upon.

DR. MARTINO: Thank you. Next I would like to invite the sponsor to present their data to the committee.

Sponsor Presentation:

Tarceva (erlotinib) Tablets Pancreatic Cancer

Introduction

DR. CAGNONI: Good afternoon.

[Slide]

Members of ODAC, FDA representatives and guests, my name is Pablo Cagnoni and I am head of medical affairs and transitional research at OSI Pharmaceuticals. I would like to start by thanking the Food and Drug Administration for giving us the opportunity to present to the Oncologic Drugs Advisory Committee the results of Tarceva in combination with gemcitabine in patients with pancreatic cancer. I would also like to thank the patients who participated in the study that will be presented today, without whom this could not have been possible.

[Slide]

The supplementary NDA for pancreatic cancer was submitted on April 29 of 2005, and is based on a 569 patient study, study NCIC-CPA.3, that showed a statistically significant improvement in survival with a combination of Tarceva and gemcitabine compared to placebo and gemcitabine.

The indication that we are seeking is for Tarceva in combination with gemcitabine for the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer. The recommended dosage for Tarceva in this indication is 100 mg once daily in combination with gemcitabine at the standard approved dose and schedule.

[Slide]

The agenda for our presentation is shown here. After a short introduction, Dr. Malcolm Moore, study chair for study NCIC-CAP.3, will provide some background on pancreatic cancer and he will review the design for study PA.3. Following Dr. Moore, Dr. Gary Clark will summarize the efficacy data from the study, and Dr. Karsten Witt

will then summarize the safety data. Dr. Mace Rothenberg will then give some closing remarks on the risk and benefit assessment of Tarceva in this indication.

[Slide]

A distinguished team of external advisors will be available for the question and answer session. Dr. Randolph Hecht was the lead investigator of study PA.3 in the U.S. Dr. Malcolm Moore was the study chair. Dr. Wendy Parulekar, from the National Cancer Institute of Canada Clinical Trials Group, was the physician coordinator for study PA.3 and Dr. Mace Rothenberg, a well-known expert on the treatment of this disease.

[Slide]

In addition to our external advisors, we have a team of experts from OSI that will be available for the question and answer session. Their names are listed here, grouped by area of expertise.

[Slide]

Tarceva is an orally available, small-molecule inhibitor of HER1/EGFR tyrosine kinase. It is a potent and selective EGFR-TK inhibitor with an IC50 of 2 nM. Tarceva is the first clinical development candidate from an OSI/Pfizer research collaboration in cancer, and its clinical development has been conducted by OSI in collaboration with Genentech and Roche since January, 2001.

[Slide]

The original NDA for Tarceva received full approval by the Food and Drug Administration on November 18 of 2004. The approved indication is as monotherapy for the treatment of non-small cell lung cancer after failure of at least one prior chemotherapy. This approval was based on a 731-patient study, study NCIC-BR.21, that showed a statistically significant improvement in overall survival with Tarceva versus best supportive care. Since approval of Tarceva more than 18,000 patients have been treated with this agent, and over 100 clinical trials are currently ongoing in almost

every type of solid tumor.

[Slide]

This slide summarizes some key results from study BR.21 in patients with non-small cell lung cancer. This slide shows the overall survival curves for study BR.21. In yellow we can see the survival curve for patients treated with Tarceva and in white the curve for patients in the placebo arm. The curves separate after the first 3-4 months and they remain apart for the duration of the follow-up period. The study showed a statistical significant hazard ratio for death of 0.73 in patients treated with Tarceva.

[Slide]

The rationale for targeting the EGFR pathway in patients with pancreatic cancer is summarized here. Over-expression of this receptor is common in pancreatic tumors and elevated EGFR and EGF levels are associated with more aggressive disease and poor prognosis. In preclinical models EGFR inhibitors enhance gemcitabine-induced tumor apoptosis.

[Slide]

The objectives for the remainder of the presentation are summarized here. Dr. Moore will review the data supporting the need for new treatment options for patients with pancreatic cancer. We will provide evidence that Tarceva, when added to the current standard of care, gemcitabine, provides the first statistically significant and clinically meaningful increase in survival compared with gemcitabine alone and this is achieved without any detrimental effect on the patient's global quality of life. We will demonstrate that the combination of Tarceva and gemcitabine offers an effective and tolerable new therapy for the management of pancreatic cancer.

[Slide]

I would now like to introduce our next presenter, Dr. Malcolm Moore. Dr. Moore is professor of medicine and pharmacology at the University of Toronto, and chair of the GI committee of the National Cancer Institute of Canada Clinical Trials Group. Dr. Moore was

instrumental in the design of study PA.3 and chaired the study. Dr. Moore?

Background of Pancreatic Cancer and NCIC PA.3 Study Design

DR. MOORE: Thank you, Pablo, and good afternoon.

[Slide]

In my presentation I will provide a brief overview of pancreatic cancer, then describe the design and conduct of NCIC CTG study PA.3. In the United States and Canada there are approximately 35,000 cases of pancreatic cancer diagnosed each year. Almost all of these patients will die from their disease. Pancreatic cancer is an important health problem. It is the fourth leading cause of cancer-related deaths. Most patients have advanced disease at diagnosis and 25 percent of these patients will live less than 3 months.

[Slide]

The 5-year survival for pancreatic cancer is less than 4 percent, the worst prognosis of all solid tumors. These patients also have a multitude

of associated problems, including pain, malnutrition and thromboembolic disease, and they generally tolerate therapies poorly.

[Slide]

The only FDA approved drug for the treatment of pancreatic cancer is gemcitabine. This was approved 10 years ago on the basis of a randomized study published in the journal of Clinical Oncology. This 126-patient study compared gemcitabine to intravenous 5-FU, which at the time was considered the standard of care.

The study was somewhat unique in that the primary endpoint was clinical benefit response, an algorithm designed specifically for that study that combined pain intensity, analgesic usage and performance status. To be classified as a clinical benefit responder, patients had to have improvement in at least 1 of 3 three categories without deterioration in any other.

As you can see from data, 24 percent of gemcitabine-treated patients versus 5 percent of 5-FU had a clinical benefit response. Survival was

a secondary endpoint. The median survival on gemcitabine was 5.7 months and the 1-year survival was 18 percent as compared to 4.4 months and 2 percent with 5-FU.

Another important point from this study is that responses in pancreatic cancer are uncommon. the partial response rate was 5.4 percent. If you combine partial response and stable disease, you will see that about 45 percent of patients treated with gemcitabine had disease control as opposed to only 19 percent on 5-FU. So, the survival benefit of gemcitabine came from the ability to control disease as opposed to producing a tumor response.

[Slide]

In summary, patients with pancreatic cancer have a very poor prognosis and we have limited treatment options. Gemcitabine is the only FDA-approved treatment and is currently recognized as the standard of care. Over the last 10 years there have been major efforts to improve outcome in this disease. However, until PA.3 was reported no study had demonstrated an improvement in survival

over what could be achieved with gemcitabine alone so pancreatic cancer remains an important and serious health problem with an unmet medical need.

[Slide]

NCIC study PA.3 was a randomized, placebo-controlled trial of gemcitabine with or without Tarceva in patients with locally advanced or metastatic pancreatic cancer.

[Slide]

Study PA.3 was an international study, led by the National Cancer Institute of Canada Clinical Trials Group and I was the principal investigator. The study was co-sponsored by OSI Pharmaceuticals. Both the patient and physician were blinded to treatment assignment to minimize bias in the evaluation of both efficacy and safety endpoints.

[Slide]

As the study was a cooperative venture of both NCIC and OSI, I would like to briefly outline the roles of both organizations. NCIC CTG served as the overall study coordinating center. We developed the protocol, all protocol amendments and

the case report forms. NCIC provided medical monitoring for the study as well as study site monitoring in Canada. Oversight of the study was done by our independent data safety monitoring committee. We maintained the clinical database which was blinded to treatment assignment until the final analysis, and NCIC conducted an independent analysis of the data once the database was locked and unblinded. The presentation of this data at ASCO 2005 was based on the NCIC analysis.

[Slide]

OSI Pharmaceuticals provided the study drug as well as financial support for the study. OSI recruited and managed the CROs who monitored study sites outside of Canada. OSI had no access to the database prior to database lock and unblinding. OSI has performed the statistical analyses for regulatory filing.

[Slide]

Summarized in this slide are the key eligibility criteria for the study. These are typical for a study in advanced pancreatic cancer,

including both locally advanced and metastatic disease. No prior chemotherapy for metastatic disease was allowed. Of note, EGFR status was not a baseline eligibility criterion.

[Slide]

The study schema is shown on this slide. Patients were stratified by study center and by the 2 known prognostic factors in advanced disease, namely, performance status and stage of disease. Patients were randomized in a 1:1 ratio to receive gemcitabine plus Tarceva or gemcitabine plus placebo. The gemcitabine dose and schedule in both arms was identical to the regimen used by Burris and colleagues in a registration study of gemcitabine versus 5-FU.

[Slide]

The primary endpoint of study PA.3 was overall survival. The key secondary endpoints that will also be described in our presentation today are listed below.

[Slide]

The survival benefit was estimated by the

hazard ratio for death for patients receiving Tarceva plus gemcitabine versus placebo plus gemcitabine. The hazard ratio is a global assessment of survival benefit that does not focus on any individual time point on the survival curve. It was selected by the NCIC as the most robust and meaningful measure of efficacy.

