agent, the choice which is directed to me by the present standard of care is DTIC. The issue then becomes what I think I brought up earlier, and that's the question David perhaps does not want to ask or answer, does DTIC give a meaningful response and effectiveness, and in a way he answered the question, and I think a lot of us feel that same way. But I go back to my experience with ease of administration, convenience, and otherwise, as will reflect perhaps my vote, unless it changes between now and then.

DR. SCHILSKY: Are you suggesting --

DR. KROOK: I guess I'm saying since at the moment those of us who practice clinical medicine have DTIC available, and at least I perceive that the mechanism of action is similar or at least close to the same and the toxicity is no worse, that this may be an ease of administration and other factors to consider for those of

us who practice community medicine. I mean, is this a form of a drug that is approved that is simply going to be able to be administered easily, more conveniently for both a physician, or a provider, as we're now called, and the patient? That influences my vote as we come to this.

DR. SCHILSKY: So perhaps I could just ask you, in view of your vote on the first question, whether you're telling us that you would prefer to give an oral placebo to an I.V. placebo?

DR. KROOK: Yes. In a way the answer is yes. We give in to this -- and all of us face this in practice, what do you do with somebody who wants to do something, and you realize -- I mean, I pass out, as a lot of people do, hormonal drugs, realizing they may not do much, but be that, again, an improved quality of life, the person who's taking it feels better. Now, this may be the American way, but I do practice that way, and I do practice do no harm.

DR. SCHILSKY: I guess I would just comment that it seems to me that there are oral placebos available that are even less toxic than temozolomide.

DR. KROOK: Agreed.

DR. OZOLS: If you want to use this kind of an agent, you're still talking about response rates being so extraordinarily low that at most you're talking about probably giving a patient one or two cycles before they

progress. So it's not like long-term oral versus long-term I.V.

DR. SCHILSKY: Dr. Temple?

DR. TEMPLE: Let me make sure about one thing. The second half of the first question gave you the opportunity, but in a somewhat hard-to-follow way probably, to say, "We don't actually care if effectiveness has been shown by these trials, it's probably the same as DTIC, and maybe that's good enough." What I heard in the discussion was that you do not agree with that thought. But if I'm wrong, you should tell us. What you said was, "It doesn't really matter whether there's just another way to give DTIC. The fact that 25 years ago we reached the conclusion that that was effective shouldn't influence us now to declare this drug effective."

I'm just describing what I heard you say. If we've got that wrong -- that's what this question was designed to raise, and we just need to be sure we understand you. We certainly know that for reasons that have been widely discussed, these trials don't show effectiveness in terms of survival. But another view could have been, "Well, you wouldn't really expect much, it's the same drug, and we're willing to live with the past." But I think you've told us, no, we're not.

DR. SCHILSKY: Okay. So you've prompted a lot

of discussion.

PARTICIPANT: Well, I think Derek had his hand up the longest there.

DR. SCHILSKY: All right. Derek, go ahead.

DR. RAGHAVAN: Well, I think the key issue is that it's almost the year 2000, and we have the opportunity to maybe say that in 1975 an error was made, and the problem is this, that patients with melanoma deserve effective treatment, and they don't deserve ineffective toxic treatment, and that's probably what DTIC is. That's not the fault of the sponsor, because they're absolutely right in saying that oncologists -- and it's not a North American phenomenon, it happens in Europe, it happens in Australia as a function of their frustration with the inability to offer effective therapy to people with melanoma. Recognizing that getting treatment helps some patients get through that crisis period, people give DTIC with good intention, it just happens that they're giving a toxic drug that requires the patient to present repetitively.

The reason that I think many of us who are active clinicians on the committee are choking on this is, we keep thinking to ourselves, "Well, given that that's a systematic error in the system, maybe we can make the error less by having a less unpleasant mode of delivery of a

useless drug." And I think David Johnson, with his usual slow-speaking, very, very clear thought, has gotten to the crux of the matter, which is, that's the wrong way to think about this. We have to take this drug on its merits, and basically, unfortunately, I guess through no fault of their own, the sponsor has compared and demonstrated essentially an absence of real difference from an ineffective drug that happens to have some toxicity. The one bit of difference is it probably has less toxicity based on delivery.

So I think that the issue that you're reading, Bob, is the fact that none of us likes DTIC, we get presented with patients, and we sometimes use it, remembering the one anecdotal case. Tamoxifen will give you anecdotal -- the longest response I ever saw was in Australia, to a patient who was treated with tamoxifen and nothing else for biopsy-proven metastatic melanoma in the liver.

We all have the odd anecdote, but I think the reality of the situation is, the way this has played, Dr. Calvert has shown that there are occasional responders of long term. On the balance of the data today, most of the patients who did well were doing okay, except for having a terrible diagnosis, when they hit the trial. So it makes it very difficult to get really excited about this. The fact that this now gives you an avenue for giving a pill,

as Dr. Schilsky said, there are lots of pills that don't make you sick at all.

