FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Oncologic Drugs Advisory Committee

WEDNESDAY, DECEMBER 16, 2009

9:00 a.m. to 2:30 p.m.

Washington Hilton DC North/Gaithersburg

620 Perry Parkway

Gaithersburg, Maryland

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I N D E X

P R O C E E D I N G S

8:00 a.m.

DR. WILSON: I would like to welcome you all to this ODAC. We are going to be considering a proposed indication from OSI for Tarceva monotherapy, as indicated, as first-line maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer

who have not progressed on first-line treatment with a platinum-based therapy.

Let's go ahead and go around the room. Let's start at the left side. And please say your name and where you're from for the record.

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

DR. JUSTICE: Robert Justice, Division of Drug Oncology Products.

DR. COHEN: Martin Cohen, Division of Oncology Drug Products.

DR. CHATTOPADHYAY: Somesh Chattopadhyay, statistics, from FDA.

DR. KRASNOW: Steve Krasnow, chief of oncology at the VA in Washington, D.C.

MS. MOFFITT: Pam Moffitt, Sioux Rapids, Iowa, lung cancer representative.

MS. MASON: Virginia Mason, Inflammatory Breast Cancer Research Foundation, consumer rep.

DR. LYMAN: Gary Lyman, medical oncologist and outcomes researcher from Duke University.

DR. RICHARDSON: Ron Richardson, medical oncologist, Mayo Clinic, Rochester, Minnesota.

DR. KELLY: Kevin Kelly, medical oncologist, Yale University.

DR. VESELY: Nicole Vesely, Designated Federal Official, ODAC.

DR. WILSON: Wyndham Wilson, medical oncologist, National Cancer Institute.

DR. SEKERES: Mikkael Sekeres, medical oncologist, Cleveland Clinic.

DR. TEMPERO: Margaret Tempero, medical oncologist, University of California San Francisco.

DR. LINK: I'm Michael Link, a pediatric oncologist at Stanford.

DR. FREEDMAN: Ralph Freedman, gynecologic oncologist, MD Anderson Cancer Center.

DR. LOGAN: Brent Logan, biostatistician, Medical College of Wisconsin.

DR. FLEMING: Thomas Fleming, Department of Biostatistics, University of Washington.

DR. HUBBARD: Richard Hubbard, respiratory physician with Pfizer. I'm the

industry representative.

DR. WILSON: And let me ask Dr. Johnson, who was late, to say his name into the record.

DR. JOHNSON: John Johnson, clinical, FDA.

DR. WILSON: Thank you very much. At this time we will have a conflict of interest statement read.

DR. VESELY: And before the conflict of interest statement, for topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine

Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

For the conflict of interest statement:

The Food and Drug Administration is convening today's meeting of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies, and are subject to federal conflict of

interest laws and regulations.

The following information on the status of the committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 USC Section 208 and Section 712 of the Federal Food, Drug and Cosmetics Act is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when

necessary to afford the committee essential expertise.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and, for purposes of 18 USC Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves discussions of Supplemental New Drug Application 021-743/S-016, with the trade name Tarceva, erlotinib tablets manufactured by OSI Pharmaceuticals, Inc. The proposed indication for this product is first-line maintenance, monotherapy treatment in patients with a form of lung cancer called non-small cell lung cancer that is either locally advanced of metastatic and who have not progressed on first-

line treatment with platinum-based chemotherapy.

This is a particular matters meeting during which specific matters related to Tarceva will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

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

We would like to remind members and temporary voting members that if the discussions

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

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

DR. WILSON: We will start with the sponsor presentation, but prior to that, there's a new statement that I would like to read.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsors, non-employee

presenters, and responders to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interests in the sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you, at the beginning of your presentation, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

So with that, I would like to ask Karsten Witt to start.

DR. WITT: Good morning, Dr. Wilson, ODAC members, Dr. Pazdur, FDA staff, and guests. I am Dr. Karsten Witt, Senior Vice President, Oncology Development at OSI Pharmaceuticals. We have a longstanding commitment to improving outcome for lung cancer patients, and I would therefore like to thank you for the opportunity to present the data

in support of the supplementary NDA for Tarceva as first-line maintenance treatment.

OSI submitted an application on March 18, 2009 seeking approval for Tarceva based on the SATURN study conducted by our development partner, Roche. This was a global, randomized placebo-controlled study in 889 patients with advanced non-small cell lung cancer.

The study met its co-primary end point by demonstrating significant improvement in progression-free survival in both the overall population and in patients with EGFR immunohistochemistry-positive tumors.

The study also demonstrated that Tarceva treatment resulted in significant improvement in overall survival. In addition, there were no new safety signals from this study.

The proposed indication is Tarceva monotherapy, as indicated, as first-line maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer who have not progressed on first-line treatment

with platinum-based chemotherapy.

Before introducing the other presenters, let me just orient you to the background on Tarceva, including the regulatory history for the application.

Tarceva is an orally available small molecule EGFR tyrosine kinase inhibitor which is approved in more than 90 countries. More than 400,000 patients worldwide have been treated with Tarceva since the initial approval five years ago for the treatment of patients with non-small cell lung cancer after failure of at least one prior chemotherapy regimen. The large body of data has enhanced our understanding of the side effects resulting in a well-established safety profile.

The approval of Tarceva was based on the pivotal study NCIC-CTG BR.21 in patients who had not progressed after receiving at least one prior chemotherapy regimen. This was a randomized placebo-controlled trial that demonstrated an overall survival improvement with a hazard ratio of 0.73 in favor of Tarceva treatment.

Survival benefit was seen across multiple relevant subgroups. This included a statistically significant overall survival benefit, regardless of histology, as shown by a hazard ratio of 0.71 in patients with adenocarcinoma and a hazard ratio of 0.67 in patients with squamous cell histology.

In a hypothesis-generating analysis, EGFR protein expression by immunohistochemistry was evaluated in a subset of patients and correlated with overall survival and apparent greater benefit was seen in patients with EGFR immunohistochemistry-positive tumors. Therefore, EGFR immunohistochemistry was identified as a biomarker to be explored prospectively in future trials.

The SATURN study design was in the planning stage during the FDA review of the initial lung application and prior to the second third-line lung cancer approval in November of 2004. Therefore, SATURN was selected as the study to evaluate the relationship between EGFR protein expression and clinical outcome. Following special

protocol assessment discussions with the FDA on the protocol, the SATURN study was initiated in 2006.

The dialogue with the FDA during special protocol assessment procedures, included reaching agreement on study design details, defining acceptable first-line platinum doublets, the statistical assumptions, including powering the study for overall survival. The co-primary end points for progression-free survival in the overall population and in a sub-population of patients with EGFR immunohistochemistry-positive tumors were defined. Thus, tumor tissue collection was mandated. The protocol was accepted by the FDA in September of 2005.

The next speaker, Dr. Federico Cappuzzo, the principal investigator, will provide rational and study design details for the SATURN study. Dr. Angela Davies will summarize the efficacy and safety results. And Dr. Paul Bunn from the University of Colorado Cancer Center will provide his expert opinion on how Tarceva should fit into the treatment paradigm in the management of non-

small cell lung cancer patients.

Dr. Cappuzzo?

DR. CAPPUZZO: Dr. Pazdur, Dr. Wilson, ODAC members, FDA staff, and guests, my name is Federico Cappuzzo, a medical oncologist from Milan, Italy. And first of all I want to thank you for the opportunity to present at this meeting. And before starting, I would like to thank the patients who participate in the SATURN trial and their relatives, as well as the other investigators and staff.

Lung cancer remains a challenging and devastating disease. Most patients will present with advanced stage disease without possibility for a curative surgery. Lung cancer is accountable for the death or more patients than colon, prostate, and breast cancer combined, and the average two-year survival for patient with stage III or IV disease is between 10 and 20 percent.

The currently approved regimens for advanced non-small cell lung cancer are outlined in this table. Pemetrexed was recently approved as

first-line maintenance treatment, but limited to non-squamous histology. Thus, the maintenance paradigm has now been recognized by regulatory agencies in both Europe and the United States. And despite the survival improvement achieved with multiple regimens in advanced non-small cell lung cancer, current treatment options are not adequate.

The greatest impact in improving disease outcome is mainly achieved in the first-line setting. Inevitable, the disease will progress, and the goal is therefore to provide active therapy while patients still are able to benefit.

Practice data have shown that only about 60 percent of patients completing first-line therapy even receive second-line treatment, and of those, only about 50 percent will receive third-line therapy.

Maintenance therapy, therefore, represents an important opportunity to improving outcome and by building on the benefit from first-line therapy and by maximizing the number of non-small cell lung cancer patients who get access to

active therapy early in the course of their disease before performance status and disease-related symptoms deteriorates.

Current maintenance options are, however, limited to patients with non-squamous histology with an intravenous cytotoxic chemotherapy. That is why the convenience of an older agent like Tarceva with a proven benefit, regardless of histology, can meet this unmet medical need.

The rationale for the strategy of maintenance with a new single agent after platinum doublet therapy includes the fact that Tarceva prolongs the survival in the second- and third-line setting. But many patients progress rapidly after they start chemotherapy and never receive second-line therapy.

Therefore, instead of waiting for a radiologic or a symptomatic progression, maintenance therapy with Tarceva could delay disease progression and prolong survival. And this hypothesis formed the basis for the SATURN study design.

Depicted here is the study schema. And it's important to note that the study consisted in two periods. On the left side you can see the chemotherapy running period. Nearly 2,000 patients with newly diagnosed stage IIIB not amenable for chemoradiation, or stage IV, non-small cell lung cancer, were entered into this period. They all provided mandatory tumor tissue for EGFR immunohistochemistry analysis.

After completion of four cycles of platinum-based chemotherapy, patients with no progressive disease were randomized one to one to Tarceva, at the standard dose of 150 milligrams per day, or placebo, until disease progression or death.

Stratification factors included EGFR immunohistochemistry status, stage of disease, ECOG performance status, chemotherapy regimen, and smoking history, and region.

The primary objective of the study was to evaluate progression-free survival in the overall population and the progression-free survival in the

population with the EGFR immunohistochemistry-positive tumors. Progression-free survival duration was evaluated from the time of randomization until the time of disease progression or death, and the primary analysis was based on the investigator's assessment. But this was corroborated by blinded independent review. Scanning intervals were performed every six weeks.

The rationale for choosing PFS as the primary end point is based on the fact that the number of treatment options for patients with advanced non-small cell lung cancer was increasing. As mentioned earlier, there are now three approved second- or third-line drugs which have a proven survival benefit, and therefore the possibility to bias the ability to detect the survival effect of earlier lines of therapy.

Thus, clinical relevant PFS improvement is a meaningful measure of treatment benefit without being confounded by subsequent therapies. This approach has been adapted in diseases such as breast and colorectal cancer, where multiple

subsequent agents are used.

Key secondary objective included overall survival and progression-free survival in patients with EGFR immunohistochemistry-negative tumors. Correlation with outcome was also evaluated in the prospectively defined biomarker sub-populations listed here. Quality of life assessment included time to symptom progression using the FACT-L instrument. And finally, the safety profile was assessed by evaluating adverse events and key laboratory abnormalities.

The study was powered at 80 percent to detect a 25 percent increase in progression-free survival in the overall population. The alpha span for this analysis was at the 3 percent level using a two-sided test. A total of 731 events were required for the final analysis. This required randomization of 427 patients to each of the study arms.

The co-primary end point of progression-free survival in the EGFR immunohistochemistry-positive population was expected to have a greater

benefit. And, therefore, there was 85 percent power to detect a 43 percent increase in progression-free survival. The assumption was that 50 percent of the population would be EGFR-positive by immunohistochemistry.

The predefined primary analysis was conducted using an unadjusted log rank test. Having six relevant certification factors makes it logical using this test for the primary analysis.

Finally, the study was also powered to detect the survival improvement in the overall population. This was a key secondary point. A total of 641 deaths were required to detect a 25 percent increase in the overall survival. The analysis conducted here was also using an unadjusted log rank test.

So let me conclude by saying that I was really fortunate to be a part of this important study as the principal investigator aiming at advancing lung cancer care. SATURN is a global, adequate, and well-controlled trial in patients with advanced non-small cell lung cancer who have

non-progressive disease after first-line platinum-based chemotherapy.

Biomarker evaluation was a key component, which is why diagnostic tumor tissue was mandated for all patients. In this trial, the first patient was randomized in March 2006 and the last patient was randomized in February 2008.

Now, I would like to welcome Dr. Angela Davies to the podium to present the efficacy and safety result from the SATURN study.

DR. DAVIES: Good morning. Dr. Pazdur, Dr. Wilson, ODAC members, FDA staff, and guests, I am Dr. Angela Davies, Vice President of Clinical Development at OSI Pharmaceuticals. It is my privilege to present the results of the SATURN clinical trial on behalf of my colleagues at OSI, Genentech, and Roche.

As you have heard, the SATURN clinical trial resulted in a significant improvement in progression-free survival and survival in the overall population and in the co-primary patient population of immunohistochemistry-positive. This

benefit was seen across a broad range of clinical and exploratory biomarker subgroups, and compatible quality of life was seen between arms. No new safety signals were observed.

I would now like to provide more detail for you on the study results.

Patient characteristics were well-balanced across arms of the trial. In particular, known prognostic subgroups such as female sex, Asian ethnicity, never smokers, and adenocarcinoma were well-balanced. In addition, the EGFR IHC status, a co-primary end point, was well-balanced across treatment arms.

An initial 1,949 patients were screened during the chemotherapy run-in or screening period, and ultimately, 889 patients were randomized after completing four cycles of platinum-based chemotherapy without progression or unacceptable toxicity.

Once randomized, the majority of patients came off study due to progressive disease, with a small number of patients coming off study due to

safety reasons, 29 versus 12 in the Tarceva and placebo arm respectively.

At the time of the primary data cutoff on May 17, 2008, there were a total of 98 patients remaining on study drug, 66 patients in the Tarceva arm and 32 patients in the placebo arm.

The study met its primary end point by improving the progression-free survival in the intent-to-treat population, with a significant hazard ratio of .71. This benefit was durable and sustained across the treatment period.

The point estimate of median progression-free survival, 12.3 weeks versus 11.1 weeks in the Tarceva versus placebo arm, does not accurately capture the benefit demonstrated across the treatment period. An additional point estimate of progression-free survival at six months was 25 percent compared to 15 percent in favor of Tarceva treatment.

In addition, the study met its co-primary end point by improving the progression-free survival in the EGFR IHC-positive patient

population. The hazard ratio of .69 was similar to the hazard ratio in the intent-to-treat population of .71.

The primary end point was investigator-assessed PFS, but this was later corroborated by a central independent radiologic review. The independent review committee received radiographs and clinical data when relevant. The investigator-assessed and independent review resulted in an identical hazard ratio of .71 in favor of treatment with Tarceva. The concordance rate for progression events was high, 78 percent in the Tarceva-treated group and 82 percent in the placebo-treated group.

The robust PFS benefit was seen across key clinical subgroups, and this forest plot highlights clinical subgroups of interest, including sex, race, histology, and smoking status. Of particular note, patients with squamous histology had benefit, with a hazard ratio of .76.

As you have heard, mandatory tumor collection in all patients was a required part of this study, and biomarker analyses were secondary

objectives in this clinical trial. As you can see in this forest plot, benefit was seen across biomarker subgroups, with hazard ratios falling to the left of 1 in favor of Tarceva treatment.

More specifically, patients with EGFR IHC-negative tumors derived benefit, with a hazard ratio of .77, and the interaction test for treatment effect by IHC was not significant. It is also reassuring to note that the patients in the subgroup of KRAS mutation-positive also derived benefit, with a hazard ratio of .77. This data, therefore, does not support excluding patients from Tarceva based on biomarker status alone.

PFS benefit was seen regardless of EGFR mutation status, as noted by the hazard ratio of .78 in the EGFR wild type subgroup, with the EGFR mutation-positive patients having the greatest clinical benefit.

I'd like to give you a visual representation of the benefit of Tarceva in patients with EGFR mutation-positive tumors. And as you can see in this Kaplan-Meier curve, there

was remarkable benefit in terms of progression-free survival for this subset of patients, with a hazard ratio of .1, which translated into a 90 percent reduction in the risk of progression.

The clinical relevance of prolonged PFS was further supported by an improvement in overall survival in the intent-to-treat population. The hazard ratio of .81, which was significant, translated into a 19 percent reduction in the risk of death. This overall survival benefit was sustained, as noted by differences in the overall survival at both 12 and 24 months, favoring Tarceva treatment.

In addition, there was a significant improvement in the EGFR IHC-positive population with respect to survival, with a hazard ratio of .77, translating into a 23 percent reduction in the risk of death.

The primary analysis for overall survival was an unstratified log rank test. Additional preplanned sensitivity analyses were performed to assess the robustness of the primary survival

results. The multi-varied analysis and stratified log rank test supported the primary analysis, with similar hazard ratios ranging from .8 to .85.

Data on subsequent therapies was collected once patients progressed on study treatment. Greater than 60 percent of patients received subsequent systemic therapies, and this was balanced across treatment arms. This table outlines specific subsequent therapies that were received in at least 5 percent of patients. And with the exception of subsequent EGFR tyrosine kinase inhibitors, therapies were balanced across arms.

This is a Kaplan-Meier curve of overall survival in patients who received subsequent therapies. And while this study was not designed to evaluate an early versus late question, we performed an exploratory analysis to evaluate the overall survival benefit in patients that did receive second or further lines of therapy.

As you can see by this Kaplan-Meier curve, the overall survival benefit favored Tarceva

treatment, with a hazard ratio of .70. The overall survival benefit was seen across key clinical subgroups, with all hazard ratios falling to the left of 1, as demonstrated in this forest plot.

Because of the strong PFS benefit seen in patients with EGFR mutation-positive tumors, overall survival was also evaluated based on EGFR mutation status. The significant and durable improvement that was seen in the EGFR wild type patient population is noted here, with a hazard ratio of .77, and thus the significant improvement in survival that was seen in the overall population cannot be explained by the great benefit that was seen in patients with EGFR mutation-positive tumors.

This Kaplan-Meier curve represents the survival for the subgroup of patients with EGFR mutation-positive tumors. The lack of survival benefit seen in this patient population is likely confounded by the high rate of crossover, at 67 percent, to an EGFR TKI in the placebo arm. It's certainly notable that patients in both treatment

arms that received an EGFR TKI had a survival of approximately two years, highlighting the benefit of Tarceva as maintenance or subsequent therapy in this patient population.

Evaluation of another efficacy parameter, response rate, was performed based on resist criteria. A doubling of the response rate was seen in the Tarceva-treated arm, 11.9 percent, compared to 5.4 percent in the placebo arm. In addition, the composite end point of disease control rate favored Tarceva treatment at 60.8 percent compared to 50.8 percent.

Patient-reported health-related quality of life was a secondary end point and consisted of three parameters: time to symptom progression, time to deterioration in the trial outcome index, time to deterioration in quality of life. These results indicate that quality of life was comparable for those patients receiving Tarceva compared to the treatment-free period, and thus Tarceva did not result in any additional symptom burden when given in the maintenance setting.