The sample size was based on 80 percent power to detect a hazard ratio of 0.075, which corresponds with 33 percent improvement in survival with a 5 percent level of significance. Based on these criteria, a minimum number of 381 deaths were required for an event-driven analysis.

In the initial part of the study the plan was to randomized 800 patients over a 9-month accrual period and then follow them for a minimum of 2.8 months. This would allow for analysis shortly after study closure. Approximately 11 months after the study was open, the sample size was reduced to 450. This decision was made solely for resource reasons and was agreed to by both NCIC and OSI. The scientific integrity of the trial was

preserved by lengthening the minimum follow-up period to 18 months. With this longer follow-up, the required number of events, 381, would still occur and the power of the study was not altered.

When PA.3 was being designed a Phase 1 study of Tarceva plus gemcitabine was ongoing. It was assumed that the Tarceva and gemcitabine doses would be defined by study onset. However, in November, 2001 when the study was ready to open the MTD of this combination had not been clearly defined. After a review of the available Phase 1 data the trial committee elected to open the study at a Tarceva dose of 100 mg per day with full dose gemcitabine, with a plan for interim blinded safety analysis. Three such safety analyses were conducted after 8, 16 and 50 patients were entered and no safety concerns were identified.

After the third safety analysis with 50 patients, we elected to continue accrual worldwide at 100 mg and to enter patients at a dose of 150 mg in selected Canadian centers, with a planned safety analysis of this higher dose cohort after 16

patients were entered.

After accrual and evaluation of 16 patients at 150 mg per day, over 85 percent of the total accrual goal to the study had been achieved. Therefore, the trial committee elected to continue accrual worldwide at 100 mg to the planned sample size of 450, and not to open accrual at 150 mg per day outside of Canada.

[Slide]

This final slide outlines the key time points in study conduct and analysis. The first patient was randomized to PA.3 on November 29, 2001. The final patient was entered on January 31, 2003. At this time there were 521 patients randomized at 100 mg and 48 patients at 150 mg. On January 13, 2004, approximately one year after the last patient was randomized, the 381st death in the 100 mg cohort was documented and logged into the NCIC CTG database. Consequently, January 15 was declared the field cut-off date and final data cleaning was initiated. That final data sweep did identify additional deaths that had occurred prior

to January 15, 2004. In total, 44 deaths in the 100 mg cohort occurred prior to January 15, 2004.

The database was locked and unblinded on September 17, 2004, and an analysis was conducted by NCIC. The database was subsequently transferred to OSI Pharmaceuticals for final statistic analysis for the regulatory submission.

[Slide]

I would now like to introduce Dr. Gary Clark, head of biostatistics and data management at OSI Pharmaceuticals, who will review the efficacy results for study PA.3.

Clinical Efficacy Data

DR. CLARK: Thank you, Malcolm. Members of ODAC, FDA representatives and guests, for the next few minutes I will review the clinical efficacy data from study PA.3. As Dr. Moore just described, the NCIC designed the clinical protocol of the study and conducted the clinical trial. In addition, the NCIC statistical center developed the statistical analysis plan.

[Slide]

OSI Pharmaceuticals submitted this plan to the FDA before database lock and unblinding. Agreement was reached on the primary analysis of a stratified log-rank test for overall survival. The protocol specified that the performance status, extent of disease and the pain intensity score at baseline would be the stratification factors. At the request of the FDA, the pain intensity score was dropped and the 2 stratification factors used in the randomized process were retained. It was agreed that all randomized patients, that is, the intent-to-treat population, would be included in the primary analysis. No interim analyses were planned and none were performed.

[Slide]

Two hundred and eighty-five patients were randomized to the Tarceva/gemcitabine arm and 284 to the placebo/gemcitabine arm. This is the intent-to-treat population. The baseline characteristics were generally well balanced between treatment arms, with the exception of gender where the proportion of females was higher

in the Tarceva arm. However, as I will show in a few minutes, this did not appear to bias conclusions about treatment benefits.

[Slide]

Seven patients did not receive any protocol therapy, 3 in the Tarceva arm and 4 in the placebo arm. Two patients did not receive the assigned treatment, one in each arm. As previously stated, all randomized patients were included in the efficacy analyses. All safety analyses, however, were performed on the as-treated population.

After the data were unblinded and submitted to the FDA, an FDA review of the case report forms identified 18 patients who were declared to be ineligible based on the primary diagnosis, 10 in the Tarceva arm and 8 in the placebo arm; 9 patients did not have adenocarcinoma of the pancreas. For the remaining 9 patients confirmation of the diagnosis of the primary tumor was missing or insufficient. These patients were all included in the intent-to-treat analyses but a

sensitivity analysis was performed after excluding these patients.

[Slide]

The primary efficacy endpoint was overall survival in the intent-to-treat population.

[Slide]

The survival curve for the Tarceva patients is shown in yellow and the placebo patients are shown in white. Notice that the survival curves separate early and remain separated throughout the observation period. The hazard ratio for death, adjusted for the stratification factors of performance status and percent of disease at randomization, was 0.80, with a statistically significant p value of 0.018. These results are slightly different than those in your briefing document because 2 data entry errors in the database regarding survival information have been corrected for this analysis. These errors had been identified and were documented in our clinical study report but the database was only recently updated.

The assumption of proportional hazard was satisfied so the hazard ratio can be thought of as the average ratio of risk of death throughout the entire observation period. A hazard ratio of 0.08 implies a 20 percent reduction in the risk of death for patients on the Tarceva arm compared to patients on the placebo arm. This can also be interpreted as a 25 percent increase in survival by taking the reciprocal of the hazard ratio.

[Slide]

Although the primary endpoint was overall survival as measured by the hazard ratio, particular points along the survival curves are also often examined. For example, the median survival for the Tarceva arm was 6.24 months compared to 5.91 months for the placebo arm. Notice, however, that the 2 survival curves come together precisely at the estimated medians, an indication of the instability and perhaps inappropriateness of the median as a measure of overall treatment benefit in this study. The overall 25 percent survival benefit based on the

hazard ratio translates to approximately a 5-week improvement in medians rather than the 2 weeks as suggested by these point estimates.

Another point estimate commonly used is the estimated 1-year survival rate, 23 percent for the Tarceva arm compared to 17 percent for the placebo arm, an absolute increase of 6 percent but a relative improvement of 35 percent.

Because the median and the 1-year survival rate reflect treatment benefit at arbitrary points in time, I will focus most of my attention in the rest of this presentation on the global assessment of the treatment benefit as reflected by hazard ratios.

[Slide]

We performed a series of robustness analyses of survival to minimize the risk that the observed results were simply due to a particular statistical methodology. As shown in previous slides, the primary stratified log-rank analysis included 485 deaths and produced a statistically significant hazard ratio of 0.80. To address the

concern about imbalance in gender between the treatment arms a Cox model was created that included the stratification factors plus gender. The hazard ratio is unchanged, indicating that this imbalance had no impact on the estimate of the survival benefit from Tarceva.

An additional multivariate model was created that included not only the stratification factors and gender but also other potential prognostic factors. The results remain statistically significant.

Approximately one-third of the patients received subsequent anti-cancer therapy after disease progression. To minimize the effect of this subsequent therapy on overall survival we censored the survival times of those patients on the date of initiation of the first anti-cancer therapy. As a result, the number of deaths in this analysis was reduced to 341, which slightly increased the resulting p value but notice that the hazard ratio was unchanged.

At the request of the FDA, we also

performed an analysis in which we censored the survival of patients beyond the date of the 381st death. That is the minimum number for an event-driven analysis. Since the number of events was reduced, the p value increased but, again, the hazard ratio was essentially unchanged.

After the supplemental NDA was submitted the FDA requested that we update the follow-up of all patients who were still alive at the time of database lock. This follow-up sweep identified a total of 551 deaths as of June of this year. An updated stratified log-rank test produced a hazard ratio of 0.81 with a p value of 0.016.

Since the suggested dose in our proposed indication is 100 mg of Tarceva daily, I will present results only from the 100 mg cohort for the rest of this presentation. There are simply too few patients in the 150 mg cohort to support firm conclusions about either efficacy or safety.

[Slide]

Here are the survival curves from the 100 mg cohort. Because most of the patients received

100 mg of Tarceva or placebo, the results in this cohort are nearly identical to those from the overall population. The hazard ratio remains essentially unchanged at 0.81, with a highly statistically significant p value of 0.028, indicating a 23 percent improvement in overall survival. The median survivals and one-year survival rates are essentially unchanged from those in the ITT population.

[Slide]

Here are the results of the robustness analyses focusing on the 100 mg cohort. The primary stratified log-rank analysis included 444 deaths and produced a statistically significant hazard ratio of 0.81. The hazard ratio from a Cox model that included the stratification factors plus gender was unchanged, again confirming that the gender imbalance had no impact on the estimate of the survival benefit for Tarceva. Results from a multivariate Cox model that included other potential prognostic factors remained statistically significant.

After censoring survival of patients who received subsequent anti-cancer therapy the number of deaths was reduced to 313, which slightly increased the resulting p value but, again, the hazard ratio was unchanged. The hazard ratio after censoring patients after the 381st death was also unchanged but the p value increased to 0.59.

After the follow-up sweep in June, 2005, 504 deaths were documented in the 100 mg cohort. An updated stratified log-rank test produced a hazard ratio of 0.82 with a p value of 0.028. With only 17 patients censored in this analysis, these results provide the most accurate estimate of the survival benefit from Tarceva in this 100 mg cohort.