DR. SCHILSKY: And just one comment. I don't believe we've seen any data here to suggest that temozolomide is less toxic than DTIC. I think we all agree that it's easier to give, but it doesn't appear to be less toxic.

David, do you have a comment?

DR. SLEDGE: Do you ever look in this direction?

(Laughter.)

DR. SCHILSKY: I'm sorry. Dr. Sledge?

DR. SLEDGE: Go ahead, Stacy.

DR. NERENSTONE: I just wanted to agree with what's been stated, but also to suggest that if it does become orally available, that you'll actually increase the toxicity, because performance status 2 and 3 and 4 patients that we would never consider because they can't come into the office, and can't be monitored because their performance status is too poor, are now going to be given this medication. So instead of decreasing the overall toxicity, I think it's going to perhaps do the opposite.

DR. SCHILSKY: Dr. Sledge?

DR. SLEDGE: Thank you.

You know, Derek said earlier, quoting George

Kinellas, that melanoma was the disease that gave cancer a bad name. I think I'd extend that a little bit further, which is, DTIC is a drug that gives medical oncologists a bad name, in that the contempt that Hilary's plastic surgeons hold medical oncologists in England is not just an English phenomenon, but is a phenomenon in the United States, and it's a contempt that's based on us arguing over very tiny differences with fairly mediocre drugs, and I think this is a fairly classic case of that.

DR. SCHILSKY: Other comments?

Have we clarified where we stand for you, Dr. Temple?

DR. TEMPLE: Yes, that was very helpful.

DR. SCHILSKY: Mr. McDonough?

MR. McDONOUGH: As one sitting here hoping not to become Stage 4, especially after this discussion, I almost have to wonder why we're not voting to outlaw dacarbazine. Because faced with the possibility of this coming back and I'm told I'm going to get dacarbazine, I'm not going to have a hell of a lot of faith in it.

DR. SCHILSKY: Any comments on how we outlaw drugs?

(Laughter.)

MR. McDONOUGH: The second and last point is this. I don't see how you can leave one kid on the block

that has a bad reputation and not let the other one on the block, too. I mean, if you're going to purge, then you ought to purge.

DR. TEMPLE: Well, that's obviously an interesting and provocative question. I believe many of the older therapies that have been approved would have difficulty supporting their effectiveness in modern terms, and an important question is which ones to go back and try to extirpate, and I'd be interested in what people think.

To some extent we live with the past and figure that drugs that don't work very well dwindle. If there's something really bad about them, we do try to remove them from the market if it's very clear. If it's not clear, it's a difficult chore, and we don't usually undertake it. But we're prepared to listen to advice on that subject.

DR. SCHILSKY: Of course, everything is relevant, and it's likely that drugs that we've approved in the last year, 20 years from now, we would hope, will be viewed as being largely ineffective therapies.

DR. TEMPLE: Well, oncology is a little different from some other disciplines. In a lot of situations where there are standard, well-controlled trials with standard, easy-to-measure endpoints, you can be fairly sure that what you've got is what you've got. It's very unusual for you to go back and decide that a drug just

doesn't have any effect. And even in this case, you haven't decided that the drug's inactive, you've decided that the endpoints that were used in the past aren't really valuable, which is slightly different from concluding it has no effectiveness at all. But still it's an interesting question.

DR. SANTANA: I'd like to comment on the PK, because I think you asked for that advice, and we haven't commented on it.

I think it's very intriguing that when you give this agent orally, you get a greater systemic exposure. But what I think we didn't see was, how does that systemic exposure translate to something either related to the tumor or to the toxicity? So clearly the issue is that maybe this drug, yes, the systemic exposure is important, but you have to use it in the setting in a tumor in which the drug is truly active that you can say there will be some patients that don't respond because they're not getting the appropriate systemic exposure, but if I use it this way, I'm increasing systemic exposure, it's likely that other patients will respond. But we didn't see that. I think it's just not there.

So the observation is there that systemic exposure is higher when you give it orally, but what does that mean? I don't know. There's no data to support

beyond that observation.

DR. SCHILSKY: Except that I think we could probably say that within the limits of this study there doesn't seem to be a concentration/effect relationship, because the patients on temozolomide got twice the drug exposure and didn't seem to have any greater benefit.

DR. SANTANA: Well, be careful, because that was the point I made earlier. That was only 14 patients or 15 patients in each of the arms, so you're now trying to generalize those observations for the group at large, and there was a lot of variability, interpatient variability, in those numbers. There may be a lot of overlap, so you've got to be careful.

DR. SCHILSKY: Good point.

Derek?

DR. RAGHAVAN: I think the other point that comes out from the point Mr. McDonough made is, we should remind ourselves that we shouldn't be doing harm. We have at least one cooperative group prominently represented at this table -- all the groups, but one chairman of a group at the table -- and I guess it serves to remind us that the issue of placebo control in this disease becomes very important, and the fact of the matter is that private practitioners who are practicing oncology don't have an ethical responsibility to give DTIC, and it should remind

us that patients with metastatic melanoma should be entered into clinical trials.