A subsequent post hoc exploratory analysis of lung cancer-related symptoms was also performed, and demonstrated that there was a delay in the time to pain, time to analgesic use, time to cough, and time to dyspnea in favor of Tarceva, with hazard ratios ranging from .61 to .77.

I'd now like to turn to the safety results. The only adverse event occurring in greater than 10 percent of patients was rash or diarrhea. In addition, rash and diarrhea were the most common adverse events, and this is consistent with the known safety profile of Tarceva.

Forty-nine percent of patients experienced any grade of rash, and 20 percent of patients experienced any grade of diarrhea. Few patients, however, had rash or diarrhea of grade 3 severity, and there were no grade 4 rash or diarrhea. It is notable in this population that rates of fatigue were low, 9 versus 6 percent in the Tarceva and placebo arms respectively.

These adverse events, however, were manageable, and Tarceva was well tolerated, as

evidenced by the low rate of dose modifications. Only 11 percent of patients required a dose reduction from 150 milligrams once daily to 100, and less than 1 percent of patients required a further dose reduction to 50 milligrams once daily.

Six percent of patients receiving Tarceva required a dose interruption for greater than one week, and 4.6 percent of patients required a discontinuation due to adverse events, with 2.8 percent of patients requiring a discontinuation for adverse events that were considered related to study drug by the investigator.

This is a summary of the serious adverse events occurring in two or more patients, regardless of causality, or an individual patient if considered drug-related. Numerically, there were more adverse events occurring in the Tarceva-treated patients, 10.9 percent compared to 7.6 percent, with the most common serious adverse event being pneumonia, occurring in seven patients compared to four patients in the placebo-treated arm. Serious adverse events seen in this study are

also consistent with the known safety profile of Tarceva.

This slide outlines deaths occurring during the study period, which includes the treatment phase plus 30 days. The total number of deaths were similar in both treatment arms, 31 -- excuse me -- 35 versus 31 patients. And amongst the patients dying while on study, most were due to progressive disease.

Deaths attributed to adverse events are outlined here, in nine versus four patients. One death was considered due to progressive disease by the investigator, but was also associated with interstitial lung disease and may have been drug-related. This is the only death on study that was considered to be possibly treatment-related.

In summary, SATURN is a phase 3 randomized, placebo-controlled trial in the first-line maintenance setting, which resulted in a significant improvement in progression-free survival and survival in both the intent-to-treat population and in the EGFR IHC-positive population.

This benefit was seen across a broad range of clinical and exploratory biomarker subgroups, and the benefit was seen regardless of EGFR mutation status, although patients with EGFR mutation-positive tumors, had a remarkable reduction in the risk of progression. There was comparable quality of life between arms, and there were no new safety signals observed.

I would now like to introduce Dr. Paul Bunn, professor of medicine from the University of Colorado, who will provide his clinical perspective on the significance of SATURN data within the current treatment paradigm of advanced non-small cell lung cancer.

DR. BUNN: Dr. Wilson, members of ODAC, Dr. Pazdur, FDA staff, and guests, I'm Dr. Paul Bunn, professor of medicine at the University of Colorado Cancer Center. In response to Dr. Wilson's question this morning, I'm employed by the University of Colorado. I have no stock in OSI, Genentech, or Roche. The company has sponsored my travel here, and I'm being paid as a consultant for

this meeting.

I'm here because I'm a practicing medical oncologist, and my primary interest in both patient care and research is in lung cancer. I treat lung cancer patients in both an academic and a community setting in Colorado.

When I began my term on ODAC in the 1990s, there were very few drugs approved, but several single agents had been shown to increase survival, and median survival in those days was increased from four months to six months by these single agents. Few patients lived beyond a year.

During my ODAC term, several new drugs were approved in first-line therapy. These included Navelbine, gemcitabine, docetaxel. And by the turn of the century, it was clear that platinum doublets improved survival times to a median of about eight months, with 15 percent of patients surviving at two years. Was that progress? Yes. Was there room for improvement? Plenty. Certainly we need new drugs, and we need better ways to apply the drugs that we have.

Maintenance strategies continuing induction platinum doublets were studied in prolonged progression-free survival, but did not prolong overall survival and were associated with a considerable increase in toxicity. Thus, ASCO and NCCN guidelines do not support this strategy of maintenance chemotherapy.

The second- and even third-line therapy with new agents, docetaxel, pemetrexed, and erlotinib, were shown to prolong survival in these settings. But was that the optimal way to apply these drugs, and to whom should they be applied?

Many patients progress rapidly after initially chemotherapy and never receive a second- or third-line therapy proven to improve survival. The rationale for maintenance was thus to deliver efficacious therapy earlier, before progression, allowing active therapy for more patients to prolong time to progression, relieve symptoms, and improve survival. The rationale for whom to deliver the agents to was to examine biomarkers, clinical features, and histologic features.

There have been four randomized maintenance trials comparing these new single agents to placebo. Two of these randomized trials used cytotoxic chemotherapy. Progression-free survival results from the pemetrexed study are shown on the left and the docetaxel study on the right. The docetaxel study compared immediate versus delayed docetaxel.

Progression-free survival was significantly improved in both trials. The hazard ratio was 0.6 in the pemetrexed study, and a near doubling of the median survival was in the docetaxel study.

In both trials, the curve separated relatively early, by three months, came together at 12 to 18 months, and few patients had not progressed by 12 months, indicating a short-term benefit to a large fraction, but a lasting benefit to few.

Based on these results, the recently-published ASCO guidelines endorsed maintenance therapy as an option for lung cancer patients, but

also cautioned, and I quote, "The improvement in PFS is tempered by an increase in adverse events from additional cytotoxic chemotherapy."

Survival was significantly improved in the pemetrexed study but not in the docetaxel study, despite the similar-appearing curves. Survival curves separated by four months were maximally separated near the median and came together at 18 to 20 months. Like the PFS data, this indicates a lack of durable results from either agent. These pemetrexed data formed the basis of the FDA's approval for this indication earlier in 2009.

What are the limitations of this approval that could be improved by approval of a maintenance TKI? It is clear the pemetrexed produced no improvement in squamous carcinoma, was associated with hematologic and other toxicities of chemotherapy, as well as the associated requirements for intravenous infusion, concomitant medicines, and the benefits were not durable.

To address these issues, two other

randomized trials evaluated an EGFR TKI as maintenance after induction platinum doublet therapy. The PFS results from the SATURN study comparing erlotinib to placebo are shown.

PFS was significantly in favor of erlotinib, with a hazard ratio 0.71, similar to the chemotherapy studies. In SATURN, however, the curve separated, not till six weeks, but remained separated beyond this time. And this long-term advantage indicates a durable benefit occurring in some of the patients.

As you have heard, in the SATURN trial, survival statistically favored erlotinib with a hazard ratio of 0.81. Unlike chemotherapy studies, the survival curve separated at about six months and remained separated throughout the follow-up period to at least two and a half years. The persistent separation indicates a lasting benefit.

This overall hazard ratio could be considered by some as modest. But as I indicated in the beginning, progress in lung cancer is in steady, small steps. And I can remind you that the

hazard ratio for adjuvant chemotherapy in prolonging survival is 0.82, and the hazard ratio for pemetrexed maintenance in the overall population is 0.8.

For completeness, a large Japanese trial evaluated gefitinib maintenance and demonstrated a statistically significant improvement in PFS hazard ratio of 0.68, but not in overall survival, hazard ratio .86. Both PFS and overall survival curves were similar to those seen in SATURN but different from chemotherapy curves, showing long-term separation throughout three to four years, indicating a durable benefit.

When survival results by histology were evaluated in the pemetrexed study, patients with a non-squamous histology had a statistically significant improvement in survival, with a hazard ratio of 0.7. However, patients with squamous histology had a hazard ratio of 1.07, above 1, indicating no benefit from pemetrexed. Thus, the FDA's pemetrexed maintenance approval was for non-squamous, non-small cell only.

In this instance, the histology end point was preplanned based on nearly identical data in two other large randomized pemetrexed studies in both first- and second-line therapy that showed no advantage for patients with squamous histology.

There is no specific reason, scientifically, to expect that erlotinib would have differences in outcome based on histology. EGFR expression is higher in squamous tumors. The BR.21 and SATURN study demonstrated benefits across end points, both PFS and OS, regardless of histology. Hazard ratios slightly favored squamous tumors in BR.21 and slightly favored adenocarcinoma in SATURN.

The small inconsistencies in these unplanned subset analyses must be tempered by the fact that primary end point of PFS and OS were highly significant in both trials. It is generally appreciated that it is inappropriate to include positive subsets from a negative trial and, likewise, inappropriate to exclude subgroups in the setting of a positive overall trial unless there's

a preplanned hypothesis or safety issue. My interpretation of the histology results is that benefit occurs in all histologies, and it would be inappropriate to exclude an unplanned subset.

Major toxicity results from the four maintenance trials are shown. Not surprisingly, chemotherapy regimens produced hematologic toxicity. Although the rates of grade 3 and 4 hematologic toxicity were deemed acceptable, they were higher with chemotherapy compared to the EGFR TKIs. And they were also associated with a higher rate of hematopoietic growth factor use, of red blood cell transfusions, as well as other supportive medications. Not surprisingly, rash and diarrhea were more frequent with the TKIs, but were infrequent and manageable by dose reduction.

While these studies did not directly compare erlotinib or gefitinib to chemotherapy, a number of other trials have done this, both in first- and second-line settings. Toxicity profile has uniformly favored the oral pill tyrosine kinase inhibitor.

Studies over the past decade have taught us that there's no evidence to continue induction chemotherapy doublets. But using new drugs in new ways, we have strong evidence that early maintenance pemetrexed and erlotinib prolong progression-free and overall survival with acceptable but quite different toxicity profiles. There are major differences in convenience of administration, a pill versus intravenous therapy, the amount of supportive care drugs, and the era of personalized medicine assists us in selecting the best agent for each patient.

With respect to histology, we appreciate that pemetrexed is not indicated in squamous tumors. With respect to molecular features, we recognize erlotinib's huge benefit in EGFR-mutated patients. And it is critical that patients with these mutations have early access to erlotinib.

We need additional research on biomarkers because erlotinib's benefit cannot be excluded in any subset known at this time, including EGFR wild type, IHC negative, FISH negative, squamous

histology, male gender, or smoking status.

The PFS and overall survival benefits from erlotinib were durable, and I'm pleased to see in my own clinic many patients now at five years. As a point of fact, the five-year survival rate for stage 4 non-small cell lung cancer at my hospital, the University of Colorado hospital, was 5 percent last year. This was never seen previously. However, of course, it leaves plenty of room for progress.

The 2009 NCCN guidelines endorse a maintenance paradigm using either pemetrexed or erlotinib. As a treating lung cancer physician, I realize advances are made in sequential small steps. During the first decade of this century, we have applied new therapies, and these small benefits are helping patients. Early maintenance therapy improves survival and provides the opportunity for improved symptom control and prolonged progression-free survival.

Clinical decision-making between erlotinib and pemetrexed is based on histology,

molecular features, side effects, co-morbidities, patient preference, and convenience. Erlotinib's advantages are this oral convenience and safety profile, which allows for a break in chemotherapy and its benefit across histology and clinical features. These benefits are durable and patients need not stop erlotinib from toxicity or from decreasing quality of life. The ability to select these options is a major therapeutic advance for lung cancer patients.

Thank you very much, and I'd like to ask Dr. Witt to return for his concluding remarks.

DR. WITT: Thank you, Dr. Bunn.

You have now heard results from a large and well-controlled phase 3 trial providing level 1A evidence in support of the proposed indication.

The SATURN protocol went through FDA's special protocol assessment to ensure study design, statistical assumptions, and analysis plan were adequately discussed. The agency raised several issues in their briefing document for ODAC to consider, which I briefly would like to address.

First and foremost, the study showed that Tarceva as first-line maintenance provides clinically meaningful benefit in the setting of multiple approved second-line therapies.

We, the study sponsor, are committed to developing personalized medicine, and therefore conducted the largest randomized phase 3 trial in advanced non-small cell lung cancer to date, which included mandatory tissue from all patients in order to perform prospectively defined biomarker analysis.

The results, however, from the co-primary end point do not support using EGFR protein expression by immunohistochemistry as a mean to select or deselect patients for Tarceva treatment since benefit was observed regardless of EGFR IHC status.

Presence of EGFR mutations appear to be the strongest predictive biomarker for benefit to Tarceva based on results from this study, and this is also supported from a large body of published data. The crossover effect biasing overall

survival interpretation just emphasized that progression-free survival is a better measure of clinical benefit in points with EGFR mutations.

Finally, results from the SATURN study do not support excluding any individual exploratory subgroups in particular not based on histology. There was no a priori reason to believe Tarceva benefit would be different in patients with squamous cell histology, and it's therefore scientifically inappropriate to exclude patients based on post hoc observations.

In conclusion, the SATURN study met its prespecified primary and key secondary end points. Tarceva therapy delays disease progression and improves overall survival. The results are consistent with benefit across all clinical and biomarker subgroups, regardless of histology and regardless of EGFR immunohistochemistry status.

Tarceva is a convenient oral drug with manageable adverse events. Therefore, Tarceva has a favorable benefit/risk profile and should be made available as a treatment option for patients with

advanced non-small cell lung cancer in the first-line maintenance setting.

In addition to the presenters you've just listened to, we have a group of experts, internal experts from Roche and OSI, and once the chair opens up, they will be available for questions.

Thank you for your attention.

DR. WILSON: I would like to thank OSI. And at this time, may I have Dr. Cohen present?

DR. COHEN: Good morning, ladies and gentlemen. My name is Martin Cohen, and I'm going to present the FDA review of the erlotinib application being discussed today.

The FDA team reviewing the current application, including primary and secondary reviewers for each discipline, is listed on this slide. As you've heard, the proposed indication for today's discussion is that erlotinib is indicated for maintenance therapy of locally advanced or metastatic non-small cell lung cancer patients who have received four cycles of platinum-containing doublet therapy without disease

progression.

When this trial was initiated, the standard of care for regionally advanced or metastatic non-small cell lung cancer was to administer four to six cycles of platinum-based doublet chemotherapy, and then to discontinue treatment while continuing to regularly observe the patient until disease progression. At that time, depending on the patient's clinical status, additional therapy could be offered.

The present study, based on the above standard of care, is an attempt to determine the worth of adding erlotinib treatment immediately after completion of four cycles of platinum-based doublet chemotherapy in patients who do not have progressive disease.

As you've heard, the FDA had approved pemetrexed as maintenance therapy based on this design. Pemetrexed approval, as will be seen on later slides, was based on a 5.2-month increase in median survival observed in non-squamous, non-small cell lung cancer patients.

The outline for my presentation is shown on this slide. I'll talk about the design of a study to determine the worth of maintenance therapy; the appropriate end point for such a trial; the regulatory history of the present application; issues with the exploratory biomarker studies that the sponsor performed; overall results of the erlotinib maintenance study; and results in specific subgroups of patients, including patients who are epidermal growth factor receptor-negative by immunohistochemistry, patients with squamous cell non-small cell lung cancer, and patients who are EGFR mutation-positive.

I will also talk of other treatment options rather than erlotinib maintenance therapy. And finally, I will consider the safety of erlotinib treatment.

The preferred study design for a maintenance trial is shown on this slide. Patients initially receive four cycles of a platinum-containing doublet chemotherapy regimen. Patients with an objective response or stable disease after

this treatment are then randomized to immediate maintenance therapy or to delayed therapy to be started at the time of disease progression.

An important point in the study design is that the identical drug or a closely related drug must be given to progressing placebo-treated patients so as to demonstrate that early maintenance therapy is better than delayed therapy. Subsequent therapies for patients in both arms can be based on physician choice. This should result in relatively similar treatments for patients in both study arms so that survival results are not confounded.

An example of an appropriately designed maintenance therapy trial is shown on this slide. All patients receive four cycles gemcitabine plus carboplatin chemotherapy. Non-progressing patients were randomized to immediate or delayed docetaxel, an approved second-line advanced non-small cell lung cancer drug. The delayed docetaxel group received best supportive care until disease progression.

There were 309 randomized patients, 153 to immediate docetaxel treatment and 156 to delayed treatment. The primary efficacy end point was overall survival. As seen on the last two lines of the slide, there was a significant improvement in progression-free survival and a non-significant increase in overall survival favoring maintenance therapy. It should be noted, though, that docetaxel is not approved for a maintenance indication.

Turning now to efficacy end points, it is important to consider whether progression-free survival or overall survival is the appropriate end point for a maintenance therapy trial. The FDA believes that progression-free survival does not demonstrate that maintenance therapy is beneficial.

Patients in this study comprise a relatively unique group of advanced metastatic non-small cell lung cancer patients who have had an objective response or stable disease after initial treatment. They generally have no, or only minimal, cancer-related symptoms. Progression-free

survival has no clinical benefit in this setting unless it predicts for improvement in overall survival.

An argument made this morning by the sponsor that overall survival is not an appropriate end point because overall survival in the placebo group may be prolonged to equal overall survival in the maintenance group by tyrosine kinase inhibitor treatment to progression defeats the claim that maintenance therapy has clinical benefit.

The next item on the presentation outline is regulatory history, which is summarized on this slide. The study protocol was submitted for special protocol assessment in April of 2005. The FDA did not agree with the sponsor's primary end point of progression-free survival and told the sponsor that overall survival was the preferred efficacy end point.

In addition, the SPA letter answered 13 specific questions asked by the sponsor. These questions did not deal with drug treatment of controlled patients at the time of progression.

The SNDA meeting was held in February of this year. At that time, survival data were immature. The final survival analysis was to be submitted in August/ September of this year, and it was submitted as promised.

The next item on the presentation outline is biomarkers. In this application, in addition to epidermal growth factor receptor by immunohistochemistry, the sponsor proposed to evaluate other biomarkers as well.

Because it was recognized that tumor tissue might only be available in small quantities, a prioritization scheme was established in the order listed on this slide. That is, epidermal growth factor receptor by immunohistochemistry would be done first.

If there was tumor tissue remaining, then epidermal growth factor receptor gene copy number by FISH would be done, and so on through the list, with KRAS mutation determined next, following by epidermal growth factor receptor mutation. In addition, it was also planned to evaluate several

exploratory biomarkers as listed on this slide.

As might be expected, tumor tissue often ran out before the latter assays could be performed. This slide indicates the number of biomarkers that were missing or indeterminate and the total of missing plus indeterminate biomarkers.

As seen, the assay for epidermal growth factor receptor by immunohistochemistry had relatively few missing or indeterminate values, 12 missing and 5 percent indeterminate. As might be expected from the biomarker prioritization shown on the previous slide, the epidermal growth factor receptor mutation assay had the largest number of missing or indeterminate results.

The sparsity of the data for all biomarkers, except for epidermal growth factor receptor by immunohistochemistry, and the uncertainty about the compatibility of treatment and controlled patient groups with available biomarker data, makes any conclusions regarding biomarkers other than epidermal growth factor receptor by immunohistochemistry tentative and

useful only to generate hypotheses that can be tested in future trials.