[Slide]

We also performed some sensitivity analyses to determine if patients who did not receive the assigned treatment or patients who might have been ineligible for the protocol could have affected the observed treatment benefit. So, here are the results for the 100 mg cohort, first

at the time of database lock and then after the updated survival. As you can see, the hazard ratios are unaffected by this post hoc exclusion of patients and the p values remain statistically significant.

[Slide]

Based on these robustness and sensitivity analyses, we conclude that the survival benefit for Tarceva does not depend on the statistical analytical approach used. It remains statistically significant in a variety of multivariate analyses. It cannot be explained by benefit from subsequent anti-cancer therapy. It persists with additional follow-up and it persists when ineligible patients are excluded from the analysis. In summary, this study met its primary endpoint of demonstrating that the hazard ratio is statistically significantly different than 1.0.

[Slide]

Now let's consider the secondary endpoints. The progression-free survival curves for the 100 mg cohort demonstrated a hazard ratio

of 0.77 which was highly statistically significant. This translates into a 30 percent improvement in progression-free survival. Here are the median progression-free survivals. It is readily apparent how inappropriate these statistics are for summarizing the treatment effect in this study. The 6-month progression-free survival rates are 33 percent for the Tarceva-treated patients and 25 percent for the placebo-treated patients.

[Slide]

Tumor response for patients with measurable disease at baseline are summarized in this slide. The response rates are quite similar between the 2 treatment arms. However, the rate of stable disease is somewhat higher for patients in the Tarceva arm. When complete response, partial response and stable disease are combined and considered disease control there is a 9.6 percent difference between the treatment arms, which was statistically significant with a p value of 0.036. The median durations of response were nearly identical in the 2 treatment arms.

[Slide]

Now let's consider EGFR status by immunohistochemistry. Submission of tumor samples for EGFR testing was voluntary and required a separate informed consent. It should be noted that patient consent does not guarantee an adequate tumor sample, especially if the diagnosis is based on fine-needle aspirates. Tumor samples with interpretable assay results by immunohistochemistry were available for 25 percent of the patients.

[Slide]

Shown here are the survival curves by EGFR status. Patients with EGFR positive tumors are on the left and patients with EGFR negative tumors are on the right. The hazard ratios of 0.78 and 0.71 suggest a possible benefit for Tarceva/gemcitabine over placebo/gemcitabine regardless of the EGFR status, although neither result was statistically significant. More importantly, the statistical interaction between treatment and EGFR status was strongly non-significant. Based on these results, we conclude that the survival benefit from adding

Tarceva to gemcitabine does not appear to be related to EGFR status as determined by immunohistochemistry.

[Slide]

Now let's consider quality of life. The objective was to evaluate the impact of adding Tarceva to gemcitabine on the patient's self-reported quality of life. All analyses are exploratory and the results should be considered hypothesis-generating.

[Slide]

The NCIC used the EORTC QLQ-C30 validated questionnaire. This questionnaire produces a global quality of life assessment, 5 functional domain scales, 3 symptom domain scales and 6 single item scales. We performed a series of analyses on each of the various QLQ scales to compare the two treatment arms.

[Slide]

The only scale for which a statistically significant difference could be found was the single item diarrhea scale. More patients on the

Tarceva arm reported diarrhea compared to patients on the placebo/gemcitabine arm. This is to be expected since diarrhea is a known side effect of EGFR tyrosine kinase inhibitors. Response from QoL response analyses for the intent-to-treat population are in your briefing document. The results for the 100 mg cohort are very similar.

[Slide]

Another approach is to compare the mean change from baseline of each of the QoL scales over time. Shown here are the results of the diarrhea single item scale. An increase from baseline represents more diarrhea. As you can see, patients in the Tarceva arm reported significantly more diarrhea, although, as Dr. Witt will show you, only 6 percent of Tarceva-treated patients experienced grade 3 or 4 diarrhea.

[Slide]

For the social functioning domain an increase from baseline represents an improvement in quality of life. Despite the potential negative effects of diarrhea and rash associated with

Tarceva, the social functioning domain was numerically better for patients on the Tarceva arm during the first 24 weeks of treatment.

[Slide]

Shown here are the results of the global quality of life scale. Both groups of patients indicated that their global quality of life improved over time. This is partially because patients who progressed went off study and could not be included in analyses at subsequent time points. But note that patients in the Tarceva arm indicated slightly more improvement in the first 24 weeks of treatment compared to the placebo arm, although the differences were not statistically significant. A conservative conclusion from these data is that the global quality of life was no worse for the Tarceva arm despite the known side effects from Tarceva.

[Slide]

So, to summarize the efficacy results, Tarceva treatment in combination with gemcitabine resulted in a statistically significant 23 percent

improvement in overall survival in the 100 mg cohort; a statistically significant 30 percent improvement in progression-free survival. No difference in response rates was observed but there was a significant improvement in the disease control rate. These treatment benefits were achieved with no detrimental effect on global quality of life compared to the placebo group.

[Slide]

I would now like to introduce Dr. Karsten Witt, vice president for drug safety at OSI Pharmaceuticals, who will now summarize the safety results from study PA.3 and put them into perspective with the already existing safety profile of Tarceva.

Clinical Safety Data

DR. WITT: Thank you, Gary. It is a pleasure to be able to share the safety experience of Tarceva during this ODAC meeting today.

[Slide]

As Dr. Cagnoni mentioned earlier, more than 18,000 patients have received Tarceva since

the launch in November until July of this year and, aside from the safety update, revealed no new safety signals beyond what is described in the current package insert. The safety profile of Tarceva has been evaluated in approximately 6,300 subjects who have received Tarceva or placebo in company-sponsored trials. This includes data from 562 patients in study PA.3 who received at least one dose of protocol therapy and will be the focus of the presentation today with emphasis on the 100 mg cohort. Because some patients didn't receive any protocol therapy, all safety analysis was performed on the as-treated population.

[Slide]

Here is the Tarceva/placebo exposure for patients in the 100 mg cohort. The median duration of exposure for Tarceva was about 3.5 weeks longer than for placebo and, importantly, most patients in each arm received the targeted dose intensity of 100 mg per day.

[Slide]

Here are the same calculations for

gemcitabine exposure. The median, absolute and relative gemcitabine dose intensities were similar in each arm, indicating that Tarceva did not compromise the dose intensity of gemcitabine.

[Slide]

Patients were allowed to discontinue the oral drug, which was Tarceva or placebo, due to toxicity, and continued gemcitabine, or vice versa. Shown here is a summary of discontinuation of Tarceva or placebo due to drug-related adverse events. Ten percent of the patients discontinued the oral agent in the Tarceva/gemcitabine arm compared to 5 percent in the placebo/gemcitabine arm. Gemcitabine was discontinued due to toxicity in 9 percent and 6 percent of the patients in each arm respectively. Therefore, overall discontinuation of either agent due to toxicity occurred in 12 percent of the Tarceva arm and 7 percent in the placebo/gemcitabine arm. The toxicities resulting in discontinuation were not limited to any specific events. The most common reasons included rash, transaminase elevation, lung

infiltration, decreased platelet count and diarrhea.

[Slide]

Adverse events in the 100 mg cohort are displayed on this slide for 3 groups of events, fatigue, a common disease-related event and also the single most frequent event reported in this trial. Those events that occurred more frequently in the Tarceva/gemcitabine arm are eye disorders, a class effect associated with EGFR inhibitors. Both fatigue and eye disorders occurred at the same incidence in each treatment arm. As expected, more patients in the Tarceva/gemcitabine arm experienced rash and diarrhea.

Sixty-nine percent of Tarceva-treated patients experienced any grade of rash compared to 30 percent in the placebo/gemcitabine arm. Similarly, 48 percent and 36 percent in each arm developed diarrhea respectively. Importantly, only 5 percent of Tarceva-treated patients experienced grade 3 rash and 5 percent grade 3 diarrhea. Other adverse events frequently reported among

Tarceva-treated patients included infection, decreased weight and stomatitis.

[Slide]

Grade 3 and 4 adverse events regardless of causality that occurred in at least 5 percent of the patients in either arm are summarized here. Overall, the rate of grade 3 events was balanced, with 48 percent in each arm, while grade 4 events occurred in 22 percent in the Tarceva arm and 16 percent in the placebo arm. The majority of the events are typically associated with pancreatic cancer, such as abdominal pain which was more common in the placebo/gemcitabine arm, while diarrhea and rash, as expected, was more frequent in the Tarceva arm. In addition, more patients in the Tarceva arm developed sepsis, while more placebo/gemcitabine patients developed non-specific infections.

[Slide]

Following this summary of grade 3/4 severe events, I just want to ensure that there is an appreciation for the difference between seriousness

and severity. I am sure you are all familiar with the overlap in the use of these terms. Severity is based on CTC grade, while seriousness is a regulatory definition regardless of CTC grade. The investigators complied with these criteria, including reporting of hospitalization per protocol.

[Slide]

Serious adverse events occurring in at least 2 percent of the patients in either treatment arms are summarize here. The most frequent serious adverse event regardless of causality was fever, occurring in 8 percent and 7 percent of the patients respectively.

[Slide]

More patients in the Tarceva/gemcitabine arm experienced infections overall, mainly due to reports of pneumonia, sepsis and cellulitis. This was not due to a higher incidence of neutropenia in the Tarceva arm, as I will show you shortly. The remaining serious adverse events were infrequent, with minor differences between the arms.