That's to remind the private practice sector and the academic sector who are in practice and remind the academic sector that we should be designing trials maybe without DTIC as the control arm, because today I think we've come to the very conclusion, with a lot of work from Dr. Cohen, that we don't really know the state of the art here, and maybe we need to go back and get some very simple placebo-controlled trials that ask the question about DTIC, notwithstanding the data we've heard today.

DR. SCHILSKY: Dr. Temple?

DR. TEMPLE: I guess I would offer another observation and see what you think about it. This situation reminds me again that in the past we've urged companies to identify tumor-related symptoms, and, of course, to do that you'd have to take people who were at a stage where they were having them and in a fairly rigorous way try to show whether you can relieve them. It's still the kind of observation we hardly ever see done systematically. It's been proposed a number of times.

For what it's worth, in situations where the response rate is only modest, that may be the easiest way to make a persuasive case that you're doing good, if you can show a reasonable percentage of those, and it still

surprises me that that's so rarely attempted. Instead we see scales that evaluate social function and all that kind of stuff. Those are very insensitive to improvement. There's almost no chance of winning on those, and yet we see them over and over again, whereas something focused on the disease itself, perhaps even the particular disease from a particular patient rated on some kind of scale of 1 to 10, seems an enormously more promising way to go, and we still never see it, and I just wondered if you had any views on why.

DR. DAVID JOHNSON: Actually, I'm glad you said that, because, again, we've had this discussion here before, and it goes back to a point that Richard made earlier, and that is, if this were a Phase II presentation of temozolomide with a -- let's just give it an arbitrary 15 percent response rate, but something that Hilary's country does much better than our own, they use the symptom assessment scales and tick off the symptoms related to the patient's disease -- it's sometimes easier in some diseases like lung than it would be perhaps in melanoma, but certainly in that setting symptom improvement often vastly exceeds objective response results.

Lung cancer is a good example. In metastatic disease, where one sees only about a 30 percent response rate to the common chemotherapy regimens, up to 70 percent

of patients show symptom improvement. Now, one can argue about is that a placebo effect. It's hard to imagine if you're getting cisplatin that that's a placebo effect, but it might be.

But those are the kinds of data that in my mind -- that's what I was saying earlier. If we had seen these data just exactly as they are, but in addition to that I had seen an analysis of tumor-related symptoms that showed improvement from the patient's perspective, I could have felt -- then I would have exactly felt the way Jim has expressed himself, and that is, as a clinician I would prefer to give an oral drug to the intravenous drug, and it would have changed my perspective completely on the presentation of this product.

DR. TEMPLE: It's remarkable how infrequently we see them. Sometimes. I mean, the photophrin kinds of assessments are really those.

DR. DAVID JOHNSON: Right. That was done post hoc to some extent, so it was a little bit contrived. But I think the issue of having the patient tick off -- if you can do a quality of life assessment, if one could do a symptom assessment, it seems to me to be worthwhile. I think it's worth FDA exploring the right tools for recommending to sponsors what they might employ in that situation.

DR. SCHILSKY: Okay. Any other discussion?

DR. KROOK: As long as we're -- and perhaps I'm going to Dr. Temple here. What is the feeling of the FDA toward DTIC?

DR. TEMPLE: I think we're going to consider your remark.

DR. KROOK: Okay.

DR. JUSTICE: Can I just bring up the use in Hodgkin's disease? Does anybody want to comment on that?

DR. DAVID JOHNSON: Yes. It's used.

DR. SCHILSKY: And when there was an explosion in the Japanese factory that provides it, it's not clear that anyone was disadvantaged by that event.

DR. JUSTICE: But, I mean, you might hear from your colleagues if you recommend that we remove it from the market.

DR. DAVID JOHNSON: No, no, no. We didn't say take it off the market. Our Hodgkin's patients wouldn't like it.

DR. JUSTICE: Well, I'm not sure that it's labeled for Hodgkin's disease.

DR. DAVID JOHNSON: Then it's too bad.

(Laughter.)

DR. TEMPLE: Well, we hear you, and I think we'll consider what we're prepared to undertake and perhaps

get back to you. Perhaps in closed session.

DR. SCHILSKY: Okay. Now, are we prepared to vote on the third question, then? We've had excellent discussion. So does the committee recommend approval of temozolomide for treatment of advanced metastatic malignant melanoma?

All who would vote yes, raise your hands.

(Show of hands.)

DR. SCHILSKY: One yes.

All who would vote no?

(Show of hands.)

DR. SCHILSKY: Ten no.

Any abstentions?

(No response.)

DR. SCHILSKY: Okay. I guess we are done. Thank you very much.

DR. TEMPLETON-SOMERS: We'll be having a closed session this afternoon, so if we can ask the committee and the FDA to return by 12:45, we'll get an earlier start on that.

(Whereupon, at 11:38 a.m., the open session was adjourned.)