There were several issues raised relative to biomarker studies. The first concerned the use of the DAKO kit to determine epidermal growth factor receptor status. As seen on the slide, in an earlier phase 3 double blind placebo-controlled trial that led to approval of erlotinib, a second- or a third-line therapy for non-small cell lung cancer, 47 percent of assayed patients were epidermal growth factor receptor-negative. In the present trial, only 16 percent of assayed patients were epidermal growth factor receptor-negative.

As stated by the sponsor, there are multiple technical reasons that may account for immunohistochemistry result variation even with excellent DAKO kit performance. Reasons include: tissue storage conditions, tissue collection procedures, different fixatives and fixation times, variable times from slide preparation to staining, different staining protocols, different scoring protocols, and different pathologic

interpretations.

Standardization is obviously required if the DAKO test is to be used to select patients for targeted therapy. Another issue is that there is no FDA-approved assay for relevant epidermal growth factor receptor mutations.

The next item on the presentation outline is study results. The main eligibility criteria for entry into this multi-center, double-blind, randomized phase 3 trial conducted entirely outside of the United States are shown on this slide.

Patients were at stage IIIB or IV non-small cell lung cancer with a performance status of 0 or 1. They had completed four cycles of doublet chemotherapy with an objective response or stable disease. They had acceptable clinical laboratory values and had provided a tumor sample for determination of epidermal growth factor receptor by immunohistochemistry.

Acceptable initial chemotherapy regimens are shown on this slide. They include cisplatin or carboplatin with gemcitabine, paclitaxel, and

docetaxel, and also a cisplatin plus vinorelbine regimen. Doses and schedules of drug administration for these doublets were acceptable.

Progression-free survival results: The sponsor's proposed primary efficacy end point for the overall population and the EGFR IHC-positive population are shown on this slide. There were 889 total patients and 621 patients who were IHC-positive in the study. In both study groups, although the median progression-free survival differences were small, 2.8 months versus 2.6 months for erlotinib- and placebo-treated patients respectively, the hazard ratios were 0.71 and 0.70 for all patients, and for the epidermal growth factor receptor positive by IHC patients, respectively, and the P values by log rank were both statistically significant.

This slide shows the Kaplan-Meier progression-free survival curve for the full analysis data set and the EGFR IHC-positive subgroup. And one can see that the curves come together at the median and then diverge.

This slide indicates the second-line treatment that placebo-treated patients received at the time of progression. As you know and as you've heard earlier, erlotinib, docetaxel, and pemetrexed are the FDA-approved drugs for non-small cell lung cancer patients whose tumors have progressed after one or more prior therapies.

As you also remember from a previous slide, that demonstrating benefit of maintenance treatment requires that placebo-treated patients receive erlotinib, or possibly gefitinib, at progression. As seen on this slide, only 14 percent of patients received second-line erlotinib or gefitinib. Docetaxel was received by 31 percent of patients after initial progression, and pemetrexed was received by 14 percent. In total, only 59 percent of placebo patients who received treatment at the time their tumors progressed received FDA-approved drugs.

To look more closely at placebo-treated patients who received an epidermal growth factor receptor tyrosine kinase inhibitor after initial

progression, this slide provides data by patient race. As seen, 13 percent of white patients and 22 percent of Asian patients received erlotinib or gefitinib as second-line therapy, and smaller percentages of patients received these drugs as third-line or later than third-line treatment, where they would be expected to be considerably less effective.

Overall survival results are shown on this slide. For the full analysis data set that included 451 placebo-treated patients and 438 - erlotinib-treated patients, there was a one-month prolongation in median survival, with a hazard ratio of 0.81. For patients with EGFR positive by immunohistochemistry, the median survival was prolonged by 1.8 months, with a hazard ratio of 0.77.

The corresponding survival curves for the full analysis data set and for EGFR by IHC-positive patients is shown on this slide. The top curves on both figures represent maintenance erlotinib therapy.

Survival curves based on response to initial chemotherapy are shown on the next slide. On this slide, the survival curves on the left represent patients who had a CR or PR after four cycles of platinum doublet chemotherapy, and the right-sided curves represent patients with stable disease. It appears that survival benefit is driven entirely by patients with stable disease. Although not shown, progression-free survival improvement was not much different between the two response subgroups.

The next group of slides provide data on the value of erlotinib maintenance therapy in specific subgroups of patients. This slide summarizes efficacy results in epidermal growth factor receptor by immunohistochemistry-negative patients. For both progression-free survival and overall survival, there was no significant difference between erlotinib- and placebo-treated patients.

As these results are based on small sample sizes, namely, 62 erlotinib-treated patients

and 59 placebo-treated patients, any conclusions must be considered as tentative. It should be noted that the study that led to approval of erlotinib in stage IIIB and IV non-small cell lung cancer patients, whose tumors had progressed after at least one chemotherapy regimen, support these results. Those results are summarized on the next slide.

This slide shows results in patients whose tumors were epidermal growth factor receptor by immunohistochemistry-negative in the maintenance trial and in the trial conducted in patients whose tumors progressed after one or more prior regimens. As seen on the slide, the upper bound of the 95 percent confidence interval of the hazard ratio is greater than 1.0 in both trials.

Because the results in both studies were based on small sample sizes, 121 total epidermal growth factor receptor IHC-negative patients in the maintenance study and 111 total patients in the second- and third-line study, any conclusions must be considered as tentative.

Analysis were also done in patients with missing or indeterminate immunohistochemistry results. No significant survival differences were observed. These results raise the question of using erlotinib in patients with EGFR-negative or indeterminate tumors.

With regard to erlotinib efficacy in patients with squamous cell non-small cell lung cancer, this slide shows survival results for, one, all 889 study patients; two, for the 529 non-squamous, non-small cell lung cancer patients; and three, for the 360 squamous cell patients.

As seen, median survival difference is one month favoring erlotinib in all patients, 3.2 months in non-squamous patients, and only 0.2 months in squamous cell patients. The upper bound of the 95 percent confidence interval exceeds 1 only for squamous cell patients.

This exploratory analysis examines the effect of epidermal growth factor receptor-activating mutation on progression-free survival and overall survival. The occurrence of an

epidermal growth factor receptor-activating mutation was noted in a very limited sample of only 27 erlotinib-treated patients and 22 placebo-treated patients. There appears to be a striking improvement in median progression-free survival, 10.3 months versus 3.0 months, with a hazard ratio of 0.1.

Regarding overall survival, the cutoff date for the most recent survival analysis was October 31, 2009. At that time, 46 percent of erlotinib-treated patients and 44 percent of placebo patients remained alive and were censored. Median survival was 23.6 months and 23.8 months in the erlotinib and placebo arms respectively, with a hazard ratio of 1.01.

Because of the very small sample sizes, any progression-free survival or overall survival conclusions based on this data must be regarded as tentative.

With pemetrexed maintenance therapy, the median survival -- excuse me. The next item on the presentation outline concerns other treatment

options. The only FDA-approved drug for maintenance therapy of advanced metastatic non-small cell lung cancer is pemetrexed.

In the pemetrexed maintenance trial, patients with objectively responding or stable disease after four cycles of platinum doublet therapy were randomized to receive either pemetrexed or best supportive care. Second-line therapy for best supportive care patients at the time of progression was physician's choice.

Sixty-seven percent of best supportive care patients received post-progression second-line therapy, including pemetrexed in 19 percent, epidermal growth factor receptor tyrosine kinase inhibitors, erlotinib and gefitinib, in 31 percent, in docetaxel in 29 percent. The next slide summarizes the efficacy results.

With pemetrexed maintenance therapy, the median survival for the full analysis data set was 13.4 months versus 10.6 months for placebo-treated patients, a 2.8-month advantage in favor of pemetrexed, with a hazard ratio of 0.79. For non-

squamous patients, there was a 5.2-month advantage of pemetrexed, with a hazard ratio of 0.70.

For squamous cell patients, there was almost a one-month disadvantage for pemetrexed compared to best supportive care, with a hazard ratio of 1.07. Similar results indicating a significant treatment by histology interaction were also observed in two other pemetrexed phase 3 trials. The approved indication for pemetrexed was as maintenance therapy for non-squamous, non-small cell lung cancer.

Considering other treatment options, this slide summarizes studies that led to FDA approval of erlotinib, docetaxel, and pemetrexed in advanced non-small cell lung cancer patients whose tumors had progressed after one or more prior therapies. While we are aware that cross-study comparisons are problematic, we feel that some general points can be made.

In the present maintenance trial, performance status was limited to 0 or 1. The trials listed here included performance status of 0

to 3 patients in the erlotinib trial, and performance status of 0 to 2 patients in the docetaxel and pemetrexed trials.

In addition, these studies include patients whose tumors had progressed on one or more regimens, whereas the preset study enrolled patients whose tumors had not progressed. Moreover, there are also lead time issues in the maintenance trial.

Comparing the improvement to median survival for all patients treated with erlotinib, docetaxel, or pemetrexed at progression to that of patients receiving maintenance erlotinib raises the question as to whether treatment with these single agents at progression may be a better treatment option.

To summarize efficacy results, while the primary efficacy objectives, including overall survival in all patients and in EGFR immunohistochemistry-positive patients were met, the fact that only 14 percent of patients in the placebo arm received an EGFR tyrosine kinase

inhibitor at the time of progression does not allow evaluation of erlotinib maintenance therapy versus treatment at progression.

Regarding results in important subgroups for both EGFR immunohistochemistry-negative patients and squamous cell cancer patients, overall survival benefit is uncertain. Regarding epidermal growth factor receptor mutation-positive patients, there are two concerns. The first is the small number of patients from whom conclusions are being drawn. The second is the disappointing survival results, despite highly favorable progression-free survival results. The reason for this discrepancy between progression-free survival and overall survival in this patient group is unclear.

Finally, whether pemetrexed maintenance therapy or single-agent therapy with erlotinib, docetaxel, or pemetrexed at the time of progression gives superior outcomes to erlotinib maintenance therapy needs further evaluation.

Turning now to safety, this slide shows extent of exposure to either erlotinib or placebo.

The median duration of erlotinib exposure was 2.8 months, with a minimum and maximum exposure as shown on the slide, and the median exposure to placebo was 2.7 months, with a minimum and maximum exposure of 0.2 and 21.3 months respectively.

An adverse event summary is shown on this slide. Seventy-nine percent of erlotinib-treated patients had at least one adverse event, compared to 54 percent of placebo-treated patients. Serious adverse events occurred in 11 percent of erlotinib-treated patients and 8 percent of placebo-treated patients.

Five percent of erlotinib-treated patients had an adverse event, leading to treatment withdrawal, compared to 2 percent of placebo-treated patients. Sixteen percent of erlotinib-treated patients had an adverse event leading to dose modification or interruption, versus 3 percent of placebo-treated patients. And 2 percent of erlotinib-treated patients had an AE leading to death, compared to 1 percent of placebo-treated patients.

As you've heard, the major erlotinib adverse events were skin rash and diarrhea. Rash was noted in 49 percent of erlotinib-treated patients versus 6 percent of placebo-treated patients. Diarrhea was reported in 20 percent versus 5 percent.

One erlotinib group death was possibly related to interstitial lung disease. In addition, there were two other erlotinib-treated patients who possibly had interstitial lung disease as a serious adverse event. No lung biopsies were performed.

In summary, six points are to be made. One, overall survival is the end point that establishes clinical benefit of maintenance therapy.

Two, regarding study design, the maintenance drug, or a closely related drug, must be given to progressing control patients so as to demonstrate that maintenance therapy is better than delayed therapy. In the current study, only 14 percent of patients in the placebo arm received an epidermal growth factor receptor tyrosine kinase

inhibitor at progression.

Three, regarding important subgroup results for both EGFR IHC-negative patients and squamous cell cancer patients, overall survival benefit is uncertain.

Four, regarding epidermal growth factor receptor mutation-positive patients, the overall survival results are disappointing. The reason for the discrepancy between progression-free survival and overall survival in this patient group is unclear.

Five, regarding other treatment options, pemetrexed maintenance therapy or single-agent therapy with erlotinib, docetaxel, or pemetrexed at the time of progression may give superior outcomes to erlotinib maintenance therapy. And six, finally, there are issues with both the EGFR IHC assay and the EGFR mutation assay. The former might be inconsistent, and the latter is not FDA-approved.

To conclude and to help frame ODAC deliberations, I would like to again mention some

of the FDA-perceived unresolved issues.

First and most important, it seems that the issue of erlotinib maintenance therapy versus treatment at progression is still in issue. Next, it is important to determine which of the subgroups discussed on earlier slides have increased survival as a result of erlotinib therapy.

As seen on this slide, subgroups generally had small numbers of patients; that is, 121 total patients in the two study arms were epidermal growth factor receptor by immunohistochemistry-negative, 360 total patients had squamous cell cancer, and only 49 total patients were mutation-positive. These patients numbers do not allow firm conclusions to be drawn.

Also, there are issues with the epidermal growth factor receptor immunohistochemistry and activating mutation assays. The former may be inconsistent in non-small cell lung cancer, and the latter is not approved.

It would be optimal to have assays that are approved prior to study initiation so that the

same assays can be used post-approval to select appropriate patients for specific treatments.

This concludes my presentation. Thank you for your attention.

DR. WILSON: I would like to thank Dr. Cohen. And at this time, we will take a break and we will meet back here at 10:45. May I remind the members of ODAC to please do not discuss this application with anyone, including other members. Thank you.

(Whereupon, a recess was taken.)

DR. WILSON: Let me first remind the board members to indicate that you have a question. We will keep a running list of it, and I will call you in the order that you're on that list.

So let me now open up this session of questions to the presenters. And let me just start out with a comment first and then a question myself.

I think that the promise of maintenance therapy, as the presenters noted, is that early use of an effective agent will improve outcome over its

use at a later time. And that is the situation that we are trying to look at today. I think one of the major issues, though, is whether or not early use does in fact significantly improve outcome over later use. And that can be judged by a number of end points, such as survival as well as quality of life.

I want to comment that the presenters did note that there was no difference in quality of life. And the spin they put on it was that this drug did not cause undue side effects. But I think the other side of the coin is that this drug, early use of it, didn't appear to improve quality of life, either.

So my question really refers to slide 38 because I think the question at hand is whether or not the use of this agent, which is known to have effectiveness in the second-line setting, would be better given or equally well given as second-line therapy.

So in slide 38, the sponsors have shown us that there is in fact a continued improvement in

overall survival when they do a subset analysis by those patients who receive subsequent systemic therapy. But I think the question at hand really is what does a curve like this look like in patients that received an EGFR TKI as subsequent therapy.

So my question is: What is the result? Did the sponsor do an analysis of overall survival among the subsets of those patients on the placebo arm who received an EGFR TKI as subsequent therapy, recognizing that this was only 14 percent?

DR. DAVIES: We did perform a number of analyses looking at subsequent therapies, including the one that you referred to in my primary presentation. Our analysis looked at the three primary therapies that are approved for second- and third-line therapy. And I would request that we put up the Kaplan-Meier curve looking at overall survival for the three agents that are approved by the FDA.

The analysis that we performed was examining overall survival in patients that received subsequent single-agent Tarceva,

docetaxel, or pemetrexed. And as already mentioned, these are the approved second- or third-line agents that can be given in the United States.

What you'll notice is that the hazard ratio is .7 in favor of Tarceva treatment in that setting. To limit it to TKIs is not a reflection of current patterns of practice in the United States, and therefore that's why this was the focus of this analysis.

We did examine overall survival, also censoring for EGFR TKI therapy. And I would ask the slide up, please.

So this is an overall survival analysis. This was not a subgroup analysis. This was in the overall population, the intent-to-treat population. This was just another way to evaluate the impact of tyrosine kinase inhibitors and to isolate the effect. And therefore, this was the censoring of the patients that received the subsequent TKIS, and as you've already indicated, 21 percent in the placebo arm and 11 percent in the Tarceva arm. And the hazard ratio remains in favor of Tarceva

treatment in the maintenance setting.

DR. WILSON: All right. Thank you.

Let me open up, then, to other -- Michael?

DR. LINK: So this is a question to Dr. Cohen, probably.

So I understand that you would have -- the preferred design, to compare early versus later application of the intervention. But if one looks back at the pemetrexed trial, it's basically the same as this one. So the pemetrexed was given randomized to either best supportive care, which I guess one could assume that that was placebo versus pemetrexed. And then only 19 percent of the patients that actually crossed over after progression received the agent of interest. Yet you were convinced in that setting that the intervention was reasonable.

So why would you be so highly critical of this design compared to that?

DR. COHEN: Well, what you say is true. The basis for our approval of pemetrexed was the

5.2-month increase in median survival that was observed in the non-squamous, non-small cell lung cancer group, and the fact that whereas in the present trial, 59 percent of patients received an approved second-line drug, in the pemetrexed trial, 79 percent of patients received an approved second-line drug.

DR. LINK: But it still didn't address the question that you wanted to ask, what's now versus later.

DR. COHEN: That's correct.

DR. DAVIES: Excuse me, Mr. Chairman. If I could just have a moment to clarify a point that Dr. Cohen made. In fact, 67 percent of patients in the pemetrexed study received subsequent further therapy, not 79 percent.

DR. WILSON: Margaret?

DR. TEMPERO: My question is for Dr. Davies and her colleagues. Actually, I have two questions, if I could be allowed to.

One is an understanding about how the biomarkers were done. I mean, were these done

under CLIA conditions, or were they done just ad hoc at each site?

Secondly, the smoking status is a very strong predictor, obviously, of outcome with erlotinib. And I wondered if you did any exploratory analyses of the biomarkers relative to the smoking status. So, for instance, in smokers, were the biomarkers any more or less predictive and the similar in nonsmokers.

DR. DAVIES: I'd like to address your last question first, and then I will request that some of my biomarker colleagues come up to address your methodology question.

With regard to the relationship of smoking status, you are correct. Smoking status is both a prognostic factor and a predictive factor. Never smokers do have a better prognosis than smokers in advanced non-small cell lung cancer. We did perform the analysis based on smoking history, and I would request that we put up the forest plot for progression-free survival, which was the primary end point for smoking status.

This was the slide that I showed in my core presentation. Looking at the smoking status, you'll notice that the last three hazard ratios refer to the smoking status. For never smoker, past smoker, and current smoker, all the hazard ratios favor benefit, although as you can see, the hazard ratio has a greater magnitude of benefit for treatment with Tarceva than never-smoker status.

We also evaluated smoking status within the overall survival, and I would request that that forest plot be put up now.

DR. TEMPERO: So my question related to the biomarkers within the smoking status.

DR. DAVIES: Yes. And I will just actually show the Kaplan-Meier curve -- excuse me, the forest plot for overall survival. And then to clarify your question, the overall survival was significant for patients with smoking status. But to more specifically address your question, with regard to the biomarker interaction with smoking status, we do see that EGFR mutation status does track with the never-smoker status. But the

presence of smoking history does not preclude the ability or the presence of an EGFR mutation.

I actually do have a slide that I can put up for you. And that specifically addresses that biomarker, smoking interaction. So what you'll notice here is that in the never-smoker population, there were more -- I'll just start again to just take you through this slide.

This slide is looking specifically at the smoking status of patients with patients that have EGFR mutation. And what you'll see here is that there is a greater likelihood of EGFR mutation in never-smoker patients. But as previously mentioned, it does not preclude the presence of EGFR mutation in patients with other smoking history. There's no other correlation with the other biomarkers.