[Slide]

Interstitial lung disease, or ILD, has been identified as a serious adverse event for Tarceva and other EGFR tyrosine kinase inhibitors. Because of the diagnostic challenge of this disease entity, we have paid special attention to ensure inclusion of all cases even if they were not reported as possible drug-induced lung toxicity.

In PA.3 we used an inclusion definition of ILD-like events that includes pneumonitis, lung infiltration and acute respiratory distress syndrome. Using this inclusion definition, we identified 6 Tarceva-treated patients in the 100 mg cohort who experienced serious ILD-like adverse events.

[Slide]

These patients are listed on this slide with their age, time to onset from start of therapy, the outcome, CTC grade and the reported attribution of causality. One Tarceva-treated patient in the 150 mg cohort also experienced a serious ILD-like adverse event as did 1

placebo/gemcitabine patient. Three patients died. Two cases of pneumonitis were considered related to protocol treatment, while one patient died of ARDS secondary to pneumonia, considered unrelated. The remaining 4 patients recovered, including 1 patient who continued Tarceva treatment. None of the cases were confirmed histologically.

A summary of the cause of death within 30 days of last dose is provided in the briefing document. I would like to focus on the patients who died due to an adverse event deemed possibly or probably related to protocol treatment by the investigator. A total of 5 deaths were attributed to protocol treatment. As I mentioned earlier, 2 patients diagnosed with pneumonitis died, including 1 which was confounded by progressive disease. Two patients died of neutropenic and neutropenic sepsis, both attributed to gemcitabine only. The final patient died of a CNS bleed and progressive disease after just 8 days on the study.

As shown in the upper portion of the slide, Tarceva did not increase the frequency of

hematological toxicities when added to gemcitabine. There was a slight increase in grade 3 ALT abnormalities, and in all grades of bilirubin abnormalities because of grade 1 or 2 elevations. Note, very few patients experienced a grade 4 toxicity.

[Slide]

In summary, treatment with Tarceva 100 mg a day in combination with gemcitabine was tolerated by most patients, as indicated by the ability to deliver the intended dose and the observed incidence of dose modifications. Rash and diarrhea, as expected, were more common in patients treated with Tarceva and infrequently resulted in drug discontinuation. Reports of ILD-like serious adverse events were infrequent. However, interstitial lung disease should always be considered as a differential diagnosis in persons experiencing unexplained pulmonary symptoms. And, the hematologic toxicity of gemcitabine was not increased when Tarceva was added.

[Slide]

Dr. Rothenberg will not put the efficacy and safety results into perspective and summarize the risk/benefit assessment of Tarceva.

Risk/Benefit Summary

DR. ROTHENBERG: Thank you.

[Slide]

I would now like to put these findings into context from the perspective of someone who sees patients with pancreatic cancer. First, I would like to give you a historical context. Ten years ago this committee reviewed the application for gemcitabine for the same indication. In that data set, it showed that gemcitabine confers small but significant improvement in survival. It too was associated with a low objective response rate. It was also associated with higher rates of toxicity than the control arm of 5-FU, including grade 3-4 myelosuppression, increased LFTs, nausea and vomiting. The following year gemcitabine was granted full approval by the FDA for advanced pancreatic cancer, and in the ensuing 10 years has proven itself to be the cornerstone treatment for

pancreatic cancer.

[Slide]

In the ensuing 10 years it has also been proven that it has been very difficult, surprisingly difficult to make further progress in advanced pancreatic cancer. During this time there have been 10 Phase 2 trials and 2 Phase 3 trials of a new drug compared head-to-head against gemcitabine. Both failed to demonstrate a survival improvement. Eight Phase 3 trials in which the new drug was combined with gemcitabine and compared to gemcitabine alone or placebo also failed to show a survival benefit in any of those 8 trials. Clearly, improving outcomes in patients with advanced pancreatic cancer has been much more difficult than anticipated.

[Slide]

Pancreatic cancer is a fatal disease. The overall survival, as you have heard, is the shortest of any solid tumor. In other Phase 3 trials, as mentioned earlier, the addition of a second agent to gemcitabine has added toxicity

without an improvement in survival.

Tarceva is already marketed and was approved by the FDA in 2004 after demonstrating improvement in overall survival in patients with recurrent non-small cell lung cancer. There was considerable clinical experience and a safety profile that has been developed for Tarceva in more than 18,000 patients.

[Slide]

I would now like to put this in a regulatory perspective. What is being considered today is a supplemental NDA, a mechanism created by the FDA to encourage sponsors to submit significant clinical trial data and, thereby, promote concordance between labeled indications and the emerging clinical use of the drug.

Quoting from the FDA Guidance for Industry, if a product already has been shown to be safe and effective in the treatment of patients with a given type of cancer, a single, adequate an well-controlled, multicenter trial--such as this--demonstrating acceptable safety and

effectiveness in another form of cancer that is known to have a generally similar pattern of responsiveness to chemotherapy--such as non-small cell lung cancer and pancreatic cancer, both fatal diseases with low objective response rates and short median survival--may support labeling for that additional form of cancer.

[Slide]

This trial was a randomized, double-blind, placebo-controlled Phase 3 trial that was conducted independently by a North American Cooperative Group with support from OSI. I would like to remind the panel that these trials have been considered to be the highest quality by the FDA.

The primary endpoint, improvement in overall survival, was achieved. The therapeutic benefit conferred was both statistically significant and clinically meaningful, including a 23 percent increase in overall survival and a 30 percent increase in progression-free survival. I would also like to point out that any point estimate, median, one year--any point estimate does

not accurately capture this full benefit.

The benefit was associated with modest or infrequent toxicities. More frequent but modest toxicities were primarily rash and diarrhea. More clinically significant infrequent toxicities included rare episodes of ILD-like events and there was no worsening in global quality of life.

I would like to point out that the magnitude of toxicity is substantially less than what has been observed when other cytotoxic agents have been added to gemcitabine. I would like to remind the panel that Tarceva is an oral, self-administered drug that does not place a burden on outpatient resource utilization or inconvenience to patients.

What are the implications of this study? PA.3 is the first trial in 10 years to demonstrate significant improvement in survival in patients with advanced pancreatic cancer. Given the short survival and lack of other effective options, the type and magnitude of benefits far outweigh the risk of toxicities. A combination of Tarceva and

gemcitabine represents an important treatment option for patients and physicians who want a more aggressive, more effective treatment for advanced pancreatic cancer, and I believe they should be given that choice. Thank you.

DR. MARTINO: Thank you. I now would like to ask the FDA to do their presentation. Dr. Senderowicz, please.

FDA Presentation

[Slide]

DR. SENDEROWICZ: My presentation will be divided in several sections. First I will talk about available therapy for locally advanced or metastatic pancreatic carcinoma. Second, I will talk about the design of PA.3, the single pivotal study submitted by the applicant. Third, I will show the agency's efficacy and safety analyses of the study results and, fourth, I will show our conclusions for this application.

[Slide]

As was mentioned before, the standard of care for the treatment of locally advanced or

metastatic adenocarcinoma of the pancreas is gemcitabine monotherapy. In the pivotal study that led to gemcitabine approval, patients with locally advanced or metastatic pancreatic carcinoma were treated with gemcitabine versus 5-FU. As you can appreciate from this slide, gemcitabine prolonged the overall median survival of patients compared to 5-FU. Moreover, gemcitabine significantly increased the clinical response rate--a composite based on analgesic consumption, pain intensity, performance status and weight change--in comparison with 5-FU. Of note, more than 70 percent of patients in this trial had performance status 2 or greater. The trial was also supported by another trial of gemcitabine in 5-FU refractory pancreatic carcinoma patients demonstrating similar findings.

[Slide]

In this slide we show the results for the pivotal gemcitabine approval trial. Since then, several gemcitabine combination trials were tested. Although these other two trials were not reviewed by the Food and Drug Administration. These

peer-reviewed published trials demonstrated an increase in median and overall survival, increase in progression-free, increase in response rate, increase in 12-month survival rate and increase in clinical benefit response when compared with gemcitabine alone.

In the case of gemcitabine/oxaliplatin, the second column from the left, this combination showed almost a 2-month increase in median overall survival and almost 20 percent reduction of death compared with gemcitabine alone. In this trial the nominal p value of survival did not reach statistical significance.

Moreover, the combination of gemcitabine with epirubicin, 5-FU and cisplatin, the third column from the left, did demonstrate increase in overall survival, progression-free, response rate, duration of response and clinical benefit response compared to gemcitabine alone.

[Slide]

These are the results of the PA.3 trial, the study submitted in this application and

presented this afternoon. Of note, Liang et al. presented a meta-analysis at the last ASCO suggesting that gemcitabine chemotherapy combinations prolong the overall survival of patients with locally advanced or metastatic adenocarcinoma of the pancreas.

[Slide]

The first patient in the PA.3 trial was entered in November, 2001 and the last patient was recruited in January, 2003. A total of 569 patients were accrued to this trial. Data cut-off was in January, 2004. At that time, 484 deaths occurred in the trial and 85 patients were censored.

The statistical analysis plan was submitted to the Food and Drug Administration in August, 2004, several months after the data cut-off. Then, the applicant submitted the supplemental NDA on April 29th, 2005. At that time, there were 85 censored patients. Many of them did not have adequate follow-up to the cut-off date, January, 2004. The agency requested the

applicant to submit an updated database and to submit all available pathology reports for this trial.

The final sNDA submission was updated up to June 20, 2005 and was submitted to the FDA on July 1, 2005. At that time 551 patients already died and 18 patients were censored. The pathology reports were submitted to the FDA on July 15, 2005.

[Slide]

The applicant submitted a single randomized trial to support the indication sought. The PA.3 trial was a single, randomized, double-blinded, placebo-controlled Phase 3 multinational study in patients with locally advanced or metastatic adenocarcinoma of the pancreas. There were two arms, erlotinib/gemcitabine versus placebo/gemcitabine. From now on I will name the erlotinib/gemcitabine arm as erlotinib and the placebo/gemcitabine arm placebo respectively.

The planned sample size to obtain 381 deaths was 470 patients. The trial was stratified

by performance status, less than or equal to 1 versus 2; extent of disease, locally advanced versus metastatic; and center. Of note, the center was removed as a stratification factor at the time of the statistical analysis plan.

[Slide]

Although most of the data was already presented by the applicant, we would like to point out a few issues. Patients with either locally advanced or metastatic adenocarcinoma of the pancreas were entered into this trial. Patients with prior chemotherapy were not allowed to participate. However, patients were allowed to receive chemotherapy at radiation sensitization doses prior to study entry.

Tumor EGFR expression, the target of erlotinib, was not required for participation in the trial. The trial enrolled 569 patients. Of those, 521 patients were randomized to the 100 mg dose. Based on the indication proposed by the applicant and based on the small number of patients in the 150 mg cohort, only 24 in each arm,

erlotinib and placebo respectively, we will focus only on the safety and efficacy of the 100 mg cohort.

Thus, 521 patients were randomized to erlotinib 100 mg PO daily and gemcitabine 1 g/meter square weekly for 7 weeks of an 8-week cycle, followed by weekly gemcitabine for 3 weeks of a 4-week cycle versus placebo plus the same dose and schedule of gemcitabine.

[Slide]

The primary endpoint for this trial was overall survival. The trial had 80 percent power to detect an increase of 33 percent in median overall survival, for example, from 6.6 months in the placebo group versus 8.8 months in the erlotinib group with a hazard ratio of 0.75. There were 3 prespecified covariates, performance status, extent of disease and pain intensity score. The secondary endpoints were progression-free survival, response rate and duration of response, correlation of EGFR status and survival, quality of life and toxicity.

[Slide]

Now I want to show the results of the PA.3 study, the 100 mg cohort only.

[Slide]

Both groups were well balanced regarding the 2 stratification factors, performance status and extent of disease. They were also balanced in other categories. However, there were more males in the placebo group. Although one of the secondary objectives of this trial was to determine the role of EGFR tumor expression in survival, less than one-third of cases had available tumor EGFR expression data.

[Slide]

At the time of the 45-day meeting post sNDA submission, the agency requested the applicant to submit all available pathology reports. The sponsor submitted them on July 15 of this year. At that time, the applicant indicated that 9 patients did not meet the eligibility criteria for adenocarcinoma of the pancreas. To verify the eligibility of all patients, including these 9

ineligible patients determined by the applicant, the FDA performed a blinded analysis of all available pathology reports, along with CT scans and surgical reports for all patients.

After this eligibility review, the agency determined that several patients had either other tumor types or were unable to confirm the diagnosis of adenocarcinoma of the pancreas. The applicant requested a meeting with the Food and Drug Administration. After discussion, the FDA and the applicant agreed that in 18 of the case, 3.5 percent of all cases, the diagnosis of adenocarcinoma of the pancreas could not be confirmed.

[Slide]

The major protocol violations that the FDA observed involved no pathology reports in 2 cases; lack of confirmation of malignancy in 3 cases; other primary malignancy in the biopsy report in 10 cases. The cases were adenocarcinoma of non-pancreatic origin, colon cancer, gastric cancer, ampulla of Vater or acinar cell carcinoma;

or metastatic disease without proof of pancreatic origin as determined by CT or surgical reports in 3 case. Therefore, the FDA performed sensitivity analyses excluding these ineligible patients, as we will show in future slides.

[Slide]

The analysis population is defined as all patients randomized in the 100 mg cohort, 261 patients in the erlotinib group and 260 patients in the placebo group for a total of 521 patients. In the analysis population minus the major violations there were 503 patients, or 97 percent of all randomized patients in the 100 mg cohort. The safety population was 259 patients for erlotinib and 256 patients in the placebo arm respectively. These patients received at least one dose of treatment in the 100 mg cohort. I will show the safety analysis in later slides.

[Slide]

This slide shows patient disposition in this trial and 96 percent and 97 percent of patients in the erlotinib and placebo group

discontinued protocol drugs respectively. More patients discontinued drug therapy due to progression of the disease in the placebo group. However, there was a greater number of AEs leading to discontinuation, patient refusal and toxic deaths in the erlotinib group compared with placebo.

[Slide]

in this slide we will present the primary endpoint for this trial, overall survival. We have analyzed the overall survival in the PA.3 trial using 3 different numbers of deaths. Based on the same size calculation, the original sample size calculation, 381 deaths was used. Also, we used 443 deaths at the time of data cut-off and, finally, we used 504 deaths when the database was updated in June, 2005.

As mentioned by the applicant, the median overall survival for erlotinib in the 3 analyses was approximately 12 days longer than the placebo group--of questionable clinical significance. When stratified log-rank test analyses, adjusted for the

two stratification factors of performance status and extent of disease, was used the nominal p value ranged from 0.06 in the 381 group, not a statistically significant difference, and 0.02 in the 504 deaths. The nominal p values for the unstratified log-rank test ranged from 0.09, a non-significant difference, in the 381 death group, and 0.05 in the 504 group respectively. Of note, the stratified log-rank test was prespecified in the protocol.

[Slide]

In this figure we display the Kaplan-Meier survival curve for the surviving proportion of patients in the 504 group. Again, the median overall survival for the erlotinib group was approximately 12 days longer than the placebo arm.

[Slide]

As mentioned earlier, we will show the sensitivity analyses excluding patients with other tumor types or patients who lack pathological confirmation of adenocarcinoma of the pancreas.

[Slide]

In this slide we present the sensitivity analysis for the population analyses groups at 381, 443 and 504 deaths. Of note, all log-rank test analyses shown in this slide were adjusted for both performance status and extent of disease, both certification factors in the trial. When we excluded the 18 patients ineligible as agreed by the sponsor, the nominal p value ranged from 0.06 in the 381 death group, a non-significant difference, to 0.04 in the 504 groups respectively.

[Slide]

We performed few a exploratory analyses, the role of baseline characteristics and the role of rash. Regarding the role of baseline characteristics, as can be observed in this Forrest plot, patients with PS2, males, pain intensity score less than 20 and metastatic disease appeared to benefit the most with erlotinib. However, in patients with PS1 or lower and patients with locally advanced pancreatic cancer, females, age higher than 65 years, patients with pain intensity score more than 20 or patients from the rest of the

world, the effect of erlotinib was unclear. There was no relationship between EGFR tumor expression and survival in this trial, although the number of available EGFR samples was small. In contrast, in the BR.21 lung carcinoma trial, an exploratory analysis showed that tumor EGFR expression did, indeed, predict overall survival.

[Slide]

In this slide we can appreciate the role of rash induced by these treatments in the survival of this trial. As you may recall, in the lung carcinoma BR.21 trial, erlotinib-treated patients who developed any rash had an increase in overall survival as compared to those without rash. In this pancreatic trial, only patients that developed equal to or higher than grade 2 rash benefitted from erlotinib. However, patients with grade 1 or no rash did not benefit from erlotinib.

As appreciated in this slide, we present the results obtained for the secondary objectives in this trial, namely, response rate, duration of response, progression-free survival and survival by

EGFR tumor expression. The results for all secondary objectives were not different between erlotinib and placebo, except for progression-free survival. There was an increase in median progression-free of 10 days that was statistically significantly different from placebo.

[Slide]

The remaining secondary objective in this trial, quality of life, demonstrated that the erlotinib group had statistically significant worsening in diarrhea. However, there were mixed results for the rest of the variables. Although erlotinib had a decrement in the global health status question, it is unclear whether this is of clinical significance. These data cannot support a no decrement conclusion for the erlotinib arm.

[Slide]

As a summary of the safety analyses of the PA.3 trial, most patients in both arms have at least one adverse event. Moreover, it is clear that erlotinib/gemcitabine had a higher incidence of severe, grade 3 and grade 4, toxicities; higher

number of serious adverse events. Also, the erlotinib arm had a higher number of patients that died on therapy or within 30 days of last treatment. Of note, the increase in adverse events by erlotinib occurred in both categories, treatment-related and regardless of causality.

[Slide]

Another way of characterizing the safety for this trial is the assessment of deaths on therapy or within 30 days of therapy. A higher number of patients died on therapy or within 30 days of therapy in the erlotinib/gemcitabine group. Although the majority of patients died within 30 days due to malignant progression, a higher number of patients, approximately 6 percent, in the erlotinib group died due to toxicity or a combination of toxicity along with pancreatic cancer, while no patient died due to toxicity in the placebo group.

[Slide]

Another important aspect for the safety profile for this trial is the incidence of severe

AEs, equal to or higher than grade 3. A higher incidence of cardiovascular and ischemic events were observed in the erlotinib group. Of concern, there were more cases of severe edema and arrhythmias in the erlotinib group. The incidence of myocardial ischemia/infarction was over-represented in the erlotinib group. There were 8 cases, including 1 patient with elevated troponin levels, versus 3 cases in the placebo group. Moreover, stroke was a significant concern in the erlotinib/gemcitabine arm.