If I could move on to your first question and just get some further clarification. You had requested further information about how the tests were performed and whether they were done in a CLIA-certified lab. I'd like to invite Dr. Frank

Richardson from the biomarker group at OSI to address that question.

DR. RICHARDSON: Frank Richardson, OSI biomarkers. The four primary biomarkers that we looked at, EGFR IHC, EGFR type FISH, KRAS mutation, and EGFR mutation, all were done at central CLIA laboratories. If you would like more details on the specific assays, I can give that. Okay.

DR. WILSON: Let me follow up on that. The hazard ratio by IHC for EGFR-negative is 0.91 for overall survival. Given that overall survival is really the hardest end point here, why should we consider this a positive trial for IHC-negative patients?

DR. DAVIES: We believe the results from the study, which was designed to test the value of EGFR IHC as a biomarker, does not support that EGFR IHC is a strong biomarker. In fact, it's likely a weak biomarker.

We do see benefit in the setting of progression-free survival. You're correct that the hazard ratio was .91 for overall survival.

However, an interaction test was not significant as we looked at EGFR IHC as a specific marker, both for PFS or for overall survival.

In addition to that, as we tried to get a better understanding of the EGFR IHC-negative population, we also found that there were actually patients that were EGFR IHC-negative that had EGFR mutations. And when we examined the interaction between EGFR IHC-negative and EGFR mutation -- and again, these are exploratory analyses to help us understand; slide up, please -- I'd like to take you through the slide.

This is specifically for PFS. And I can take you through the fact that it's looking at the PFS benefit. For EGFR IHC-negative, there were actually nine patients that also had EGFR mutation. And the hazard ratio, in fact, was not reported because of the small number of patients.

But when we look at EGFR IHC-negative and EGFR wild type, that included a population of 55 patients, and there was a hazard ratio favoring benefit.

If we now move on to overall survival, as you indicated, which is considered potentially a harder end point, and as we did this exploratory analysis, we found that even in the setting of overall survival, when the EGFR mutants are removed from this analysis and look just at EGFR wild type and IHC-negative, we see that the hazard ratio still favors overall survival.

If we were to exclude patients based on EGFR IHC-negative, which is a weak biomarker, it would have meant that nine of these patients would not have had the opportunity to have the significant benefit that was seen with EGFR mutation.

DR. WILSON: So I think that I would agree that IHC doesn't appear to be a very good biomarker for you. I do think that it is necessary, or at least for me necessary, to drill down into some of the subset analyses, which I prefer not to do in settings like this, simply because I have to say that I do agree that to really evaluate maintenance therapy, at least for

me, you really want to know whether or not maintenance versus delayed therapy, whether or not maintenance is better than delayed therapy.

So when we do go and look at the group that has EGFR mutations, from your progression-free survival data it looks to me like that is a very powerful biomarker, while recognizing that it's not a validated test.

But when I then go to look at the overall survival, I see no difference. And I'd like to get your thoughts on that because it seems to me that it's likely that it's the EGFR, that that really calls out, probably, the group that is going to be most benefitted by this drug. And it looks like there's no survival benefit. And I want to know is that simply because those patients on the placebo arm were in fact getting EGFR TKIs at relapse. And if that's the case, haven't you shown data here that there is no benefit to using this drug early?

DR. DAVIES: I'd like to pull up the overall survival Kaplan-Meier curve that I showed in my core presentation for EGFR mutation

specifically. And certainly, you are correct. As we examine overall survival in the EGFR mutation-positive patient population, we don't see a significant benefit in terms of overall survival, which could be confounded by the high rate of crossover. And this was very intriguing for us, to get an understanding of why that would be. And although it's a small subset, what we chose to do was to look at the patients that did not receive subsequent TKI who were EGFR mutation-positive.

What I would like to do is show you that Kaplan-Meier curve -- again, an exploratory analysis. And so this Kaplan-Meier curve looks at the overall survival in patients that were EGFR mutation-positive. This was based on our updated evaluation of the EGFR mutation subgroup, which was requested by the FDA.

These are patients that did not receive subsequent TKI therapy. And if we look at this exploratory analysis, with Tarceva treatment being the upper red line, and the placebo-treated arm in the maintenance setting, what you'll notice is that

in the absence of subsequent TKI, it does not -- the Tarceva treatment is favored.

Now, what this suggests is that EGFR mutation is a very strong biomarker, and that the benefit that's achieved from erlotinib in this setting can be seen in multiple lines of therapy.

The problem is if you don't get the drug, you're not going to have the benefit. And many patients, potentially because of declining performance status or rapidly progressive disease in advanced non-small cell lung cancer, may not get to second- or third-line therapy. And therefore, it's important to deliver efficacious agents early in this setting.

Dr. Bunn would like to add an additional clinical comment with regard to that.

DR. BUNN: I'd like to clear up a couple misconceptions I think that have occurred. Patients with lung cancer, over 90 percent have two or three symptoms at the time they present. After induction chemotherapy, the largest group by far is those with stable disease.

It has been indicated that those patients are not symptomatic, and that is simply not the case. The majority of these patients are still symptomatic. The average time to symptom benefit from Tarceva in any line is eight days.

Unfortunately, the first assessment of the quality of life was at six weeks, and they were done infrequently to show that there wasn't any deterioration because other studies had showed the symptom benefit. This study wasn't really designed to be looking at symptom benefits in the short run.

I can speak because I've had a lot of patients like this. So frequently, the mutation testing doesn't come back until after a patient has been started on chemotherapy. And frequently, during the period of induction chemotherapy, you find out that a patient is mutated.

The majority of those are still symptomatic at the time they finish their induction therapy, and some have had no symptom benefit. Tarceva is uniformly, as you've heard, beneficial in these patients with EGFR mutation testing. So

stable patients and symptomatic patients after induction therapy that have an EGFR mutation should not wait until progression to receive this agent.

DR. WILSON: Let me just say that I don't believe anyone ever said that the patients were asymptomatic. What I think we said was the data, as presented, was that there was no improvement in quality of life, as the patients reported. And I think that is a very powerful end point because that is from the patients' perspective.

I think that one can always look at whether or not there's increased cough or decreased cough, which the data did show when they looked at dose-specific end points, that the investigators did in fact find decreased cough. But from the patients' perspective late, they do not report that the maintenance arm seemed to improve their quality of life.

So let me open up.

DR. FLEMING: Fleming. We're throwing a lot of statistics around here. I think we'd better be pretty careful. Could I just quickly review

some of the slides we've just shown? EF-21.

My understanding is this is not a time zero cohort. This is not what we call a valid subgroup. This is what some have called invalid subgroups. These are people who, post-baseline, had not received a subsequent TKI. And you're looking at the difference there in outcome. Am I interpreting correctly? Just a yes or no is adequate.

DR. DAVIES: Yes.

DR. FLEMING: Yes. And then could you show us your slide CC-38, where you're looking at patients who received subsequent systemic treatment, and again, generating fancy P values and analyses where again, this is not a valid subgroup. This is a cohort of patients who are identified post-randomization. It's leaving out 36 percent of the population who didn't.

I suspect if we show the differences in those who didn't receive subsequent treatment, there may not be a very big difference. But I don't know how to interpret that either. That's

not maintaining integrity of randomization.

Whereas CC-41 is a valid analysis. It's a subgroup analysis. Dr. Bunn's comments about caution in subgroups are well taken. But at least this is a valid subgroup, maintaining randomization, argument being it may be that you're diluting the differences that are seen here because of cross-ins. But Dr. Cohen will come back to this, I hope, repeatedly. I think it's right on target.

The question here is not treatment versus no treatment. We know second-line treatment is effective. It's if you give it earlier, is it better? So this is highly relevant to look at whether or not, when you give rescue therapy with this approved intervention or a similar intervention, does that yield a difference?

So if I just extend a little bit while I'm here, I'm also bothered greatly by I think it was CC-32, where you were looking at the effect modification of IHC. And while there is just a modest indication of attenuation, it's in very

small numbers in the IHC-negative. But there was an indication that it's not statistically significant. You reiterated that indication.

Tests for interaction are notoriously underpowered, particularly in a setting like this, with 121 people in the IHC-negatives. You could have a very large interaction, and a test for interaction would be not significant.

So a nonsignificant test of interaction is not informative. Absence of evidence is not evidence of absence. There's not sufficient data here to understand whether there's interaction, although there are other data. And we come to what Dr. Bunn was indicating, which is be careful about interpreting subgroup analyses unless they're prespecified.

Do I understand, Dr. Bunn, that's essentially your message?

DR. BUNN: That's one of my messages, yes.

DR. FLEMING: Yes. And indeed, it's a good message. One is in a position of at least

having enhanced interpretability if it's prespecified. Well, this was a highly -- this was an alpha spending prespecification.

There was such a prior sense that this could be an effect modifier that some of the alpha was specifically spent to assess the IHC-positive effect separately, given the expectation of enhancement. And that expectation, I don't know if we can show the FDA's slide 22. The sponsor may not have the ability to show that.

But if we show that slide 22, part of the evidence for this, I assume, is the bottom slide, the second and third line, where the median survival was two months longer on placebo versus erlotinib, although the overall relative risk was 1. For overall survival in the maintenance, the relative risk is relatively modest. And so following the proper principle of Dr. Bunn that one has to be cautious about interpreting subgroup analyses but their prespecification is key, this was inherently an integral prespecification.

No one has yet shown us the survival

curve. Does anybody actually have the survival curve to show us in the maintenance trial for those people who are IHC-negative?

DR. DAVIES: We do have the survival curve for EGFR IHC-negative, and we will just call that up now, please.

DR. FLEMING: So while we're calling it up, the arguments given against this being potentially a real interaction are very weak. In fact, the arguments that the interaction could be real based on totality of data are not definitive, but they are certainly substantial.

DR. DAVIES: Slide up, please. This is the overall survival Kaplan-Meier curve for the subset of patients that are EGFR IHC-negative. And as you saw on the forest plot, the hazard ratio is .91.

DR. FLEMING: So in essence, on top of a second-line study result where the median's going the wrong direction by two months, to indicate a nonsignificant test of interaction suggesting IHC is not an effect modifier is an inadequate analysis

or is an inappropriate interpretation.

DR. WILSON: Dr. Sekeres?

DR. SEKERES: Thank you, Dr. Wilson. I have a couple of questions. The first is going to continue on this questioning regarding the biomarkers.

One of the areas this committee is being asked to advise on is whether your maintenance schedule would be appropriate for a subgroup of patients, particularly those who are EGFR positive.

To help answer that question, however, we need a little more sense of what the validity and reliability are of IHC-positive EGFR mutations versus mutation-positive EGFR mutations, and the availability of these tests in the United States as well as the reliability of these tests from one lab to the next.

Can you address those issues?

DR. DAVIES: Yes. And if I could just clarify, you're looking for EGFR IHC testing specifically and EGFR mutation testing specifically?

DR. SEKERES: Well, frankly, both.

DR. DAVIES: Yes.

DR. SEKERES: I want to know what the validity is one to the other. So do you have a gold standard against which you would measure them and can report sensitivity and specificity and the reliability -- the availability of both tests in the United States, and the reliability between labs?

DR. DAVIES: Thank you. I'd like to invite Dr. Frank Richardson from the biomarker group at OSI Pharmaceuticals to address that.

DR. RICHARDSON: If I could maybe address the IHC question first. The IHC test that was used in this study was the test that is developed and marketed by DAKO, although not approved in lung cancer. And the cut point that was used was a 10 percent cut point. And that was based on the BR.21 study.

We believe that the data coming out of the SATURN trial was reliable. The pre-analytical factors were highly controlled, including the time

that the sample was put into formalin, the time before it was cut and delivered to the central lab for staining, and then the calling probe that was used. So in SATURN, we think it's highly reliable.

If you're asking can there be differences between studies, that is something that we have seen before, and I think it's reflected in the BR.21 results that came out with 45 percent approximately negative rate, with ours coming out much lower. The same test was used, but we used -- the controlling of the pre-analytical factors was much different. SATURN was much more controlled.

DR. SEKERES: So if there can be differences between two studies, particularly one that's being performed, a lot of it ex-U.S., what tests are being used in the United States and how reliable are those tests compared to what were used in SATURN?

DR. RICHARDSON: I can't comment on all the tests being used. I know that we have an example of several trials that we have run using the DAKO test, to give you an idea of the

variability that we've seen across studies.

In this slide, we have taken and looked at BR.21, which is the study we talked about before; TRUST 1, TRUST 2, MERIT, SATURN, BETA, and ATLAS. You can see the total number of patients that we have evaluable samples on, and then you can see the EGFR IHC-positivity rates.

I think there's a couple things to notice. One is we used PharmDx on all of these; and two, that the results in BR.21 were much lower than what more recent results are, where we believe more sample control is going on.

To answer your question about other tests, I can't comment. We know that there was a paper that came out that compared several tests just recently, and that showed comparable results.

DR. SEKERES: But can you give a sense of the sensitivity and specificity of IHC testing for EGFR?

DR. RICHARDSON: No, I cannot.

DR. SEKERES: Okay. The second question I had was regarding the patient-reported outcome

variable. You said that you used the FACT-L. It wasn't specified in any of your slides.

Did you use the general FACT, which includes domains in, for example, physical well-being, social well-being, emotional well-being, along with the lung subset of that questionnaire, or did you just use the lung subset?

DR. DAVIES: Both were used, both the lung subset and the other domains that you indicated.

DR. SEKERES: So given that I don't off the top of my head know the test characteristics of the lung subset, but the general fact I'm fairly well familiar with, can you give a sense of the absolute scores within those domains or for the entire instrument, for the general fact, across the course of this study?

DR. DAVIES: I'd like to invite Dr. Gaelle Klingenschmitt to address some of the issues about the specific quality of life analyses that were done and those analyses.

DR. KLINGELSCHMITT: Gaelle

Klingelschmitt, statistician at Hoffman-La Roche. We have performed three analyses based on the quality of life questionnaire.

So the time to symptom progression, we used the lung cancer subscale. For the time to deterioration in trial outcome index, we used the FACT-L questionnaire. And we also performed another analysis with all subscales. That was the time to deterioration in quality of life.

DR. DAVIES: If I could just clarify your question, actually. If I understood correctly, you were looking for specific scores on individual domains. Is that correct?

DR. SEKERES: Right. So either individual domains or the FACT-G as a whole, on what those scores looked like over time in the patients treated with erlotinib versus placebo.

DR. DAVIES: Right. We looked at the FACT-L and the FACT-G as part of a composite end point. We also looked at individual domains. And indeed, within the individual domains as well as the overall evaluation, the results were

comparable. There did not appear to be any differences. I don't have those exact results available to show you today.

DR. SEKERES: So in other words, within domains and in the instrument as a whole, there was no improvement in patient-reported outcomes for patients treated with erlotinib versus placebo despite the progression-free survival advantage?

DR. DAVIES: That's correct. Based on our analysis of individual domains, there were no significant differences. As mentioned, the patient-reported outcomes were performed every six weeks in timing with the CT scan results. The majority of patients did progress radiographically and not based on clinical symptoms or symptomatology.

DR. SEKERES: Okay. Thank you.

DR. WILSON: Dr. Kelly?

DR. KELLY: Yes. I just want to carry on with this lung cancer-related symptoms and analgesics. Did you break that down to all subset of patients and it was the same across all,

particularly the squamous and non-squamous cell patients?

DR. DAVIES: You're referring specifically to the exploratory analyses for lung cancer-related symptoms and analgesics?

DR. KELLY: That's correct.

DR. DAVIES: Yes. So we performed that as part of the analysis of the overall population. Because of the interest that the FDA had in squamous cell patients specifically, we did also evaluate specifically in squamous cell patients the time to these lung cancer-related symptoms as well as analgesic use. And it also favored benefit from Tarceva for the squamous cell histology population as well.

DR. KELLY: Do you have that data?

DR. DAVIES: I can show you the forest plot for that. One moment, please.

This was the exploratory analysis that was performed looking at the time to cough, dyspnea, pain, and use of opioids or analgesics. This was specifically in the subset of squamous

patients. And as you can see, with respect to these four parameters, it favored Tarceva treatment, with the hazard ratios ranging from .34 to .73.

At the lower part of the forest plot, you'll see the time to symptom progression, deterioration in quality of life, and deterioration in trial outcome index, which although falls to the left of 1, is not statistically significant. And so we do see an improvement in these symptoms, particularly in squamous cell tumors. These tumors tend to be fairly proximal and are associated with a lot of symptoms, such as cough, dyspnea, and pain.

DR. KELLY: Do you want to ask a question?

DR. FLEMING: Just on this point. Just a clarification. At the bottom of the slide, it seems inconsistent with CC-43. It's a trivial point, but it's .94 here and you said it's 1.06 in --

DR. DAVIES: So this slide here that I

presented initially in my core presentation is for all patients on the trial. The subset that I showed was in direct response to Dr. Kelly's question in the specific squamous population, which was an exploratory analysis.

DR. FLEMING: Okay. So a more substantive question, though, in all of these measures, did you -- so in pain, for example, were you sure to continue to assess for these measures independent of whether the person progressed or stopped therapy or did you truncate follow-up?

DR. DAVIES: The follow-up of these symptoms ended at the time of progression. Over 90 percent of patients came off study due to progression. The trial did not continue to collect symptom data beyond the timeline of progression.

DR. FLEMING: So any indication that there is a positive effect here on pain quality of life has to be interpreted with great caution because that's definitely informative missingness that's apparent here. To assess quality of life, one has to assess it in an ITT fashion in all

patients. You can't truncate follow-up at progression. It's going to lead to highly informative missingness.

DR. KELLY: Another question. Two more questions. This is related to the post-progression therapies. You know, 42 patients were enrolled from North America. What was the breakdown per regions of treatments, and were there regional differences in the treatments for patients after progression? And how does that compare to the U.S. population and treatment trends here?

DR. DAVIES: I would like to highlight the subsequent therapy slide that I did show in my core presentation, just as a reference point. There were evaluations of different regions, which was part of the stratification. And there were no specific differences that were seen across region.

As you'll note -- slide up, please -- the majority of patients that were on this study, although 42 patients were from North America, the majority of patients did receive FDA-approved agents, which include docetaxel, pemetrexed, and

EGFR TKI.

DR. KELLY: Does this parallel what we do see in the United States currently as second-line therapies?

DR. DAVIES: What I would like to do to address that question is invite Dr. Paul Bunn, who is a clinician in the United States.

DR. BUNN: Absolutely. Those are the three drugs that are FDA-approved and reimbursed and used. And I think that there's nothing different in the frequency of second-line treatment between Europe and North America, both by EMEA approval and use.

DR. KELLY: Is there more TKIs used in the United States than Europe?

DR. BUNN: I couldn't answer that. Dr. Cappuzzo can maybe address that. Not to my knowledge.

DR. DAVIES: Would you like to hear from Dr. Cappuzzo in terms of his experience in Europe?

DR. KELLY: Just a yes or no. Just a yes or no.

Is TKI use different in Europe and America?