[Slide]

One of the most worrisome adverse events observed in the trial was the development of stroke in the erlotinib/gemcitabine arm. There were 6 strokes in the erlotinib group, while no patients in the placebo group had strokes. The incidence of strokes in the erlotinib/gemcitabine arm was 2.3 percent; 5 strokes were ischemic and 1 was hemorrhagic.

The median time to stroke was 24 days. The earliest case of stroke occurred by two days

from drug initiation and the latest was 35 days after drug initiation. Of note, this clinically significant adverse event was not observed in the placebo group nor in the BR.21 lung cancer trial, suggesting that strokes may be due to the combination of erlotinib and gemcitabine.

[Slide]

The Erlotinib/gemcitabine arm also had higher numbers of thrombotic and pulmonary categories. Of note, there were 2 episodes of thrombotic thrombocytopenic purpura in the erlotinib group, a life-threatening disorder with an estimated annual incidence of 3.7 cases per million. Of note, there are 2 additional cases of TTP in the erlotinib postmarketing database, for a total of 4 cases out of approximately 20,000 cases.

Moreover, there was a higher number of pulmonary events in the erlotinib arm. The osteomyelitis worrisome pulmonary adverse event, as mentioned by the applicant, was interstitial lung-like disease. The incidence in this trial was 2.3 percent, a much higher incidence comparing with

placebo at 0.4 percent.

[Slide]

The erlotinib/gemcitabine arm had higher gastrointestinal and hematological adverse events. A very prevalent adverse event was severe diarrhea, as was mentioned before in quality of life issues. Moreover, severe GI bleeding was over-represented in the erlotinib group, along with ileus, pancreatitis and odynophagia stomatitis. Also, there were more cases of thrombocytopenia and non-gastrointestinal bleeding disorders in the erlotinib arm. Also, there were 2 cases of hemolytic anemia in the erlotinib group. As expected, there were more severe cases of rash in the erlotinib group. The median time to rash was 10 days.

[Slide]

The erlotinib/gemcitabine arm had a higher number of CNS events. There was a higher number of cases of severe neuropathy and depression in the erlotinib group. Moreover, there was a higher number of other infections and renal failure in the

erlotinib group.

[Slide]

A higher number of patients refused further therapy in the erlotinib/gemcitabine group. The causes for refusal in the erlotinib/gemcitabine arm were in the majority of cases due to adverse events.

The adverse events associated with refusal of therapy in the erlotinib group were liver function elevation, deep venous thrombosis, sepsis and pneumonia. Moreover, both groups have other causes of adverse events as reasons for discontinuation, as depicted in the footnote of this slide. Of note, the total number of AEs for each column in the lower table does not add up as patients could reuse further therapy due to more than one adverse event.

[Slide]

As a summary of the toxicity profile for the PA.3 trial, the erlotinib/gemcitabine arm had a higher incidence of grade 3 and grade 4 toxicity, regardless of causality and treatment related.

Serious adverse events--the erlotinib arm had a higher number of patients that discontinued due to adverse events. The erlotinib/gemcitabine arm had a higher number of toxic deaths and patients that refused further therapy. The erlotinib arm had a higher number of patients that died on treatment or within 30 days of last treatment. The most frequent adverse events in the erlotinib group was rash and diarrhea.

The erlotinib/gemcitabine arm had a higher incidence of interstitial lung-like disease compared to placebo. Moreover, the incidence of interstitial lung-like disease in the PA.3 trial was higher than the one observed in the erlotinib lung carcinoma trial.

Finally, in the PA.3 trial other severe toxicities appear over-represented in the erlotinib/gemcitabine arm, such as stroke, TTP, myocardial infarction, arrhythmias, edema, renal failure, bleeding disorder GI and non-GI related, ileus, pancreatitis, odynophagial stomatitis and neuropathy.

[Slide]

The information presented today by the applicant and the agency to the committee was about the single randomized clinical trial in pancreatic carcinoma. For your discussion and consideration, the FDA Clinical Guidance determines when a single trial is sufficient for approval without independent substantiation. The criteria used for the FDA are as follows: The single study needs to be large and multicenter and no single investigator or site is disproportionably responsible for the favorable effects. The study appears to meet these criteria.

The results need to be consistent across study subjects, such as age, gender, disease state and stage. This study appears to meet these criteria.

Multiple endpoints, primary and secondary, involving different events need to be positive. In this trial, the overall survival and progression-free survival were positive. However, response rate, duration of response and quality of

life show no effect over placebo.

And, it needs to be statistically very persuasive, with a very low p value, and it would be unethical to repeat the trial. We are asking the committee's advice on this point. This issue will be asked in questions number one and four to the committee.

[Slide]

So, the conclusions--PA.3 is a single add-on trial where the addition of erlotinib to gemcitabine in locally advanced or metastatic pancreatic adenocarcinoma adds marginal efficacy, clinical and statistical, while adding severe toxicity.

Erlotinib increased overall survival with a median difference of approximately 12 days--of questionable clinical significance. Also, erlotinib increased progression-free survival with a median difference of approximately 10 days.

However, there was no difference in response rate or duration of response. Moreover, there was no improvement in quality of life.

However, diarrhea was significantly worse in the erlotinib arm. With the limited available data, there was no relationship between tumor EGFR expression and survival.

With respect to safety, the erlotinib/gemcitabine arm had a worse safety profile. There was a greater number of grade 3 or 4 adverse events, serious adverse events, discontinuation due to adverse events, refusal of therapy, toxic death and death on treatment or within 30 days of last treatment. The higher incidence of stroke, thrombotic thrombocytopenic purpura and other toxicities in the erlotinib/gemcitabine arm are a safety concern that deserve to be investigated further.

Of note, when gemcitabine was approved by the Food and Drug Administration 10 years ago, gemcitabine demonstrated increased overall survival and clinical benefit response in the pivotal trial and in one supportive pancreatic carcinoma trial. In summary, given the marginal efficacy with added toxicity, is the effect statistically very

persuasive and of clinical importance? Thanks for your attention.

DR. MARTINO: Thank you. At this point, ladies and gentlemen, I am going to deviate slightly from the agenda. I am going to let you take a break for 15 minutes. When we come back we will have the open public hearing and then we will have the questions and discussions. So, I want you back at no later than 2:25.

[Brief recess]

Open Public Hearing

DR. MARTINO: The next portion of this meeting is the open public hearing. Those of you who have asked to address the committee, there is a microphone available for you at the bottom of the table that we would like you to use. Before we announce who you are, there is a statement that I need to read to you:

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing

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

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

Ms. Clifford will introduce the speakers.

MS. CLIFFORD: Our first speaker is Selma Schimmel.

MS. SCHIMMEL: Hello, and thank you for

the opportunity to be heard. My name is Selma Schimmel. I am the CEO and founder of Vital Options International. It is a not-for-profit cancer communications and advocacy organization that produces the Group Room. It is a cancer talk radio show and it gives me the opportunity to speak with a great many patients and physicians. I am also a breast and ovarian cancer survivor.

I have no financial interest, investment or gain associated with my presence here today. OSI, nor any other company, did not pay for my transportation nor my lodging.

I am here to help represent the voices of patients and their loved ones dealing with pancreatic cancer, and because the dialogue happening right now has far-reaching implications for patients and the oncology community at large.

There seems to be a growing perception that governmental agencies are engaged in scientific witch hunts that could delay approval of drugs, which may not offer a cure or striking survival benefits for dying patients. Recent "Wall

Street Journal" editorials directed at the FDA have been attacking and destructive, unbalanced and overboard. They point to the erosion of public trust and intolerance for the regulatory process. At the same time, regulatory agencies are in a no-win situation--attacked if they accelerate drug approval and later data doesn't support early findings, and attacked if they don't approve drugs quickly enough.

Approval of new drugs or new indications for an already approved drug often requires the FDA to walk a fine line in weighing the relative risks and benefits. Ideally, we all want to have certainty about scientific data and results that show strong benefits without added toxicities. But in cancer, more often than not, we are faced with drugs that give us only modest benefits and are accompanied with a range of toxicities, such as the case today with the supplemental application of Tarceva for an additional indication in pancreatic cancer.

Then the question is, is one single study,

showing a modest survival benefit with a modest increase in toxicities sufficient for approval? Or, do we need more data for approval? Perhaps the question is as philosophic as it is clinical.

Pancreatic cancer patients know that they are more than likely to die. Repeating a positive study, conducted by a reputable group like the NCI Canada, simply to confirm results a second time raises significant ethical issues. It is unthinkable to ask pancreatic cancer patients to be randomized to receive standard therapy plus placebo when the survival benefit from the addition of Tarceva, however modest, will be denied.

At a time when clinical trial resources are limited and patient participation is meager, and with virtually no advances other than gemcitabine in the last decades, should we not be building on this combination rather than moving backward? A confirmatory study before granting an approval is a luxury that pancreatic cancer patients cannot afford to wait for.

As pancreatic cancer patients search the

web, they are finding hope reading that Tarceva in combination with gemcitabine can improve survival in people with advanced pancreatic cancer. Survival curves from the study reinforce this and patients are encouraged to speak with their doctors. Patients have been receiving Tarceva off-label for some time now, and if approval is denied doctors will continue to do so but with no access to prescribing information. The issue of toxicity cannot be overlooked, but it is a choice that should be dealt with between the physician and the patient, and approved labeling assures that it is an informed choice.

For such a deadly disease, while the absolute gain in survival does not appear to be much, the relative gain is clinically and psychologically significant. For a terminal patient the option of buying time, even just a little time, can make a difference not only for the patient but for everyone that that person leaves behind.

How do you judge the value of a 20 percent

reduction of the risk of death or the improved odds of being alive after one year? Clinicians may look at median survival and think that weeks or days are not meaningful but for someone who is trying to hang on for the marriage of a child, the birth of a grandchild or a chance to try a new investigative therapy it represents a lifetime. It is the difference between curing an healing.

One of the driving forces which brought me here today is because of my neighbor who was diagnosed with pancreatic cancer in his mid-50s. He was told he would have six months, maybe a year at most. However, he lived more than four years on clinical trials and on off-drug combinations. So, listening to the discussion happening here today, I don't really understand the issue.

The company said prospectively that they were looking for statistically significant improvement in overall survival and that they wished to look at just survival analyses considering the treatment arm performance status and extent of disease. They did that and have

shown a statistically significant improvement in survival. Given that, what else are you asking for? That is the question that many patients and their loved ones will want to know. You face many horribly difficult decisions but giving pancreatic cancer patients drug access when they inevitably face a death sentence should not be one of them. Thank you very much. Copies of my statement are available.

DR. MARTINO: Thank you.

MS. CLIFFORD: Our next speaker is Julie Fleshman.

MS. FLESHMAN: Good afternoon. Thank you for allowing me to present during the open public hearing of today's ODAC meeting. My name is Julie Fleshman an I am the president and CEO of the Pancreatic Cancer Action Network, otherwise known as panCAN, the first national non-profit advocacy organization for the pancreatic cancer community.

While my organization receives funding from both of the companies presenting today, neither is covering my expenses for attending this

committee meeting.

I am here today to speak on behalf of pancreatic cancer patients. While I am neither a pancreatic cancer patient nor a survivor, I am a caregiver who watched my father die from this devastating disease. When he was diagnosed in 1999 at 52 years of age my family wasn't given many options. We were provided with absolutely no hope. My dad died four months after his diagnosis which, in my role as president and CEO of panCAN, is a story we hear way, way too often.

Unfortunately, even today pancreatic cancer patients don't have many options either in early detection or in treatment. We all know the facts. They were mentioned earlier today. Pancreatic cancer has a 99 percent mortality rate and it is the fourth leading cause of cancer deaths in the United States. It affects the lives of patients and families of 32,000 Americans a year and has the lowest five-year survival rate of any form of cancer, at just four percent.

As the National Cancer Institute

indicates, there has been little change in overall mortality rates for pancreatic cancer in the last 30 years. Despite these statistics, however, pancreatic cancer receives the least amount of federal funding of any major cancer, and there are not enough researchers in this country with 100 percent dedication to studying this disease. Therefore, progress in finding new effective treatments and diagnostic tools has been slow.

The pancreatic cancer community needs more treatment options that can provide hope in their fight against this devastating disease. At our core, panCAN supports the research and discovery of new treatments to extend the spectrum of life of the patient, whether that is a week, a month or a year. We have seen in other cancers that the steps toward scientific discovery are incremental and that the rewards for patients and for researchers are important each step along the way. With motivation and hope researchers will continue to work toward finding the key to unlock the mysteries related to pancreatic cancer. Little by little we

will make progress with this disease and individuals like my father, Jim Fleshman, will not die unnecessarily at the age of 52. Thank you for your time today.

DR. MARTINO: Thank you.

MS. CLIFFORD: Carolyn Aldige.

MS. ALDIGE: Good afternoon, everyone. My name is Carolyn Aldige and I serve as president and founder of the Cancer Research and Prevention Foundation. We are a national, non-profit, cancer-related organization whose mission is cancer prevention and early detection through research and education.

I asked to speak here today though on behalf of pancreatic cancer patients because, as you heard, there are very, very few treatment options and there are virtually no tools to detect this disease in its early states. So, I wanted to speak in support of the NDA for this drug, Tarceva, with the proposed indication for first-line treatment in combination with gemcitabine for patients with locally advanced, unresectable or

metastatic pancreatic cancer.

I won't repeat the comments of my friends and colleagues Selma Schimmel and Julie Fleshman. They spoke both brilliantly and eloquently on behalf of this patient population and I can simply underscore what they said by mentioning the fact that virtually every day of the week I get a call--even though our organization is focused on prevention, I receive phone calls from individuals and their friends and colleagues and family members who have just been diagnosed with certain kinds of cancer. In many cases I can say, well, there is a lot of hope here; your prognosis could be excellent. Let's get you to the very best place we can to see what we can do to get you appropriately staged and treated. But when I hear the words pancreatic cancer my heart sinks. I still say, well, let's get this person to the very best place and the very best person we can for the treatment of this disease. But my heart goes out to every single one of those individuals because we know that this diagnosis is virtually a death sentence.

So, I appreciate the opportunity to address you. I do want to mention I have absolutely no financial connection with either of the sponsors, either of the companies that sponsor these drugs and I paid my own way to be here, even though the gas was pretty expensive!

That is really all I needed to say. I just want to make a plea for your open minds and hearts to be as thoughtful as you can when you weigh the evidence of the studies that you have heard presented here today because I agree that there is no value or price that we can put on extending a life by a day, a week or a month. My daughter was just married on Saturday and I don't know what I would have done if one of us had had a diagnosis--her new father-in-law was diagnosed with lung cancer on Friday. So, it sort of underscores how getting an extra day or a week or a month. Thank you.

DR. MARTINO: Thank you. The sponsor has asked me for about 90 seconds of time to readdress the group and I graciously granted that. Please

don't abuse it!

[Laughter]

DR. CAGNONI: Dr. Martino, we are ready for the question and answer session. In fact, the statement will not be necessary. Thank you.

Answer and Question Session

DR. MARTINO: That was good! Go ahead.

DR. PERRY: It seems to me that if you take the most optimistic scenario we are talking about a gain of 21 days, and if the drug is still priced at about $100 a day that works out to be about $550 a day for the patients who are treated. Can society afford this amount of money for this amount of gain, or should we keep looking until we find something that is a better drug?

DR. CAGNONI: That is a very good question and let me first ask Dr. Clark to review what the true benefit provided by Tarceva for patients with pancreatic cancer is, and then we can address the second part of your question.

DR. PAZDUR: Could I answer it for the company? You are not supposed to be bringing into

consideration financial concerns here about drug pricing and how much a drug costs. Okay? That is a separate issue from a regulatory decision that is being made here. So, again, if somebody wants to answer the question, feel free to do so but I want to emphasize that a decision regarding this drug should be made on the basis of safety and efficacy that is presented to you, not on any potential cost considerations of how much the drug may cost; what is the benefit per patient life year or life month or life day, etc. That is a non-FDA question and should not, and must not, impact on a decision regarding the approval or non-approval of the drug. Sorry, but you did ask.

DR. PERRY: Then can I withdraw my question?

DR. MARTINO: Yes, you can. Thank you very much. Next, Dr. Mortimer?

DR. MORTIMER: This is a question for either Dr. Moore or Dr. Rothenberg. We seem to have spent a lot of time talking about the increased thromboembolic complications and I

wondered if there is any data, either from the Tarceva standpoint correlating the rash and response or in the pancreatic literature, supporting thromboembolic disease as a marker of response or subsequent benefit.

DR. CAGNONI: I will ask Dr. Moore to comment on that.

DR. MOORE: That is kind of a tough question. I think you asked about rash and thromboembolic disease. In this trial it is true that if you look at the patients who got Tarceva, which was around 283, they divide into almost 3 groups who had grade 1 and grade 2 rash, all about equal size, and if you do that analysis the patients who got a grade 2 rash, their median survival was 1.5 months and their 1-year survival was 43 percent.

This phenomenon of an association of rash with a longer benefit for EGFR inhibitors is something that has been seen with other inhibitors in other studies. I think this is sort of a hypothesis-generating analysis and I think you have

to be a little bit careful because, in a sense, the ability to generate a rash may be because you have a better performance status that may impact on some of these analyses. So, I think it is an interesting finding but I think that we have to look at it more.

In terms of thromboembolic disease, you are right, the frequency of these sorts of events is higher. I am not aware of any association of thromboembolic events with survival per se in pancreatic cancer. One thing I would say is that in any study where patients are on one therapy longer than the other--and that did occur in this case, patients were on gem/Tarceva longer than on gem/placebo--you likely will see more thromboembolic disorders on gem/Tarceva because this is a baseline risk that is going to occur over time in any case.

DR. MARTINO: Dr. Levine?

DR. LEVINE: Just to go back to the thromboembolic disease again, as we all know, Trousseau, with pancreatic cancer, was the first to

show that pancreatic cancer itself is associated with an increased risk of clots. Being on Coumadin, having a prior clot did not exclude somebody from being on this study, and if you were weighted differentially more people happened to be on Coumadin on the Tarceva arm and less on the placebo, and that might have explained the increased clots. What were the data as far as who was on low-molecular weight heparins; who was on Coumadin? How that was weighted? How does that reflect? Then I have another question too but let's do that one.

DR. CAGNONI: I will ask Dr. Witt to comment on the question.

DR. WITT: I can mention that with respect to Coumadin approximately 50 patients in each arm were on Coumadin either before they went into the study or started while they were on the study. It was approximately the same rate in each arm. I cannot answer the question about heparin.

DR. LEVINE: Did you look at INRs? Were they both controlled properly? Did you look at

anything of that sort?

DR. WITT: Yes, we did. In fact, we did require more careful monitoring of INR if patients who were on Coumadin or Coumadin derivatives. Let me just show you a summary.