DR. CAPPUZZO: Well, in Europe we have two agents that have been approved. One is gefitinib, Iressa, and the other one is Tarceva. The only difference is that the indication for using Iressa is restricted to patients with EGFR mutations, while we don't have any restriction for the usage of Tarceva. For the usage of the drug, approximately the same. There is no difference, I guess, compared to U.S.

DR. WILSON: I would like to use my prerogative here. I think in the absence of data, you cannot say that.

DR. DAVIES: Thank you.

DR. WILSON: Dr. Link?

DR. LINK: My question has been answered already.

DR. WILSON: Dr. Hubbard?

DR. HUBBARD: Yes. I'd like to go back to the regulatory history of this trial and your interactions with the agency. Did you understand

that the agency wanted overall survival to be the primary end point?

DR. DAVIES: Yes, we did. The agency had requested that the study be powered for overall survival.

DR. HUBBARD: And can you give us, perhaps, some of your thinking as to why the trial was left with progression-free survival as the primary end point?

DR. DAVIES: I'd like to invite Christine Boisclair from regulatory at OSI to further outline the FDA interaction.

DR. BOISCLAIR: Christine Boisclair, vice president of regulatory at OSI.

Actually, the topic of the end point for the study was discussed on a couple of different occasions with the FDA. In the first instance, it was discussed when we were discussing the overall design of the study as opposed to approval commitment for the original Tarceva approval.

At that point, it was agreed that PFS should be the end point in light of the concern

about the confounding effect of subsequent therapies. And in fact, the PFS end point is included in the agreed-to wording of the post-approval commitment that's in the Tarceva approval letter.

It was subsequently discussed in a meeting we had with the FDA in December 2004. And at that point, we specifically asked the question again about the acceptability of the PFS end point. At that point, the FDA asked us to power the study for overall survival, which as you've seen, we did do.

We then went back as part of the SPA process to the FDA and again raised the question about whether the study was appropriately powered with survival. And at that point, we got the response that you see in the FDA briefing document, that they would wish to see an improvement in overall survival, which of course you've seen.

At no point were we asked to change the primary end point to overall survival.

DR. WILSON: Dr. Freedman?

DR. FREEDMAN: I have just one question, and it relates to the fact that the population that was studied was primarily in Europe, with 42 patients in Canada. And of course, it does not include large sub-populations from the United States.

So the question is anything known about erlotinib in terms of its AE profile or interaction with genetic factors that could provide either a selective benefit, selective adverse effect, for certain sub-populations in the U.S. that were not studied in this trial?

DR. DAVIES: If I could clarify your question, you're looking specifically for any differences in AE profiles that could exist between the United States and the population studied in this trial, or other factors that could influence the likelihood of efficacy?

DR. FREEDMAN: As you know, the African Americans have the highest frequency in males in terms of lung cancer in this country, so they would be an important target group for drugs such as

this. And the question is, what is known about the genetic profiles or unanticipated responses to drugs such as erlotinib?

DR. DAVIES: I'd first like to address the second part of your question. And what we do know, as we've done multi-varied analysis based on region as well as multiple other baseline factors, is that patients of Asian ethnicity do have an improved prognosis in advanced non-small cell lung cancer, as well as it's a predictive factor for benefit from erlotinib, as it tends to track with the presence of EGFR mutation.

With regard to regional differences in our multi-varied analysis, we did not see any specific differences across region. And as you'll note, as I presented, the percent of Asian patients, approximately 14 percent in this study, approximates what we've seen in U.S. studies.

With regard to adverse event profiles that may be different, I'd like to invite Dr. Karsten Witt to address that question.

DR. WITT: Yes. As part of this

application, we did evaluate the safety profile based on ethnic origin. But because there were about 1 percent of patients that were non-Asian or non-Caucasian, it's very difficult to draw a conclusion from those small subsets.

There were between -- we did primarily focus with respect to ethnicity differences between Caucasians and Asians. And there were small numerical differences in various adverse event reporting rates, but nothing worth noting.

With respect to region differences, we also looked at that as part of the application. And the safety profile of Tarceva versus placebo by region again did not really pick up anything noteworthy.

DR. FREEDMAN: I was particularly concerned about the African Americans in this country. And do you have any data?

DR. WITT: We don't have any data specifically for African Americans because there were too few patients on the study.

DR. DAVIES: Dr. Bunn, if I could invite

you up to address the issue with regard to African American ethnicity.

DR. BUNN: We recently published a paper in the Journal of Clinical Oncology regarding this. This was multiple biomarkers found in African Americans in the U.S. There was fewer, a lower rate of EGFR mutations than in Caucasians. There was a significantly higher rate of FISH positivity in African Americans. The rates of EGFR positivity were similar. There was no difference in response to TKIs that could be discerned.

DR. FREEDMAN: Can I ask another question?

Do you have any feeling for how erlotinib would -- what the AE profile might be in African Americans who receive erlotinib?

DR. BUNN: I have only anecdotal data from treating patients. I can't give you a large -- I don't have a statistical database. I can only give you my clinical impressions. But I certainly don't treat them any differently and haven't seen any differences in toxicity profiles. But that's,

you know, anecdotal, so you can take it for what it's worth.

DR. WILSON: Dr. Fleming?

DR. FLEMING: I'd like to pursue the question of my colleague, kind of understanding a bit more clearly the rationale for the choice of the end point PFS.

My sense is the FDA has given a compelling perspective here that in this setting, overall survival is critical to understand, and that the relevant question in this setting is erlotinib is established as second-line therapy. The question is, is earlier administration at maintenance in those people who've been on for four cycles and are non-progressive, is that earlier administration going to yield enhanced benefit relative to a delay until the time of progression for second-line?

So the sponsor's argument on slide CC-19 that PFS was used to "avoid the confounding by subsequent treatment" seems to be completely missing what it is that this trial is intended to

show and needs to show.

Now, could PFS still be in some sense an interpretable end point? If one has a really, really big effect that's large magnitude and statistically highly persuasive, it would be an interesting scenario to interpret that.

But the design of the trial, as laid out on slide CC-21 by the sponsor, is to provide 80 percent power to detect a relative risk of .8. We kind of get lost in statistics. It's good to kind of get up and away from the statistics and think about what things mean.

Essentially, what this means is you need 731 events. That's a correct calculation. With 731 events, we know today what the statistical significant relative risk will be. It's .852; .852 is what this trial was, in effect, designed to declare as the threshold for a win, for positivity.

.852 translates, when you have a 2.6-month median, to about a .45 median month estimated improvement, 10 to 14 days. So this trial set forward a threshold for positivity that would be

achieved with an estimated improvement in PFS of 10 to 14 days and a two-sided P value of .05, .03 for this end point but .05 when you're doing your alpha sharing.

So I guess my question to the sponsor is, you're going for a single trial approval, where results need to be robust and compelling. Why is essentially a two-sided .05 alpha spending statistically persuasive on an end point PFS, which is a surrogate, where the estimated improvement could be 10 to 14 days? Why is that compelling?

Isn't this the poster child for the issue that many of us have been talking about, which is, we should not be designing our trials on statistical significance. You're hearing this from a statistician. The world is not about statistics. Okay? It's not about statistics here.

It's about getting statistically persuasive evidence of clinically meaningful effects. So if we're going to hang our hat on PFS, what is clinically meaningful here? A 10- to 14-day difference in PFS with a two-sided .03 to .05 P

value? Can someone clarify why that is a robust and compelling effect that is very statistically persuasive on a very clinically impressive magnitude?

DR. DAVIES: We believe that the median estimate for both PFS and overall survival doesn't accurately reflect the benefit that the hazard ratio indicates. But I think your point is well taken that ---

DR. FLEMING: If I might -- sorry, but that has nothing to do with what I just said. I am not talking about medians here. I was talking about relative risks. I was talking about the totality of the effect, as represented by relative risks. So the median, what I'm talking about for magnitude of effect, is not getting at my question. My question is, you're targeting an effect that effectively translates to an overall 10- to 14-day difference if you look at it as area between the curves or if you look at it as crossing the median line.

DR. DAVIES: You are correct. The

results are statistically significant. In terms of whether that's clinically meaningful to a patient and whether it's clinically relevant, I would like to invite Dr. Bunn, who is a clinician and treats lung cancer patients, to give you his opinion about what he believes the clinical relevance of this data is.

DR. FLEMING: I'm sorry. I'd like to address the question, not a different question. We will separately address the question, are the magnitude of the effects actually observed viewed to be clinically persuasive? I was getting at a follow-up to my colleague's question about the intention of the design.

The design of the trial is what I'm getting at here. The design of the trial was declaring positivity, i.e. statistical significance, with this number of events for what would have been a 10- to 14-day overall improvement on a surrogate end point of PFS, with a two-sided P value that, adjusted for multiple testing, is .05.

Single trial application. How is that

statistically persuasive evidence of clinically compelling effects where in context, what I think a number of us would argue is it's conceivable you could use a PFS measure here, but the magnitude of the benefit would have to be large and the statistical persuasiveness would have to be compelling for a single trial. There seems to be a huge disconnect between those two.

DR. WILSON: Do you have any comment on that?

DR. DAVIES: We believe that the results are clinically meaningful. And I apologize, Dr. Fleming, that I'm not able to directly answer your question. I think that your points are well taken and that in terms of how these results can be interpreted within the context of the current treatment paradigm is that it offers another option to patients in this setting that could significantly benefit that wouldn't otherwise be candidates for second or further line of therapy.

I still believe that the interpretation of what this means clinically is something valuable

to discuss. And if you would like to, I can invite Dr. Bunn back up to the podium to do that.

DR. FLEMING: I suggest we go on because it is relevant to go on and change the question; i.e., it is relevant to talk about do these data establish sufficient evidence for benefit?

It was also, though, relevant to determine whether the trial's design in fact made sense in this setting, which is not being addressed by this response. So I'm happy to go on. I think it's compelling that the design of this trial is not defensible.

How is that relevant here? It's relevant to say just achieving a two-sided .05 or two-sided .03 or two-sided .01 on PFS of a small magnitude, even though that's what the trial was designed to achieve, should not be viewed as persuasive evidence of true favorable benefit to risk. One has to look now at the totality of the data to make that judgment.

But moving forward, it's really important to design our trials ideally such that when you hit

the threshold in the trial design, it would be defensible as being the strength of evidence and magnitude of effect that would in fact be clinically important.

DR. WILSON: So, you know, I'm trying to find a silver cloud here. And I think that I agree with Dr. Fleming and Dr. Bunn's statements regarding the problems with subset analyses. But, you know, I think one needs to look at those here because of the way the study was designed.

I think we've already seen that if you're IHC-negative, your overall survival curve is no different. And so it really raises the question of whether or not IHC-negative patients are having any benefit from this.

The other group, though, that we haven't really discussed are the patients who have squamous cell. And, you know, I guess one could make a regulatory and a clinical argument that perhaps an unmet need is in the squamous cell group for maintenance because that's the one group that the pemetrexed didn't seem to have benefit for and is

hence not approved for.

When one looks at the non-squamous cell, non-small cell cancer, using pemetrexed -- and again, I don't like to do cross-trial comparisons. But if you look at that versus the benefit of erlotinib maintenance, certainly they were at least as good, although in absolute terms the pemetrexed looked to be more effective. But again, when one turns to the squamous cell group, though, the overall survival hazard ratio is .86, and this is not statistically significant.

But could I ask OSI to put up a Kaplan-Meier curve of overall survival for the squamous cell groups and we can see what that looks like?

DR. DAVIES: Yes. Slide up, please. This is the Kaplan-Meier curve for overall survival for squamous histology, with a hazard ratio of .86, as you've already seen in the forest plot.

DR. WILSON: So, I mean, I think it's fair to say that the benefit here is extremely small.

DR. DAVIES: So this was a subset

analysis.

DR. WILSON: Right.

DR. DAVIES: And as we've previously said, that this is an exploratory subset analysis and could be confounded by known and unknown biases.

DR. WILSON: Right. Any further questions? Go ahead, Dr. Logan.

DR. LOGAN: I had two questions, one to Dr. Cohen. One of the issues was the adequateness of the second-line therapy, and you raised the pemetrexed trial as one possible baseline.

Can you comment on the compatibility of the eligibility criteria, as well as was that done in the U.S., or outside the U.S., or both?

DR. COHEN: In terms of eligibility, it was relatively similar, the pemetrexed trial and the erlotinib maintenance trial. They both involved the same stage IIIB-IV non-small cell lung cancer. They both have four cycles of a platinum-containing doublet regimen. Performance data is comparable. And post-progression treatment was

relatively comparable.

DR. LOGAN: And in the U.S. or --

DR. COHEN: In the -- oh, specifically for U.S.?

DR. LOGAN: Well, was that trial done outside the U.S. or also in the U.S.?

DR. COHEN: No. No, it included -- it was worldwide.

DR. LOGAN: My second question is to the sponsor. One of the concerns that's been raised is about the proportion of IHC-positive patients in this study versus the previous second- and third-line therapy study.

Have you looked at the selection of patients in terms of that being one possible reason for the difference in the proportions of IHC-positive? For example, in the patients that -- in the placebo arm that proceeded to second-line therapy, what is the proportion of IHC-positive in that cohort?

DR. DAVIES: If I could clarify your question, please. You're asking that in the

placebo arm specifically, how many patients proceeded to second- and third-line of therapy that were EGFR IHC-negative?

DR. LOGAN: Yes; positive versus negative, in the group of patients that proceeded to second-line therapy. Because that was the cohort that was studied -- may be more compatible to the cohort that was studied previously.

DR. DAVIES: Correct. We actually do have the percent of patients that proceeded on to second- and further-line therapy in the IHC-negative group. It was imbalanced in favor of the placebo arm. And if you can give me one moment, I can't exactly remember the percentage in that setting. And again, that was exploratory data that we had.

So in the EGFR negative subset, the patients that were EGFR IHC-negative on the Tarceva-treated arm, 60 percent had second and subsequent therapy. For the EGFR IHC-negative subset in the placebo arm that went on to subsequent therapy, it was 71 percent.

DR. WILSON: Dr. Fleming?

DR. FLEMING: I have four questions. I'd like to keep them very brief in the interest of time. And if the sponsor could give just very brief answers, that would be sufficient from my perspective.

First, the cutoff for the PFS data when you had 749 events was May 17, 2008. The cutoff for survival, 648 events, wasn't till one year later, 5/17/09.

In the interval from May of '08 to May of '09, were the survival data results kept completely blinded; i.e., was the sponsor not provided any access to the interim survival data between '08 and '09?

DR. DAVIES: The data was blinded with respect to survival.

DR. FLEMING: So when you were provided the PFS results, there was no release of any survival results to anyone outside of the data monitoring committee between May '08 and May '09; is that correct?

DR. DAVIES: So that I can be certain that I'm answering that question correctly, I would like to refer that question to Gaelle Klingelschmitt, who's our statistician from Roche.

DR. FLEMING: All right. Let me keep going, and she can think about it and we'll come back to that answer, just in the interest of time here.

Second question. We've heard in Dr. Cappuzzo's presentation, slide CC-14, the greatest impact is in the first-line setting. I think the greatest potential for impact was what you were saying.

My understanding is you have two first-line trials, TALENT and TRIBUTE; is that correct? Can you quickly tell us, were those trials survival trials? Were those trials positive or negative on survival? Could you just quickly inform us? Am I correct about those two trials?

DR. DAVIES: Correct. TALENT and TRIBUTE were randomized phase 3 trials that looked at Tarceva in the front-line setting. However, that

was not as a single agent.

DR. FLEMING: Of course.

DR. DAVIES: That was in combination with a front-line platinum doublet.

DR. FLEMING: Of course.

DR. DAVIES: And not in the maintenance setting.

DR. FLEMING: Of course. Of course.

DR. DAVIES: Those studies were powered for overall survival.

DR. FLEMING: And their status in terms of positivity and negativity?

DR. DAVIES: Those studies have been completed and reported. Tarceva, in combination with chemotherapy, did not result in an improvement in overall survival in either one of those studies.

DR. FLEMING: Okay. The third question. Can someone provide us overall survival by region? The FDA has provided PFS by region in their briefing document. And if you don't have it immediately on hand, I'd be happy just to see that after the break, unless you actually have it

immediately.

DR. DAVIES: We do have the forest plot for overall survival based on region. This forest plot includes region as well as smoking status just because these two were stratification factors.

As you'll see here on this analysis, the hazard ratio does favor benefit, although, because this was a subset analysis, the confidence intervals do cross 1 in some cases.

DR. FLEMING: So we see the same thing as we saw for PFS, and that is Southeast Asia seems to be a particularly strong part of where the signal is. We saw that with PFS as well. So it shows up in survival. The last question, CC-27 progression, you in that slide revealed there were 52 Tarceva and 36 placebo patients. Is it accurate to say those 88 patients were then censored for progression in your analysis, or did you continue to follow them? How were they handled in the progression assessment?

DR. DAVIES: They were continued to be followed. At the time of the PFS data cutoff, they

were censored.

DR. FLEMING: So they were censored, then. So they induced missing data from the time that they were withdrawn?

DR. DAVIES: Correct.

DR. FLEMING: Okay. Did your statistician have a response, then, to the question? Is it true that only the data monitoring committee had access to survival data between 5/08 and 5/09?

DR. DAVIES: Thank you.

DR. KLINGELSCHMITT: At the cutoff of the PFS analysis, the overall survival analysis was done and was known in our team. It's not only the DSMB who was aware of the results. And it was published in the CSR (ph).

DR. FLEMING: Okay. So it wasn't kept blind at the DMC. Is that what I just heard? I believe that's what I just heard. Thank you.

DR. DAVIES: Excuse me, Dr. Fleming. If you could just repeat the question for Dr. Klingelschmitt.

DR. FLEMING: So did I understand correctly that after -- from May '08 on, the survival data weren't kept confidential solely to the DMC?

DR. KLINGELSCHMITT: We didn't perform intermediate overall survival analysis between the PFS cutoff and the --

DR. FLEMING: That's not my question. That's not my question. Simple question. I thought you answered it.

Was the DMC the only body that had access to the survival data between May '08 and May '09? I thought you said no.

DR. KLINGELSCHMITT: No.

DR. FLEMING: Thanks.

DR. WILSON: Dr. Lyman?

DR. LYMAN: Just a quick question around, again, the regional differences here and the generalizability of the data to, say, a U.S. population. As I understand, the primary inference here was drawn on unadjusted log rank comparisons. However, in adjusted comparisons for everything

except regional status, treatment remained significant. When regional status is also adjusted for, it becomes nonsignificant.

So searching for what might be different across these, I wonder if you have a breakdown on the primary therapies other than we know about a third of them got gem or docetaxel in combination. And we understand they're all platinum-based.

But do you have a breakdown of all the other combos that were utilized, and maybe some idea of whether these are similar to the way these patients are treated in the U.S.?

DR. DAVIES: Yes, we do. The study was actually designed to be applicable to the United States based on platinum doublets that were currently used in the United States and were reviewed by the FDA. This slide outlines the percent on the Tarceva and placebo arm on the individual regimens that were considered appropriate on study, and were required for any patient to be randomized.

DR. WILSON: Dr. Sekeres?

DR. SEKERES: Thank you, Dr. Wilson.