[Slide]

Actually, this slide is a summary of INR shifts from baseline. They only required INR evaluations if patients were on Coumadin derivatives. So, it is about 60 patients in each arm. What this indicates is that patients that had an unknown at baseline are probably the ones that didn't receive it before going into the study. There was about 5 percent increase between 4 and 6 and 11 percent to greater than 6. It is approximately the same in both treatment arms. Looking at the ones that were within therapeutic range when they started the study, approximately the same frequency of patients developed ranges outside of the therapeutic range.

DR. LEVINE: An INR greater than 8? That is an INR level you are talking about?

DR. WITT: No, it is less than 4, 4-6 or greater than 6.

DR. LEVINE: INR levels?

DR. WITT: Yes.

DR. LEVINE: Those are very impressive. So, we can't really answer the question is the bottom line. I mean, I don't think you have data there to answer my question.

My next one is this, it is a pill. How did you monitor the compliance of this pill? How do you know that they were taking it the way they were supposed to?

DR. WITT: This was done by counting pills when patients came for follow-up visits.

DR. LEVINE: Was there equivalence on the placebo pill versus the Tarceva pill?

DR. WITT: The placebo bills are matched to the Tarceva pills. They were identical, yes.

DR. LEVIN: Were they equally compliant on both arms?

DR. WITT: Yes.

DR. LEVINE: At what level?

DR. WITT: The intended dose intensity--basically 100 percent of the dose intensity that was intended for the oral compound in the placebo arm was delivered.

DR. LEVINE: They gook all of their pills?

DR. WITT: Yes.

[Slide]

This is the data that summarizes dose intensity by treatment arm in the North American cohort for the Tarceva/gemcitabine side and the gemcitabine arm. This is the median dose intensity. It was 99 percent, 100 percent. So, when you see the numbers it is pretty clear that most of the patients took most of their pills. In fact, 90 percent or higher of the patients, as you can see--I am sorry, 88 percent of the patients took 90 percent or more of their pills in the control arm, as you can see in this slide.

DR. LEVINE: In other words, 77 percent of the treatment group, the Tarceva group, took greater than 90 percent of their pills.

DR. WITT: That is correct.

DR. LEVINE: Meaning that you got the responses that you got when not everyone was taking those pills the way they were supposed to.

DR. WITT: There were dose discontinuations and dose interruptions in the study, yes.

DR. MARTINO: Dr. D'Agostino, you are next.

DR. D'AGOSTINO: This is directed to the FDA. There has been repeated showing to us of the build-up of the number of deaths and the changes of the p values. I mean, you are obviously bothered by that. Why are you bothered by that? Don't you believe the bottom line for the number of deaths and the p value that is associated with that?

DR. SENDEROWICZ: There were some disagreements between the Food and Drug Administration about what was the target population, the number of patients needed for the primary survival endpoint. So, based on our point of view, 381 deaths will be the primary survival endpoint. However, the company took the position

of 484 deaths at the time of the cut-off date. So, to try to be open, in a sense, we presented the 3 death groups, 381, 484 and 504 deaths in the 100 mg cohort only because this is what we have information on. That is different from the company. The company has accumulated both the 100 mg and the 150 mg.

DR. D'AGOSTINO: But it doesn't appear that they kept adding people to the study, following them--

DR. SENDEROWICZ: No.

DR. D'AGOSTINO: --to build up death profiles.

DR. SENDEROWICZ: No. Basically, as expected, when you have a higher number of patients you have a p value that is less than 0.05. So, some people may claim that this is an over-powered study or not. I am not a statistician so that is my point of view.

DR. D'AGOSTINO: This may be a case where we have statistical significance and we can actually talk about clinical significance.

DR. SENDEROWICZ: That is another issue. That is part of the question.

DR. D'AGOSTINO: Can I raise one more question, which may be better held off for later? In terms of the ethical issue of having still another study, is the Division open to historical control studies?

DR. PAZDUR: I think I want to address that issue about one trial versus two trials because, again, some of the presentations and some of the questions are made by the review staff and review teams and do not necessarily represent the entire viewpoint of the FDA.

We have to make sure that we understand that there are many instances where the FDA has accepted one trial. We have numerous examples of instances where we have approved drugs on the basis of one trial. Oncology is a bit different than other therapeutic areas, and let me go over some of the concepts that I would like to illustrate with you.

Number one, we have secondary endpoints

that frequently corroborate the primary endpoint. In this trial we have the time to progression or progression-free survival endpoint. In some cases we have response rates. In other therapeutic areas, for example, we may just have 2 survival curves that are separating and that is the only thing that we have. That is not true in oncology. We frequently have more information, as an example in this case.

Secondly, it is difficult many times in developing drugs in oncology, and I think we have to have a practical perspective on the development of drugs in oncology where we don't have good predictive models that this drug is going to work in pancreatic carcinomas, going to work in lung cancer, going to work in breast cancer. So, to do 2 large trials in a certain disease is somewhat difficult and somewhat onerous to actually ask sponsors to do. Here, again, I think we have to take a look at our past experience in approving drugs, including this drug's first approval which was based really on 1 randomized trial that showed

a survival benefit. The other point that we have discussed in our endpoint meetings that I think deserves some discussion is how much survival constitutes clinical benefit. That is a very, very difficult question, very difficult question for anyone of us to answer, and I am very sympathetic to the views that have been expressed by our patients that have come to the microphone regarding that. In general, we have stated publicly that we take a look at really any meaningful benefit in terms of survival. We are not setting a limit here. This endpoint is a hard endpoint frequently to achieve in many diseases here. It doesn't have the ambiguity of other endpoints such as progression-free survival where we could be arguing whether this is a real finding or just the timing of x-rays. One has certainty; it has a degree of concreteness to it, concrete that it is a real endpoint.

So, to say that X amount of days is a benefit and X minus 2 days is not a benefit is something that I think might not be really the most

appropriate conversation to be having. I think the question here is do we truly have a true finding and then, given the relative prospectiveness of that finding in terms of the toxicity in a risk/benefit relationship, is it of clinical benefit in terms of the toxicity, not what is X number of days in benefit. Those are impossible questions to answer.

DR. MARTINO: Mrs. Wells?

MS. WELLS: Yes, I am not quite sure who I should forward this question to. I am going to approach the FDA but I would be more than glad to hear from the company if you have an answer. In the package that I received from the Food and Drug Administration there was Table 2, efficacy comparison of gemcitabine and other chemotherapy protocols-- whatever. My anecdotal experience is that gemcitabine is seldom given to pancreatic patients by itself. I was wondering if you could tell me--I know you have spoken to oxaliplatin and irinotecan in your table, but can you tell me how this drug compares to the other combinations that

we see all the time with pancreatic cancer patients? I mean, from a median survival standpoint?

DR. PAZDUR: Could I answer that? I think those comparisons are very, very dangerous to make. Okay? First of all, I think when Adrian presented this, basically it is kind of background information. This data did not go through the same scrutiny that this NDA did. So, we may be really comparing apples and oranges here. Okay? It was basically meant as a background information package, that there may be other therapies that are out there. But by no means has the FDA looked at this, and to make cross-study comparisons of how this NDA and the results of this NDA compares to what is reported in the literature is very, very dangerous and not something that I would want to get involved with.

Furthermore, there is no comparative efficacy standard when we are talking about clinical benefit and a certain survival advantage here. One has to demonstrate an effect on

survival, not that it is better than anything else, especially anything that happens to be in the literature that may or may not even be a real finding that the FDA has now reviewed. So, it is a very tenuous situation. The presentation of these results was mainly to give other examples of therapy, not meant as a comparison and certainly not to be made use of in any regulatory decision-making.

MS. WELLS: I would then guess that you would not want to discuss the toxicities of these other combinations as compared to the toxicity of the one that is the subject today.

DR. PAZDUR: I think that would be a fair decision since we have not reviewed that data. They are not held by any means to compare themselves against unapproved therapies. They have to show that they are safe and effective, not show a greater safety or a greater efficacy profile than something that is not approved or that is not considered available therapy.

DR. MARTINO: Dr. Eckhardt?

DR. ECKHARDT: Well, I guess what I have been struggling with, and I guess what Rick is talking about a little bit may change this, but, you know, I do get concerned about the magnitude of the change certainly with regards to the risk/benefit ratio. I was just curious. Either Malcolm or Mace could make a comment about the question with regards to the fact that, you know, the initial anticipated parameters were set up to detect a certain magnitude, and there were certainly enough events here to pick up a smaller change. You know, I think going forward I guess the question would be based upon these results and the potential availability of Tarceva being out there combined with gemcitabine is sort of a given, then we really are committing ourselves to triple drug regimens or other larger studies. I would just like to hear a comment from one of them, being really the top clinical trialists in the U.S. and Canada that work in this disease.

DR. CAGNONI: Certainly. If I could ask Dr. Clark first to comment on the degree of

benefit, and then I will ask Drs. Moore and Rothenberg to put those results into context.

DR. CLARK: In my position, the question about statistical significance is best asked with the data at the time of unblinding at database lock. But since the FDA asked us to update the follow-up, I think it is fair to take the most complete data set and say what is the magnitude of that difference.

[Slide]

Here are the survival curves for the 100 mg cohort with the updated survival. Again I will remind you that all but 17 of the patients have actually died in this particular analysis. It is true, it continues to be true that the median survivals would appear to be about 2 weeks. But, again, take a look at where these median survivals are. Those in the back have no chance to see this but they pinch together really very closely right at the median.

Statisticians have been preaching that we should not use means to represent survival