In the briefing document that you provided to the FDA, you state that, "Unblinding the patients after progressive disease was possible if, in the opinion of the investigator, the use of an EGFR TKI was the only option in this setting for the patient." That's page 11.

Can you give us a number of patients who were unblended, and do you have any survival curves for those patients?

DR. DAVIES: Very few patients, in fact, were unblinded. It was not recommended, only in exceptional circumstances. The rate of unblinding, I'm just waiting for that exact number. We don't actually -- if you could just clarify your second question, though, while I'm waiting for that data?

DR. SEKERES: Survival curves.

DR. DAVIES: For those that were unblinded?

DR. SEKERES: For those that were unblinded. And it looks like double the patients in placebo arm got TKI subsequently, which would hint

that there was a decent amount of unblinding to then move those patients onto TKIs afterwards.

DR. DAVIES: Correct. So there were 27 -- excuse me -- 21 patients that were actually unblinded, 17 percent in the Tarceva arm and 26 percent in the placebo arm. The analysis that you've described was not performed.

DR. WILSON: Let me ask a question. I think that Dr. Bunn in his very nice presentation did suggest that there might be patients who would get too ill to get EGFR TKI as subsequent therapy. And, therefore, that was a rationale for its use in the maintenance setting. And I certainly think that that's a cogent argument if there was in fact evidence that actually showed that.

So far, because of the lack of formal crossover among the placebo group, we can't answer that. But we do know, when we actually look at the subsequent systemic therapies in the Tarceva versus placebo group, that 63 percent of the Tarceva group went on to get subsequent therapies and 66 percent of the placebo group did.

So I guess my question is, what is the evidence that patients will not be able to get an EGFR TKI, or any meaningful number of patients will not get it, if we wait till they have progressive disease or is this simply based on anecdotes?

DR. DAVIES: In fact, it's not based on anecdotes. The data that was shown in Dr. Cappuzzo's study was pattern of practice data. But we also have data from other clinical trials which I could share with you -- slide up -- to show that in fact these are a series of clinical trials, including both the Fidias study, which was the docetaxel maintenance study, as well as the Ciuleanu pemetrexed study, although I do have to indicate that the 50 percent should be updated to the 67 percent based on the publication.

And what you'll notice is that in fact this is not an anomaly that we see in our particular clinical trial, but is consistent not only with U.S. pattern of practice data, that 60 percent of patients move on to second- or third-line therapy, but also consistent with other

clinical trials.

DR. WILSON: Okay. I think that's fine. But the question is whether or not using maintenance makes it -- whether or not there's any difference in the outcome when you use maintenance. And you have no data showing that.

DR. DAVIES: So the trial was not designed to evaluate early versus late. That is correct.

DR. WILSON: Right.

DR. DAVIES: But it did demonstrate an improvement in overall survival in that setting. And when we have performed, although albeit exploratory analyses, censoring for subsequent therapy and also evaluating overall survival in the presence of subsequent therapy, we have seen that it favors overall survival.

DR. WILSON: Right. But again, I think the point is that there's no evidence that if they don't get it in maintenance, they have a significantly lower chance of getting it at disease progression. That may be true, but there's no

evidence for that.

Okay. Well, it's 12:00 noon, so if we don't have any more pressing comments, why don't we adjourn.

Oh, sorry. We have one more. Dr. Logan? Oh, no. Okay.

Yes, sir?

DR. RICHARDSON: One question. I apologize for delaying this further.

I'm just curious about the fact that one really can't consider this a blinded trial in the sense that 60 percent of the patients on Tarceva had rash, and I suspect the -- although I couldn't find the figure for diarrhea or loose stools readily, I suspect it's substantially higher in that group as well.

I'm wondering if there's a difference in time to progression in those folks who had either rash or loose stools or diarrhea versus those who didn't. This is in the Tarceva group. And I guess what I'm getting at is since the investigators obviously could tell who was getting Tarceva, is

there a tendency to keep those folks on study longer?

DR. DAVIES: I think there are many components to your question there, and I'll try to answer them in a sequential format.

In terms of the presence of rash, there was 50 percent of patients, in fact, that experienced any grade of rash. And to the best of the ability of the trial design, as a placebo-controlled study, the blind was attempted to be maintained. Fifty percent of patients did not experience rash, and while there was a risk that that could confound the PFS end point, it was corroborated by a central independent radiological review and wouldn't have ultimately impacted on the overall survival secondary end point.

DR. RICHARDSON: But at the same time, there are those who have felt that the presence of rash is a predictor for response.

DR. DAVIES: Yes. That's in fact correct. So I will address that issue about the correlation because we did evaluate the presence of

rash on that arm. But we also looked at differences in the timing of the CT scans that were performed to see whether there were any imbalances in the assessment of PFS. And in fact, there was rigorous adherence to the six-week scanning intervals on both arms.

So based on that data that we have, it does not suggest that there was a bias in that setting. With regard to the correlation with rash, as previous studies have shown, as you mentioned, we did see a correlation, but in an exploratory analysis just on the placebo-treated patients with respect to overall survival. And I can show you that Kaplan-Meier curve.

DR. RICHARDSON: Say that again? Tell me how the placebo group enters into that. I'm asking specifically about the Tarceva group.

DR. DAVIES: Yes. And one moment, please. If we could please put up the overall survival comparison based on rash in the Tarceva-treated patient population.

So if I understood your question

correctly, you had asked about for those that were on the Tarceva-treated arm because very few patients on the placebo arm actually had rash. So this exploratory analysis that was performed for overall survival was in the Tarceva-treated arm only, and it looked at rash, any grade of rash, versus no rash. And consistent with previous data in EGFR inhibitors, there is a correlation between the presence of rash and survival benefit.

DR. WILSON: Okay. I'd like to thank the sponsor and FDA. And we will adjourn and return at 1:00. And I'd like to once again remind all the panel members, please do not discuss this among yourselves or with anyone else. Thank you very much.

(Whereupon, at 12:57 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

DR. WILSON: Okay. Let me welcome you all back. Now we're going to be having the open public hearing. But before we begin, we have a statement.

DR. VESELY: Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

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

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

DR. WILSON: Let me invite Peter Matloff to the microphone.

MR. MATLOFF: Good afternoon. My name is Peter Matloff. OSI has paid for my hotel and transportation here. Other than that, there is no financial involvement.

I was diagnosed at stage IV metastatic non-small cell lung cancer five and a half years ago. My first line of treatment was 16 radiation treatments to the spine, six treatments three weeks apart of Taxol and Taxotere, Taxol and carboplatin. The results were good. After three months, the CAT scan showed that progression was okay.

I had a break, and then three months later progression started again, and I went on carboplatin and Taxotere. The results again were good. However, after a series of nine months -- nine treatments, I was building up a lot of fluid in my right lung. After many thoracentesises, it was suggested that we do a pleurodesis. That was not successful, and resulted in pockets of loculated fluid in my right lung.

Some time after that, doctors were concerned that I had fluid around my heart and

suggested that we do a pericardial window. And since I had some fluid in the left lung, the surgeon felt that we should do a pleurodesis in the left lung since I was already on the table.

After those procedures, I went home with oxygen. A week or two later, it was apparent that something was not right. And after an emergency admission, it was determined that I had an infection in the left lung. After a week in the hospital, the infection was cleared up and a Pleurx catheter was inserted in the left lung.

This was very successful. About six weeks later the catheter was removed, and I have not had a fluid problem in the left lung since. After a while, my breathing improved and the oxygen was no longer needed.

A little over two years ago I started on Avastin, Alimta, and Tarceva, and the results were good. After nine months, the Avastin and the Alimta were discontinued, and at that time I continued with the Tarceva until some progression showed up on a CAT scan and my CEA began to elevate

a little bit.

Then I went back on Alimta and Tarceva, along with the Avastin, and in June of this year a CT showed that I had some air that had developed in the loculated fluid area of the lung and was taken off of the Avastin and the Alimta but continued on Tarceva.

It was determined that I had developed a bronchial pleural fistula, and the fistula was repaired with vascular coil placed in the bronchial tube and sealed with medical glue. The procedure was successful. A CAT scan last week showed that the air is no longer there, and the scan also showed that there is no other major changes to be concerned about. And I'm still continuing on the Tarceva.

Altogether, I have been on Tarceva over two years. For me, the side effects of Tarceva have not been anywhere near as severe as the other drugs. My quality of life is much better on Tarceva. Actually, it has been good that my family and went on a Thanksgiving week cruise for seven

days.

Yes, the past five years have been a roller coaster ride for me and my family. I have maintained a very positive attitude right from the start. The support of my wife Miriam, my son Gary, and my grandson Michael have made the journey a lot easier.

I am fortunate to have an excellent current medical team headed by Dr. Rogerio Lilenbaum, as well as medical insurance that has not denied me anything. My attribute being able to appear in front of you today speaks well for Tarceva. It needs to be considered for wider use in combating lung cancer.

I thank you for the opportunity to share my story. I look forward to the day that someone actually will find a cure for lung cancer. I'll be happy to answer any questions.

DR. WILSON: Thank you very much.

Our next speaker will be Maureen Rigney for the Lung Cancer Alliance.

MS. RIGNEY: Good afternoon. I'm Maureen

Rigney, director of community and support services at Lung Cancer Alliance. Based in Washington, D.C., Lung Cancer Alliance is the only national organization providing support and advocacy to those living with or at risk for the disease.

To support our efforts, we have hundreds of volunteers across the United States. Unfortunately, none of them could be here today, but we submitted five statements in support of the approval of Tarceva in the maintenance setting on their behalf, as well as one from Lung Cancer Alliance. We are grateful for the opportunity to give voice to the patient perspective as I now read three of those statements.

The first statement is from Mike Stevens of La Jolla, California. He was diagnosed at the age of 44. He is EGFR mutation-negative.

"My name is Mike Stevens. I was diagnosed with stage IV non-small cell adenocarcinoma on June 23, 2005. With both lungs fully involved, I was expected to live only two months. I apologize for not being able to be here

in person today.

"As I write this, I am undergoing a round of chemo at U.C. San Diego Cancer Center. Currently, I am on a clinical trial and have to stick to a timetable getting my drugs. In fact, I had chemo yesterday, which is one of the main reasons I was unable to make it here today.

"I would like to disclose that OSI was going to fly me out for this meeting today so I could present you with my statement.

"My first line of treatment was chemo every three weeks. Two of the weeks I would be flat on my back in bed, hardly able to move due to pain and fatigue. The third week I called my good week where I would have enough energy to live a semi-normal life. This type of chemo is like climbing a set of stairs. When you finally make it to the top, someone pushes you down to the bottom and you have to start the climb again.

"Due to the fact you have to be hooked up to a needle every three weeks and that two of those three weeks you are totally fatigued, I was unable

to travel very far from my house. You become almost a prisoner. I had six rounds of this treatment, which equated out to 18 weeks, basically 4.4 months of house arrest.

"After the sixth round of this treatment, I discussed with my oncologist that I was no longer getting that good week. The fatigue was dominating my life, and my quality of life was diminishing rapidly. It was at this point that my oncologist suggested I start Tarceva.

"Tarceva changed my life in many respects. The side effects were much milder than the drugs I was taking, so that instantly improved my quality of life. The greatest benefit is I was no longer connected to a needle, which allowed me to travel again. I was able to take my wife and children on a safari to southern Africa. This would never have been possible if I was doing chemo.

"After starting Tarceva in early 2005, I was on the drug until late 2009, almost four years. Most stage IV lung cancer patients do not survive

the first year of diagnosis. Every doctor I met asked if I knew how lucky I was. I know very well how lucky I am to be alive, and especially the great four-plus years I have had enjoying life.

"I've been able to travel, to watch my daughter start college at George Washington University in Washington, D.C., watch my son turn 16, and in August, I was able to travel to Tahiti to spend my 25th wedding anniversary with my wife. This would not have been possible if I was not on a drug that allowed me to be mobile and that kept me alive.

"I truly owe my life and the quality of my life to Tarceva. I strongly suggest making this drug available as a maintenance drug for those fighting lung cancer. We have few options to fight the number one cancer killer, and when we get something that improves the quality of life like Tarceva does, I think it should be made available to everyone possible.

"Thank you very much for the opportunity to hear my words today."

The next statement is from Mary Lou Fisher of Fortuna, California. She was diagnosed at the age of 65 and has nothing to disclose.

"My name is Mary Lou Fisher. I am a 69-year-old Caucasian woman who never smoked. In February 2006 I was diagnosed with stage IV adenocarcinoma lung cancer which had metastasized to my lymph nodes, bones, and abdominal wall.

"My first line of treatment was Taxol, carboplatin, and Avastin, which consisted of six rounds. In August 2006 I was placed on 150 milligrams of Tarceva.

"My experience with Tarceva. At first I had a lot of diarrhea and rash, and several months later I was put on 100 milligrams of Tarceva. I have done well on this amount, and side effects are minimal. I did not have any genetic testing before taking Tarceva.

"My cancer is being controlled by this drug, which I am so thankful for. I am able to enjoy life. I exercise, travel, and keep busy. I take my Tarceva first thing in the morning and eat

at least one hour later. I do make sure I don't get overly tired and get lots of rest. Tarceva has truly been a lifesaver for me, and I can recommend it highly."

Finally, the Lung Cancer Alliance statement. We would like to disclose that Lung Cancer Alliance has received $160,000 from Genentech and 28,000 from OSI in educational grants in 2009.

We express our support for FDA approval of the use of Tarceva as a first-line maintenance therapy for patients with advanced non-small cell lung cancer. Tarceva, when first approved as a second-line treatment in 2004, added an important and targeted therapy option for lung cancer patients. It remains so today.

The physical side effects and wear and tear on the body from platinum-based chemotherapies can be debilitating. Maintenance Tarceva can provide a much-needed break from such toxic treatments and allow patients the opportunity to regain lost strength and stamina.

The mental and emotional side effects can be just as devastating. Lung cancer patients often feel trapped, trapped in a regimented schedule of treatments in the chemotherapy room, trapped in their homes after chemo as they are too fatigued or susceptible to other disease to leave.

In addition, once first-line treatment is finished and the patient receives news of stable disease or, better yet, remission, the current next step is to stop treatment and wait. While it is a time to celebrate treatment success, for many it is also a time to worry about disease progression or recurrence.

Approval of Tarceva in a maintenance setting would allow patients to build on the momentum from positive results of first-line treatment and gain a heightened sense of control over their disease. And Tarceva's portability and often less-serious side effects allow late stage lung cancer survivors a renewed sense of freedom and the chance to resume a lifestyle more similar to that prior to diagnosis.

Lung cancer remains a leading cause of cancer death in the United States, with over 70 percent being diagnosed at advanced stage. Maintenance Tarceva would provide a valuable treatment option that may not only impact the survival time for lung cancer patients, but also allow those patients to spend that time doing things they love and not hooked up to an IV.

Thank you so much for your time and attention.

DR. WILSON: Thank you very much.

Susan Mantel?

MS. MANTEL: Good afternoon. I'm Susan Mantel. I'm the executive director of Uniting Against Lung Cancer. We're a nonprofit foundation focused on raising awareness of and research for lung cancer, including in never smokers. We have received $37,000 in awareness and educational funding from OSI in the last two years, and 108,000 from Genentech over the last four years for similar activities.

I thought Lung Cancer Alliance so

beautifully laid out the details, so I will keep my statement brief. We concur with everything that they said about the benefits of Tarceva. I'd just like to reiterate the importance of having multiple options available to patients at different points in their treatment, including the targeted agent Tarceva.

I've been executive director of this organization, which was originally founded with a specific focus on never smokers since September 2004. As a result, I've become keenly aware of the heterogeneity of this disease and the few treatment options that have been available.

I am heartened to have seen progress in the last four years in having more options available, but there is still a paucity of choices for physicians and the patients. It is particularly important to be able to offer appropriate options to patients for both their stage of treatment and their type of lung cancer.

Because I disproportionately work with never or light former smokers since we were founded

for never smokers, I've had the opportunity to witness firsthand the many patients with non-small cell lung cancer who have had additional months and years to spend with their families and friends thanks to maintenance therapy with Tarceva, and excellent care that they receive at some of the cancer centers.

In addition, they've enjoyed a high quality of life during those years, having the availability of an oral agent. That includes the ability to work, to play with their children, to travel, and to contribute to their communities.

Tarceva has represented an important new option for our population. We heartily endorse having this available as maintenance therapy. Thank you.

DR. WILSON: Thank you.

DR. VESELY: The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration

of the data before the committee as well as the public comments.

DR. WILSON: So let me read two statements, and then what we're going to vote on. And then I will open up the meeting for the members to discuss this.

The first statement is, the study was not optimally designed to demonstrate that maintenance therapy with erlotinib after initial chemotherapy is better than therapy with erlotinib at disease progression. The second statement is, results of the study demonstrated a modest improvement in overall survival.

The vote question is, based on these results, should erlotinib be approved for the proposed indication?

Let me just say, to start this, that we are not here to, I think, judge whether or not erlotinib is an effective agent. That has already been established. Erlotinib is available, and it is available at first relapse. What we are here to do is to assess whether or not, based on this clinical

trial, there is evidence that its use in maintenance is worthwhile compared to its use at first progression.

I think it's important to state the obvious. Number one, whenever you do maintenance therapies, there will be many people getting the maintenance therapies who will have no benefit from the maintenance. And that's where biomarkers come into play, to identify that group of patients that is most likely to benefit. And, unfortunately, due to a variety of issues that were well discussed today, we don't have definitive biomarkers to identify those patients in the maintenance who will benefit from this. I think one has to consider that just because you don't show that a drug has excessive toxicity that you want to necessarily expose patients unnecessarily to that drug, especially if that drug is equally effective -- and perhaps even more; nobody knows that -- at the time of relapse. And I think that's really the crux of what the committee needs to be discussing.

So with that, any takers? Don't all raise your hands at once. I'll give you a second to think.

DR. DAVIES: May I offer an additional comment from the sponsor?

DR. WILSON: Yes. Okay. Yes.

DR. DAVIES: I would like to agree with you that the study was not designed to evaluate an early versus late question. However, the study design was discussed through the SPA process, and there have been -- there's one other agent, pemetrexed, that was also approved in this setting utilizing the same design with a PFS end point. And while it's difficult to compare across studies, we do believe that Tarceva is another option in this setting.

There are some differences in the pemetrexed study that I would like the committee to be aware of. And while both were worldwide studies, both had PFS as their primary end point, there are some key prognostic factors that were different in the pemetrexed study compared to the

erlotinib study that could have influenced the magnitude of benefit that was seen.

I'd like to highlight a slide, if I may show one.

DR. WILSON: Yes.

DR. DAVIES: This is just a comparison to the pemetrexed randomized phase 3 study. This was the study that resulted in the approval of pemetrexed. Again, that study was designed as pemetrexed versus placebo in the maintenance setting and did not mandate subsequent pemetrexed.

You can see in the overall population, which is the forest plot, to the left, that in the overall population the hazard ratios are comparable to SATURN and JMEN.

If you look on the right-hand side, there was a table that was prepared comparing key prognostic factors in advanced non-small cell lung cancer, illustrating that the JMEN study, which is the name of the pemetrexed maintenance study, actually had a higher number of non-squamous, adenocarcinoma, Asian ethnicity, never smokers, and

some differences in the ECOG performance status that would favor a better benefit in the JMEN study.

While I was referring to the fact that many patients, because of rapid progression in advanced non-small cell lung cancer, are not able to get second and further lines of therapy, there was one study, which was the docetaxel study which Dr. Bunn did show in his initial presentation, that compared early versus late therapy. And what that study showed was that progression-free survival was improved. It wasn't powered for overall survival. But what it did demonstrate in the early versus delayed setting was that there were a number of patients that were unable to receive subsequent therapy.

In fact, when we look at other second-line therapies -- I showed you a couple of slides earlier looking at a broader scope of trials. This is a table that's highlighting second and further lines of therapy across different maintenance trials. And so this was the pemetrexed study,

which was 67 percent of patients received subsequent therapy; the gefitinib study, that Dr. Bunn referred to; and then the SATURN trial.

I wanted to draw your attention to the docetaxel study again because this was a patient population that protocol mandated the patients on the placebo arm were to go onto subsequent docetaxel. And despite that study being designed that way, only 63 percent of patients were ultimately able to get the delayed or second-line docetaxel, and I think this highlights the fact that patients with advanced non-small cell lung cancer tend to have rapid progression and may not be able to receive subsequent therapies.

Thank you for the opportunity.

DR. WILSON: Thank you. I just wanted to address a couple of those issues.

In terms of the last slide, I just think you have no evidence that, number one, patients who are not getting maintenance are going to have less of a chance to go on to second-line therapy. And number two, at the end of the day, what matters is

whether or not that translates into overall survival. And so I just think that we should not get diverted by that.

I also want to remark on the fact that the SPA that you discussed with FDA also isn't really relevant here. They discussed with you overall survival as being an important end point, and I think that what is at issue is whether or not the amount of benefit in the maintenance arm was large.

I think that we all agree that if the overall survival benefit was large, and in fact, you know, appeared to be much higher than the drugs used as second-line therapy, I think that we would be more impressed with that.

But I think the question here is that the overall benefit in terms of overall survival in this trial is relatively small, and so that therefore invokes whether or not this is really any different than giving it as second-line therapy.

Dr. Pazdur?

DR. PAZDUR: I just wanted to bring this

issue up about the SPA agreement or lack of agreement. And the review team is here, and I think it's important if they really address this issue.

From my knowledge, there were issues that were left unresolved. Obviously, we've quoted a sentence from that, that we really were looking for overall survival. And I know John and Marty are probably the best people to comment on that issue of was there an agreement with the sponsor on the SPA.

DR. COHEN: Well, to start off, there obviously was not an agreement in terms of the study end point. The FDA strongly recommended overall survival as the end point. The sponsor chose progression-free survival as the end point.

The SPA letter included 13 questions, 13 specific questions, regarding the study from the sponsor, and the FDA answered those 13 specific questions. But obviously, there were a lot of parts of the protocol that no questions were asked about and no FDA answers were given. And that included second-line therapy.

DR. JOHNSON: Could I just say with respect to the requirement for overall survival, the FDA sent them a letter in 2005, after our meeting, and I'll quote from the letter. I think it's unequivocal.

It says, "To demonstrate the value of maintenance-targeted therapy, superiority of survival will have to be demonstrated." And in quotes, "will have to be demonstrated." There's no question about what our stance was with respect to the primary end point.

DR. PAZDUR: In addition, I'd like to make a comment regarding the Alimta application. We internally had these same discussions regarding the appropriateness of design here. What drove the approval of Alimta was just as you had brought up, was the magnitude of benefit that we believed we saw in this application in the non-squamous cell group.

Here again, this application, if you remember, was being discussed, I believe, around the time of the ASCO meeting. There were pros and

cons of that entire discussion brought up, I think, in some of the presentations and the annual ASCO meeting. We brought those back, discussed them, and really thought that the magnitude of benefit of that benefit in that subgroup warranted approval. If we were seeing a similar magnitude of benefit here, I don't think that we would be bringing this application to this audience here.

DR. DAVIES: Mr. Chairman, may I comment?

DR. PAZDUR: I think, you know, one of the problems that we have here is -- and I don't want to stymie discussion. But the purpose of this meeting here is to get the feeling of, really, the committee members on this application. It is not to have a debate between the sponsor and the individual members, giving them conflicting opinions.

So here again, if you want to allow that to go ahead -- but here again, the purpose of this hour, or the remaining time, is really to focus on the question. And we want to hear from, really, the members of the committee regarding the

application at hand.

DR. WILSON: Rick, let me ask you, I think that as we go forward in time, we're going to be seeing more maintenance therapies.

DR. PAZDUR: And here again, I think this is one of the reasons that we brought this to the committee. Okay? We're not only going to be seeing it in lung cancer, we could be seeing it in lymphomas.

DR. WILSON: Right.

DR. PAZDUR: There are examples of lymphoma applications -- or not applications, but studies that have been done that could come to the committee in other diseases. And where do we want to go from here regarding that application, of these types of applications?

DR. WILSON: So let me just put forward, as we discuss this, that the whole question on a broader scale as to how to you design studies like this, I think slam-dunk overall survival benefits may be a little easier to handle. But you don't know going into any of these clinical trials. And

I think that at least in the world of lymphoma, a doctor named Hainsworth years ago, when he was looking at maintenance, did the very study that FDA has discussed here, which is they looked at maintenance Rituxan versus Rituxan at progression. And that was done many, many years ago. So let me just ask members to keep that clinical trial design in mind as we go forward.

Dr. Link?

DR. LINK: There are other examples where maintenance therapy works, even prolonged maintenance therapy. So, you know, we should keep that in mind.

I have two questions, one related definitely. So they demonstrated an overall survival advantage. It just wasn't the primary end point. So does that make a difference to you? In other words, does it have to be -- the study has to be designed around that as the primary end point or are you satisfied that it is an end point of the study, which is appropriately powered to demonstrate that end point but it's not the primary

end point.

Does that make a difference?

DR. JUSTICE: I think the question is really moot at this point in time. It doesn't make a difference. They have demonstrated an improvement in survival. We're not going to --

DR. LINK: Well, it seems to be a problem in terms of, you know, you said that we asked them that overall survival will be necessary to demonstrate. They've demonstrated it. It just wasn't, you know, number one on the list, is my interpretation.

So is that okay?

DR. JUSTICE: That's okay.

DR. LINK: Good. Okay. So that's not really my major question. So I need some help on -- I'm not a lung cancer expert, and so if you're -- and I don't know who is going to answer this.

But what's the expectation, having a trial published in a very high-priority journal, Lancet, I guess that was, and an FDA approval of a strategy or of a drug appropriate for, you know,

somebody who is -- I know you guys don't call it remission but, you know, like not progressive state after receiving what is the accepted induction treatment for lung cancer, what does one do with a patient?

Is it sort of the now-accepted practice that one offers this subsequent therapy with pemetrexed for patients with lung cancer who meet criteria? Is that sort of like you should at least offer it and say, there are benefits, there are risks, but, you know, overall it improves the outcome by X amount and it's sort of, you know, my obligation to suggest this to you as a strategy because it's in Lancet, after all.

So I don't know who -- I don't know.

DR. PAZDUR: That falls into the practice of medicine, basically, when you're talking about what you should do with an individual patient here. Whether or not something is published in Lancet, a throwaway journal, or whatever has no implications as far as the decision-making of this committee here. These are external issues. What you should

be looking at is basically the efficacy of this agent at the data that has been presented to you, both from the sponsor and from the FDA. Publications, et cetera, are irrelevant here at this point.

DR. LINK: Well, let me just -- so in other words, if one says that because it was five months of improvement and that's why that drug sort of stood out as being in that, you know, that it would be a worthwhile thing to do, let's say, and that's why you approved it.

One could say, well, you know, for some patients, the risk and benefit of getting that five months for whatever it is to get this drug -- the expense, the inconvenience, and the toxicity -- may not be worth as much. But somebody else may say, well, I'll take a three-month benefit, but it's less costly in terms of the side effects and in terms of the effect on my life. So, you know, that's a balancing act.

So in other words, we have to say so if it's worthwhile recommending something which

prolongs survival but, you know, there is a risk -- you know, we can say that there's a favorable risk/benefit; it's just not as favorable a benefit, but there's a lower risk, so let the patient determine that.

DR. PAZDUR: Well, here again, with reference to an individual patient decision, here again, that falls in the rubric of the practice of medicine. Okay? You know, we frequently have this discussion not only about this drug but other drugs.

You know, there are very, I would say, hard-fought battles to improve survival in particular diseases. And generally, we don't want to just say, well, we'll forego an improvement in overall survival because we'll probably have less toxicity or more convenience. Okay?

That's something that is a very, very slippery slope because once you go on that slope, why not just use half-dose chemotherapy? One-fourth dose chemotherapy? That probably would have less toxicity, but probably less efficacy.

So it's a very slippery slope. And generally, we like to take a look at the efficacy parameter, ask, really, has that been established? Are we willing to take a decrement on it, and then take a look at the toxicity issue? So it's a stepwise decision-making practice. And then lastly take a look at the convenience issue.

DR. WILSON: Yes. Dr. Fleming?

DR. FLEMING: Maybe I'll just try to jump in here with some global thoughts. The FDA, in stating the question, in essence, said there's some evidence of a modest survival effect. And that seems clear to me that that's a reasonable statement. The issue is, how compelling is the evidence? How persuasive and reliable is the evidence? Of what magnitude is the effect?

I guess I'll start by saying it's a single trial. Can we obtain definitive evidence from a single trial? Yes, we can, but there's a lot in the EMEA and FDA regulations about that. We hear words about "robust" and "compelling." What does that mean?

It means pristine, internally consistent, statistically strong, stronger than you would typically ask for from a single trial on end points that are of real importance to patients; direct measures of how a patient functions, feels, or survives. It's often used in orphan indications or in long-term settings or rare outcomes, where there's challenging feasibility. And support by related trials are important.

Looking at all of those issues gives me serious concern about this trial providing the level of evidence that would be judged as persuasive in a single trial. And there are a number of issues I'd like to quickly run through that are the basis of that judgment on my part. Some of them relate to how strong is the evidence for the effect. Some of these relate to issues of internal consistency. Some of these relate to issues of external support.

So in terms of how strong is the effect, we've had some discussion already. Okay. The primary end point was originally PFS. That's a

biomarker. But that can be used if there is a compelling magnitude of effect on such a biomarker.

It seems somewhat questionable to use it in this setting, in an immediate versus delay, where it's really ill-suited to capture what we really care about. And it's problematic, as I've argued before, to be designing a trial for a two-sided 05 where you would achieve it with so many events from only a 10- to 14-day increase.

Does it mean that that inherently means this trial isn't positive, but what it means is statistical significance on PFS isn't the proper threshold to use in judging whether the evidence is convincing for approval in this setting, and that I think this is clearly recognized in what the FDA has written.

Well, okay. What are the results? Are the results sufficiently persuasive? Well, starting with PFS, there are irregularities. There's 10 percent of people that have informative missingness. But in essence, there's a one-week median difference and a four-week difference if you

look at it in the global distribution from a relative risk perspective. That's really modest. I have no understanding of how you could say a single trial showing that effect on PFS is, in itself, substantive evidence of clinical benefit.

So we have other data. What do the survival data show? Well, the survival data show what the FDA stated it to show in my view, a 1- to 1.8-month difference. It's suggestive, but it's in my view not convincing in terms of both statistical and clinical benefit.

What are some of the issues? Alpha level is roughly 01 on a secondary end point alpha share. So the question is, does that mean you can't interpret -- no, you can interpret it. But you do have to make some accommodation in what is the level of strength of evidence that you attribute to an end point that in fact wasn't prespecified as the primary end point. But in a stratified analysis, it's a P value of .08.

How does this contrast to where we have established that Tarceva's effective in second-

line? It was a two-month difference relative risk of .73 P value less than 001. A magnitude effect, twice as large. Statistical strength of evidence an order of magnitude greater.

There are also other issues. The overall survival data was inappropriately blinded to the sponsor a year early. That's a non-trivial issue in terms of trial integrity.

There are other issues. There's a potential sub-optimal administration of rescue therapy at progression in the control. The strongest positive signal here in overall survival in PFS is in the Southeast Asia cohort. What was the nature of the availability of rescue therapy in that setting?

Because the key question here, as our chair and others have reminded us, is maintenance rather than waiting till delay, giving you an improvement. Sixty percent of patients were from Eastern Europe, from Asia, from Russia, China.

This is okay in some settings, but it's more problematic in a setting where you're looking

at an immediate versus a delay question. The FDA is specifically answering (unclear) the question, is this an intervention that has been established as more optimal in immediate versus delay in the U.S.? Do those results from elsewhere apply?

There are other trials. The TALENT and TRIBUTE trials were not positive. How do you interpret that? You might say it's not relevant. And yet these are other attempts to try to see whether delivering earlier than second-line provides improvement with Tarceva.

What about the internal consistency? What internal consistency across subgroups? I would agree with Dr. Bunn's overall guidance and interpretation about thinking about subgroup analyses. In the context of what Dr. Bunn is saying, I believe the data don't definitively establish effect modification. And yet, on the other hand, there remains substantial uncertainty about consistency across key subgroups. So while the data don't definitively establish interaction, they leave us with uncertainties that we need to be

better informed about about which are the right patients to be treated.

In the IHC-negatives, why were only 17 percent of the patients IHC-negative? The overall survival relative risk was .91. We saw the survival curves. There was evidence of minimal difference in second-line therapy. The medians were in the wrong direction. The relative risk was 1.

To address Dr. Bunn's point, this was highly prespecified. This subgroup wasn't data dredged. There was alpha spending on this. It's less clear about the EGFR mutations. It's an intriguing PFS result of .1. But the survival difference is there's no survival difference. There were only 49 patients.

The squamous cell, I understand from Dr. Bunn's point that the biological plausibility for interaction in squamous cell is at least not clear, and yet the overall survival relative risk is .86. There's an 11.3 versus 11.1 difference. There was no difference seen in this subgroup in

the pemetrexed setting.

So across these areas, I would agree with those that would say there's not definitive evidence that you are establishing different effects in squam/non-squam. But the data leave us with uncertainty. And the data certainly leave us with uncertainty, according to IHC, although they seem to be very consistent with the global evidence that the negatives wouldn't be benefitting.

This is a setting where there are other options. You know, there's erlotinib at second-line. Pemetrexed -- and we've had some discussion. The sponsor put up the pemetrexed results. But the FDA didn't approve pemetrexed overall. They approved pemetrexed in the subgroup that had a five-month difference and a P value less than 001.

Should they have? That's not our discussion. But it was certainly a level of evidence that exceeds what we're seeing here. And I guess, in essence, my sense is, does Tarceva have a role in maintenance as opposed to second-line? I'm not sure. But I don't think that's the basis

for an approval when you say, I'm not sure.

I would like to have more evidence. I think there's uncertainty, substantial uncertainty, about what the actual added benefit is in maintenance against second-line. We need additional evidence. And we've heard from the public that we need more choices.

But it reminds me what I was saying after serving on an ODAC in 2003 on lung cancer, and I was talking to the patient advocate after the meeting, saying, I agree patients want more choices. But that's really not the precise thing they want. They want more informed choices.

Don't we need more evidence in this setting to allow patients to make an informed choice about whether you truly get better benefit to risk in maintenance rather than using Tarceva in second-line?

DR. WILSON: Dr. Sekeres?

DR. SEKERES: Thank you, Dr. Wilson. I wanted to play off of something that you said earlier, and also from what Dr. Fleming was just

mentioning.

One issue that's come up a couple times is comparing the results of this study to two drugs that are on the market already. One, of course, is erlotinib in the second-line setting. So is this any better than waiting for patients to progress and giving them erlotinib then? The other is maintenance therapy with pemetrexed.

So a question I actually have for the FDA for clarification is, is an unmet medical need, which is something Dr. Wilson mentioned earlier, a consideration here? Or, I guess, refining that question is, should we be considering other available drugs on the market as part of our calculus for recommending that a drug be approved?

DR. PAZDUR: I think that's why we're asking this question, because this is the one we're grappling with in our own mind.

DR. SEKERES: I'm sorry. Can you repeat that last part again?

DR. PAZDUR: We're having the same discussion. That's why we phrased this question.

You know, you do have other drugs, other treatment options out there. That's one issue. The other issue is, really, is it a benefit to expose these people to this therapy -- and I think that's our major issue -- or simply to wait until they are at the time of progression here, and has that been shown?

DR. SEKERES: So I'm always careful in trying to paraphrase you. But in trying to paraphrase you, can I say that it's a definite maybe that we should be considering other drugs out there?

DR. PAZDUR: I think we do not have a comparative efficacy standard. However, one would not want to be giving up potential gains in survival. So, you know, one has to take a look at these issues and what is your comfort level in addressing that.

DR. SEKERES: Okay. Can I ask one other question also, just for clarification? And this is a question I'm going to actually direct to Dr. Bunn.

I'm still uncomfortable, a little bit, with otherwise EGFR is assessed in this country. So are people across the board doing IHC? Are they doing mutation status? And is an IHC positivity or mutation status positivity in one lab in the United States the same as it is in another lab?

DR. BUNN: So there are multiple commercial laboratories that do IHC testing, FISH testing, and mutation testing, and they're competing for the marketplace. So it's available in any place in the U.S. Any hospital can obtain mutation testing, FISH testing, or IHC testing results.

Now, I think from the perspective of a doctor, by far the most important of those is the mutation testing. And although the FDA hasn't improved any mutation test -- no one's asked them to; hopefully someone will soon -- but the ISLC and the CAP are developing guidelines, just like they have been available for HER2 testing and estrogen receptor testing.

There are different methodologies for

EGFR testing. They've been compared, and there are differences in the sensitivity of the test. Direct sequencing, Sanger sequencing, is not as sensitive as PCR-based amplification methods. But outcome in every trial that's been looked at has been the same in mutation patients, mutation-positive patients, irrespective of the type of testing.

So I believe that EGFR mutation testing is readily available anyplace in the U.S., and as a physician, would recommend that every patient have mutation testing done in order to select the most appropriate treatment.

Does that answer your question?

DR. SEKERES: So if mutation testing is that important, why was it performed in such a paucity of patients on this study?

DR. BUNN: The sponsor can answer that. But from my perspective, when this study was designed, the feeling was that immunohistochemistry was going to be the best test. Fortunately, since that time, we have a number of other randomized trials. We have IPASS. We have First-SIGNAL. We

have a number of other randomized trials that have shown mutation testing is a superior biomarker to mutation testing.

That was certainly not known at the time this study was designed. I think, at the time, the appropriate feeling was that immunohistochemistry first, FISH second, KRAS next, EGFR mutation testing next, I think that was the general consensus at the time. Since this trial was designed in 2005, there have been a lot of papers on this.

So this is a very important paper for biomarkers because this is the largest trial where the most biomarkers were done, and it is one of those things that helped us believe that mutation testing is the most important thing. But that's evolved a lot since this trial was designed.

DR. SEKERES: So if it's evolved since it was designed, why wasn't the trial amended to include it? I mean, that's often what happens in studies when technology comes online that trumps previously technology, is the study is amended for

sample collection to account for that.

Why wasn't that done?

DR. BUNN: I don't think I'm an appropriate person to answer that question. Do you want the company to answer that question?

DR. SEKERES: Somebody up there, yes.

DR. BUNN: But I would just make a comment. Adjuvant treatment has a hazard ratio of .82. We do it in everybody. It's pretty toxic, and most of the people don't benefit. And yet we do it. Okay? And my point about the magnitude wasn't the median. And I think, Tom, you said the clinician sometimes trumped the statisticians. You know, it's the end of the survival curve. What did you hear about from these people?

It's the four-year point. Okay? I believe that a lot of patients don't benefit from this, and that's why the medians are so close. These curves overlap. It's the separation later. When you show those curves to a patient, tell me a patient that doesn't want to be on the top curve without symptoms. Tell me. Okay?

I have patients, after stable disease, they're symptomatic. I agree quality of life does not prove it in this trial. Okay? But, you know, I think you are missing, okay, many of the points. The magnitude of benefit in this trial for a subset of patients is way more than it is for pemetrexed.

Now, I use pemetrexed. I use this drug. Okay? And there are patients who do better on pemetrexed, and ones that do better on this. We don't know perfectly how to choose them, but we're getting there. And not having this available, especially for mutated patients, is going to be a sad day in our history.

DR. WILSON: Okay. Let me just kind of just make one comment. I think adjuvant therapy is entirely different from what we're dealing with here. I don't think it's an analogy. Adjuvant therapy, by definition, needs to be given early because the intent is to cure. That's not the intent here. So I don't think that adjuvant therapy -- I think our relative threshold for adjuvant therapy is going to be very different.

And also to remark on something that Michael Link said, which is that maintenance therapy has been around a long time. And it's the same thing. It's a maintenance therapy in ALL that has led to increased cure. Those are two very different situations than what we're dealing with here. And I just think we need to be clear about that.

So you can just very quickly tell us why you didn't amend your study for EGF mutation.

DR. KLUGHAMMER: Barbara Klughammer, biomarker expert from Roche in Basel, Switzerland.

So as it was alluded already, the first patient was included in 2006. And since we had to stratify patients according to their IHC status, sample testing needed to start immediately.

So by the time the results around EGFR mutation became very well-known, we had already tested most samples already. So at that point in time, most samples were tested already so it was not possible to change the sequence of testing. Otherwise, we would have lost a lot of power. But

just to mention, we have a study ongoing, testing specifically patients who carry an EGFR mutation with Tarceva versus standard chemotherapy.

DR. WILSON: Okay. Thank you.

Dr. Kelly?

DR. KELLY: Yes. You know, just trying to put all this data together from your previous trials and this trial, the biology of disease really drives it. This is a very selective agent that targets direct biology.

I guess the question I have is that can there be differences in biology of disease treating patients earlier versus later in what actually drives the progression of that disease, and is this trial really showing that?

So really, should we be focusing on the biology of disease and treating the biology based on the disease rather than the whole population? And I guess the question -- Dr. Bunn, you might be the best one to answer this -- is do we know data that, actually, as the disease progresses from first diagnosis, first-line, second-line, third-

line, is the EGFR expression, receptor expression, increase over time? And what we're really seeing here is we're trying to divide the populations based on the natural history and biology of the disease.

DR. BUNN: There have been very few patients who have had serial biopsies. And so it would be misleading for me to indicate over time, with serial biopsies, what happens to EGFR expression. Certainly, in the presence of an EGFR TKI, patients do develop secondary mutations, and that's often a cause for patients to progress.

Although adjuvant treatment, you know, is different, the goal in stage IV disease is to make people live longer and better. And we don't have a lot of things that make people better, live longer and make them better, but this is one.

DR. KELLY: Just one final question for you, Dr. Bunn. I mean, you deal with this day in and day out, and you have a drug with pemetrexed that seems to have a much better survival than erlotinib in certain populations here.

How do you actually balance that for patient care, and how would you actually approach that?

DR. BUNN: So I'll give you two answers to that. First of all, there are patients who have an outstanding response to their induction treatment and have had side effects. You heard commentary about some of them. And if they're asymptomatic, frequently not giving any maintenance is not a bad idea, and that happens.

The patient I saw last week, who I'll see again tomorrow, was a patient who, by an outside physician, had been started on pemetrexed and carboplatin as their initial treatment. And she presented with a large pleural effusion. She was a never smoker, and I suggested she have EGFR testing, which she did. And after three weeks, when she was evaluated, she was stable. And stable meant she had a large pleural effusion and was symptomatic.

The ability to give her Tarceva was a huge advance. Giving her three more cycles of

pemetrexed was not going to be a good thing. Now, that's not to say that there aren't other patients who are stable, who have adenocarcinoma, and sometimes it's most appropriate to offer them maintenance pemetrexed.

So no maintenance for some patients is reasonable. Pemetrexed for some patients is reasonable. And erlotinib for some patients is reasonable. I personally don't know the difference in magnitude between pemetrexed benefit and erlotinib benefit in any setting. And I don't know how people are arguing for that.

A hazard ratio of .8 and a hazard ratio of .79 are not different, in my opinion, and a P value with the survival curve is the same. Patients would rather be on the good curve.

I hope I answered your question. Did I?

DR. WILSON: Dr. Fleming?

DR. FLEMING: Let me just real quickly just kind of follow up and provide a little clarification to some of the things that we were just talking about.

I very much concur with Dr. Bunn that the tail of the distribution really matters, and all of the comments that I was giving are based on relative risks, not on medians. Medians can be informative, but the relative risk is looking at the entire distribution.

So we're talking about a relative risk of .81 to .85, and just briefly to say it depends on the setting. In the adjuvant setting, maybe that is enough. If I have five years to live, that's another year. If I have five weeks to live, that's another half a week to a week.

So when your median survival -- when your true survival is very short, it's reasonable to expect a more substantial effect on the relative risk to be clinically relevant.

Just while I have the mic, just to make sure that what I'm saying is clear, I'm not talking about statisticians trumping clinicians or vice versa. That's not what we're talking about. This is a scientific issue, where we need input from everyone.

The key point is, it's not all about statistical P values. It's about whether we have statistically persuasive evidence of clinically relevant effects. And we need aggregation of statistical and clinical insight to be able to make that judgment.

DR. WILSON: You know, I think that I'll say this again. This study did not have a formal crossover for the placebo arm. So any superiority of the Tarceva maintenance may well have been offset if the patients on the placebo arm had all been crossed over. And even though they weren't all crossed over -- in fact, many of them weren't -- the effect is still very small. And everyone assumes that maintenance, even if the benefit is small, is going to be better than at relapse. And I don't think we know that.

This drug is not acting in the way we typically think of oncological drugs acting. When it was combined with chemotherapy up front, there was no benefit. When it's used in patients who have good responders, where we would think that

maintenance would be most useful, in people with minimal residual disease, it looks like its benefit is less.

So there's a lot about this drug we don't know. The clinical design of this trial did not cross people over, and the benefit we see here is very small. I am not at all convinced that if the proper study was done, we may even find out that at relapse, that the outcome may even be better. The bottom line is we don't know. But we have no evidence that maintenance is a better way of giving this drug.

Finally, I think we have to be very careful not to approve drugs based on anecdotes. There's no doubt that if you give this drug up front, there will be people who should get it, who will get it, who might not get it if it was left until progression. But there also may be many people who would be benefitted more by waiting. And that group we have no idea because this study doesn't even begin to look at it. And so, you know, I would just reiterate that approval needs to

be based on the hard numbers and not on the anecdotes.

Yes, Dr. Logan?

DR. LOGAN: I guess I would just reiterate some of the points that Dr. Fleming made. Given the context of the very modest improvement in overall survival that we're seeing here, as well as the fact that the interpretation of the placebo arm really depends on what happens to them at second line or at progression, and the uncertainty that we have there, as well as the fact that, you know, the blind was very rarely broken, I think that there's a lot of doubt about what the real impact is when comparing the maintenance therapy versus Tarceva as a second-line therapy or best care.

So I would just reiterate those concerns, given the context of modest effect that we're seeing.

DR. WILSON: Any final thoughts? Yes?

MS. MOFFITT: I'm still not sold on the fact of the efficacy for the EGFR IHC-negative and squamous cell. To me, it's weak and it's unproven.

We already have drugs out there that are not beneficial to squamous cell at all. This one I'm not saying is not beneficial at all, just that I don't think that it's proven that it's going to be beneficial. The efficacy just isn't there.

DR. WILSON: Yes, Steve?

DR. KRASNOW: I would just add in that regard that a lot of our patients in the population I see are African American. And I think there's some question about the efficacy of TKIs in African Americans. And we have no data from this trial on that group, and lung cancer is particularly prevalent -- its incidence is particularly high in the African American population. And I think it's an important group where we would need data, I think, in order to apply.

DR. WILSON: Okay. No more thoughts?

Well, then why don't we move on to the vote. Just to remind you all that on your speakerphone, there's a button that says "yes" or "no" or "abstain." And I would like you to press the button on your speaker mic that corresponds to

your vote.

I'm going to make it very clear which is "Yes" and "No" because we've had past meetings where some of us, including myself, have voted not the way they intended.

[Laughter.]

DR. WILSON: So the vote is, based on these results, should erlotinib be approved for the proposed indication? Yes means yes. No means no. So with that, let me have everybody vote.

[Vote taken.]

DR. WILSON: All right. I'd like to read the following: Yes, one; no, 12; abstain, zero.

Now I'd like to go around the room with the voting members, starting on my left. And if you could each state your vote, and if you would be so kind, tell us why. And also state your name, too. Dr. Krasnow is first.

DR. KRASNOW: Thank you. It was basically the primary problem, the fact that one couldn't tell if maintenance therapy was better than delayed therapy. I think it was simply that

issue. The study could have been designed to show that if a proper crossover for the placebo group had been built in, and it wasn't.

The second thing is that any benefit appears to be rather small benefit. And although it's not necessarily a consideration, it would come at very great cost. And so I think that one needs to show that there's clearly a benefit, at least.

As I mentioned, I was concerned about the patient populations that we see compared to the populations that were studied. That's not necessarily within the investigator's control, but it's relevant to our practices. And I think those are my major concerns.

DR. WILSON: Okay. Thank you.

Ms. Moffitt?

MS. MOFFITT: Pam Moffitt. In the back of my mind, the whole thing is that the proposed indication as the way it is worded is it should be -- in my mind, it is going to be a limited approval, if any, because it does not apply to all cases of non-small cell lung cancer. And what has

been proven, as Dr. Krasnow said, is it's marginal. It's not the robust findings we'd like to find in a study like this.

DR. WILSON: Ms. Mason?

MS. MASON: Yes. I voted in opposition as well. I'd like to see if more study brings out the subgroup population that's going to benefit the most because it appears that might happen. But at this point in time, I was not impressed enough with the very modest benefit to warrant expanded exposure to the medication.

DR. WILSON: Thank you.

Dr. Lyman?

DR. LYMAN: Yes. Gary Lyman. I voted no, primarily because of the study design limitations. And I think the subgroup analysis, where we get a little sense of what that proper study might have shown in the EGFR mutation subgroup, because there was a lot of crossover in the placebo arm, I think may be illustrative of what might have been seen with the proper study design, that is, essentially little or no benefit

to early versus delayed intervention.

DR. WILSON: Thank you.

Dr. Richardson?

DR. RICHARDSON: Ron Richardson. I voted no. We were presented with a single study, not two studies, not a small, well-designed study plus, say, a larger study as some supporting evidence, but a single study that has some design flaws showing some very modest or even minimal benefit. I don't think the sponsor answered the question on the value of this drug as maintenance therapy versus treatment at relapse.

My other concern is that I think this committee needs to be very careful about setting precedents, and particularly approval of drugs looking at single studies where the design is in issue and benefits are marginal. This is going to be coming back to this committee over and over again, and I think we need to be very careful about maintaining the integrity of the data that we look at.

DR. WILSON: Thank you.

Dr. Kelly?

DR. KELLY: William Kelly. I also voted no, for the reasons previously stated here, but basically for the marginal improvement, trial designs. But also, you know, this was a non-focused trial. I think that we really should focus the trials based on the biology in treating. We're in an era of targeted therapy now. That means targeted patients, too. And I think that the take-home point here is that we really need to focus on populations, appropriate populations, to study.

DR. WILSON: Wyndham Wilson. I voted no. I think that this is a good example of the kinds of issues that we may face in future studies of maintenance therapy. I think, when you have an active drug that is effective as second-line therapy, we have to be very careful in terms of interpreting progression-free survival as the relevant end point.

I think the relevant end point is, are you improving overall survival? Are you improving quality of life? And is that, you know, better

than giving the drug at the time of relapse? And I guess my feeling is that if I was faced with another clinical trial, I would certainly hold those principles up, at least for myself. But that's why I voted no for this.

Dr. Tempero?

I'm sorry. Dr. Sekeres?

DR. SEKERES: Hi. Mikkael Sekeres. I voted no, for a couple of reasons. The first, as has already been enunciated, the survival advantage here was statistically significant. But I didn't believe it was clinically significant.

This is particularly in the setting of having two drugs on the market which these patients could potentially receive, and that is pemetrexed, for the same indication, and erlotinib, for patients who have progressed. Once a drug has been approved for an indication, I think the bar has been raised for "me, too" drugs. And I think this is a good example of that.

The second reason is, once again, I don't think that the patient-reported outcomes were

rigorous. They weren't rigorously evaluated, and they didn't show any quality of life advantage to the drug.

DR. WILSON: Thank you.

Dr. Tempero?

DR. TEMPERO: Margaret Tempero. I'm the sole person who voted in favor of this application. Although maybe this trial wasn't the one that the committee members wanted to see, it was a trial that asked a reasonable question. It was done in full consultation with the FDA. And it met the end point that the sponsors expected to meet, and which the FDA asked for.

So the overall survival benefit was met. You know, group benefit matters only to the group. It doesn't matter to the individual. And when you do see a group benefit, even when it's small, it means that some individuals had important benefit.

We don't quite know from the biomarker studies done in this trial which those individuals were, and I think that troubles us all. And we wish that was different, I think. But I know that

clinicians are not robots. Clinicians take a careful assessment of the patient in front of them, including their smoking status and whatever molecular data is available them, and they try to make a wise choice for the patient.

So I had hoped that we could make sure that erlotinib was available to more patients at an earlier stage when it seemed to be clinically important for that patient. Thank you.

DR. WILSON: Thank you.

Dr. Link?

DR. LINK: Michael Link. It should have been obvious that I had some difficulties making a decision here. You know, the degree of benefit here, as others pointed out, is discouragingly small, but not very different from other products that have been approved. So that's one of the reasons I had difficulty because, you know, how do you draw the line there?

I thought the risks here to the patients were relatively minor, also compared to the other options available to patients, which are associated

with more toxicities. We can talk about greater inconvenience; perhaps that not a high issue.

But having said all that, as indicated by others, I am convinced that this particular study did not pass the bar that would be appropriate for giving indication. I think the drug is available, and will probably be used by clinicians anyway, even though it's not approved here. And I suspect, unfortunately, we never really got to the question which perhaps we were asked to address, which I think we'll be wrestling with, what degree of survival benefit actually constitutes a survival benefit, which is what you consider. I mean, is it five months? Is it three and a half months? I don't know. But I suspect, unless we sort of have that discussion, that we will continue to have those discussions at these meetings.

DR. WILSON: Thank you.

Dr. Freedman?

DR. FREEDMAN: Ralph Freedman. I had some difficulty, as others have, in coming to a decision. But in the end, I decided against, and

my main concerns were the doubts that were raised about the design and interpretation of the results.

We want to have to biomarker that can help us identify a population that could benefit. And basically, I think we could certainly compliment the sponsors for attempting to do this. But probably they were caught with the evolution of understanding of biomarkers. And trying to fit all this into a clinical trial, basically they come out with more doubts and certainly an inability to identify any subset that could clearly benefit.

Considering also the fact that the quality control of the biomarkers is an issue, we have only one marker that's approved by the FDA. And certainly, if treatment decisions are made and assignment of treatments are made, we know that the assays should be done in CLIA laboratories, at least in this country. This study was done mostly overseas, so there was no oversight of that aspect, either.

So given all of these issues, I had difficulty in saying yes.

DR. WILSON: Thank you.

Dr. Logan?

DR. LOGAN: I voted no, for a number of reasons that have been articulated already. One concern, of course, is a single study, especially given the modest effect that we're seeing here. Second concern, also given the modest effect, is the interpretation of the placebo group in terms of the second-line therapy and crossover.

DR. WILSON: Thank you.

Dr. Fleming?

DR. FLEMING: Fleming. I voted no, for reasons that many have articulated and that I've already articulated.

So just to be brief, it's a single trial. In my view, it would need to provide statistically persuasive evidence of clinically relevant effects. And I believe it hasn't done so.

There's much that has already been indicated as to standards for single trials. It's not the norm. It is possible that an application could be approved on a single trial. It's possible

in those settings where the results of that single trial exceed the reliability that we would typically expect of one trial from two adequate and well-controlled trials.

Robust and compelling. Terms have been used about it being pristine, internally consistent, statistically compelling, evidence of effects on measures that are direct measures of how a patient functions, feels, and survives, or a reliable surrogate that establishes such effects. And it's especially important to stay the course on those standards in settings where wide numbers of patients are being impacted by the decisions about whether to approve, and this is certainly one of those settings.

My sense is in a setting like this, survival is much more relevant and informative than PFS. A huge PFS result or effect can provide important insight about clinical benefit. But in a setting like this, where it's an immediate versus delay, survival is very critical to capturing that overall sense. And it's also really critical when

the effects on PFS, as they are here, are so modest.

The survival effects are modest. Are they sufficient? That's always a very difficult judgment decision. A rule of thumb that I've used for decades, and it's only a rule of thumb, is if you have a short time to live, I need a one-third improvement. If I have six months to live, I need two months. If I have 12 months, maybe then I only need a 25 percent improvement or a 30 percent improvement. And if I have two years to live, a 25 percent improvement, six months.

But obviously, that depends on the toxicities, the tolerability of the intervention, its convenience, cost, et cetera. There's a lot that goes into that judgment.

My sense is here it is a modest effect that's the estimated effect. Is it sufficient? It's a difficult question for me to answer. Part of what concerns me are the irregularities that occurred in the design and the conduct.

So not all .81 relative risks are the

same. It depends on the context of the nature of its trial, how it was designed, how it was conducted. And there are these uncertainties about -- from the perspective of internal consistencies, uncertainties about which types of patients truly are those that have been benefitted.

So I couldn't agree more with the comment that we need to empower people to be able to make wise choices for patients. I couldn't agree more. But it comes down to having an evidence-based justification to allow people to make informed choices.

This study is not adequate. An additional study that could provide clarifications could, in fact, allow us to be able to say, yes, there is evidence. But based on the current evidence, it's not possible, in my view, to make an informed choice about whether patients would be better served starting at maintenance rather than at second line.

DR. WILSON: Okay. Thank you. I'd like to thank all the panel members. And the meeting is

now adjourned.

(Whereupon, at 2:20 p.m., the meeting was adjourned.)