DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE

VOLUME II

Friday, March 4, 2005

8:00 a.m.

Gaithersberg Hilton
620 Perry Parkway
Gaithersburg, Maryland

PARTICIPANTS

Silvana Martino, D.O., Acting Chair
Johanna M. Clifford, M.S., RN, Executive Secretary

COMMITTEE MEMBERS

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Ralph D'Agostino, Ph.D.
Michael Proschan, Ph.D.

PATIENT REPRESENTATIVE (VOTING)

Sheila Ross - For Iressa

FDA

Martin Cohen, M.D. (a.m. session)
Grant Williams, M.D. (a.m. session)
Amna Ibrahim, M.D.
Nancy Scher, M.D.
Eric Colman, M.D.
Mark Avigan, M.D.
Richard Pazdur, M.D.
Robert Temple, M.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order and Introductions

DR. MARTINO: Good morning, ladies and gentlemen.

The topic before us this morning is some additional new data that has arisen relative to the agent Iressa. Before we start with the topic itself, I am going to ask the committee to introduce itself, and we will start on my left with Dr. Pazdur, please.

DR. PAZDUR: Richard Pazdur, FDA.

DR. WILLIAMS: Grant Williams, FDA.

DR. COHEN: Martin Cohen, FDA.

MRS. ROSS: Sheila Ross, Lung Cancer Alliance formerly ALCASE.

MS. HAYLOCK: Pam Haylock, Oncology Nurse, University of Texas Medical Branch in Galveston.

DR. LEVINE: Alexandra Levine, University of Southern California, Chief of Heme.

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

DR. REAMAN: Gregory Reaman, Pediatric

Oncologist, Children's Hospital, Washington, D.C.

DR. MARTINO: Silvana Martino, Medical Oncology, Cancer Institute Medical Group in Santa Monica.

MS. CLIFFORD: Johanna Clifford, Executive Secretary to the Oncologic Drugs Advisory Committee.

DR. HUSSAIN: Maha Hussain, Medical Oncology, University of Michigan.

DR. PERRY: Michael Perry, Medical Oncology, University of Missouri, Ellis Fischel Cancer Center.

DR. MORTIMER: Joanne Mortimer, Medical Oncology, University of California at San Diego.

DR. GRILLO-LOPEZ: Antonio Grillo-Lopez. I am a hematologist/oncologist, a five-year cancer survivor, and I am here as the industry representative on this committee. I would like to state that although I am the industry representative, I receive no support whatsoever from industry for my presence here.

DR. PROSCHAN: Mike Proschan. I am from

the National Heart, Lung, and Blood Institute.

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

DR. BRAWLEY: Otis Brawley, Medical Oncology and Epidemiology, Emory University.

DR. DOROSHOW: Jim Doroshow, National Cancer Institute.

DR. MARTINO: Thank you.

Next, I would like Ms. Clifford to read the Conflict of Interest Statement for the group.

Conflict of Interest Statement

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

Based on the submitted agenda and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest with the following exceptions:

In accordance with 18 U.S.C. 208(b)(3), full waivers have been granted to the following participants. Please note that the following

consulting activities waived are unrelated to Iressa and its competing products.

Dr. Silvana Martino for consulting for a competitor, which her employer receives less than 10,001 per year.

Dr. Michael Perry for consulting with a competitor which he receives less than 10,001 per year. In addition, Dr. Perry has been granted a waiver under 21 U.S.C. 505(n) for owning stock in a competitor, valued between $5,001 to $25,000. Because his stock interest falls below the de minimis exception allowed under 5 CFR(b)(2), a waiver under 18 U.S.C. 208 is not required.

Dr. Maha Hussain has been granted waivers under 208(b)(3) and 21 U.S.C. 505(n) for owning stock in a sponsor and a competitor. These stocks are valued from 25,000 to 50,000 per firm.

A copy of the waiver statements may be obtained by submitting a written request to the

Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

With respect to the FDA's invited industry representative, we would like to disclose that Dr. Antonio Grillo-Lopez is participating in this meeting as an acting industry representative acting on behalf of regulated industry. Dr. Grillo-Lopez is employed by Neoplastic and Autoimmune Disease Research.

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

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

DR. MARTINO: Thank you.

Next on our agenda is Dr. Richard Pazdur,

who will address the committee and give us some direction for this morning's meeting, please.

Opening Remarks

DR. PAZDUR: Thank you, Dr. Martino.

Iressa was originally approved by the FDA on May 5th, 2003, as a monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of both platinum-based and docetaxel chemotherapies.

Partial tumor responses occurred in approximately 10 percent of patients. Iressa was approved under the accelerated approval regulations. As discussed yesterday, these regulations allow approval based on a surrogate endpoint reasonably likely to predict clinical benefit and require subsequent studies to verify and define its clinical benefit.

As an approval condition, AstraZeneca committed to conduct a randomized trial examining the Iressa effect on survival in patients with advanced non-small cell lung cancer who had

received 1 to 2 prior chemotherapies. This is defined as Trial 0709.

The primary endpoint of this trial was overall survival and improved survival for Iressa-treated patients was to satisfy the requirement for the demonstration of clinical benefit. For drugs approved under accelerated approval, the FDA may withdraw approval for the failure of a post-marketing study to verify clinical benefit. I should note that there were several studies that were included in their Phase IV commitment.

The withdrawal procedure requires a formal hearing whose composition and procedures are defined in the Code of Federal Regulations. This meeting is not that formal hearing.

AstraZeneca notified the United States Food and Drug Administration on December 17th, 2004, that a large randomized study comparing Iressa plus best supportive care to placebo plus best supportive care failed to demonstrate a survival advantage for Iressa in the treatment of

non-small cell lung cancer.

The results will be reported in detail by AstraZeneca during this meeting.

The FDA has not received the complete data set for this trial, especially data that would allow pharmacogenetic or immunohistochemistry subset analysis. The FDA management plan is rapid communication of the above trial results to health care professionals and patients concurrent with the expeditious completion of the trial analysis by AstraZeneca, including the effects of EGFR status determined by immunohistochemistry and EGFR mutational status on survival.

We are interested in reviewing the immunohistochemistry subset analysis since interesting exploratory findings were included in the Tarceva label that was recently approved this year.

The FDA will not make a regulatory decision on Iressa until the data regarding subset analysis and the study results are received and reviewed. In the interim, AstraZeneca has

suspended promotion of Iressa, but will continue to make the drug available to patients who appear to be benefiting from Iressa treatment.

Actions have been taken to communicate the most recent Iressa information to health care professionals and patients.

These are delineated in the preamble to the discussion points and include: AstraZeneca press release of the ISEL study results, Dear Doctor letters notifying physicians of the study results and alternative therapies available, AstraZeneca sales force distribution of Dear Doctor letters, other Dear Doctor letters being posted on the AstraZeneca website, patient advocate groups being notified, AstraZeneca communications to known patients, information being posted on the FDA website, abstracts at meetings, journal placements of the Dear Doctor letters, advertisements on a continuing basis in all issues of the 10 most widely read oncology journals urging physicians to consider options other than Iressa.

A copy of this advertisement is attached

in today's Discussion Points.

AstraZeneca is also tracking total and new Iressa prescriptions every two weeks to ensure that the above communications are resulting in decreased Iressa use.

We are not here today to vote on the ultimate regulatory fate of this drug. We may be bringing this question back to future ODAC meetings after the FDA reviews this study and additional subset analysis.

The purpose of this ODAC meeting is to provide transparency of the process that we have undertaken and to obtain your input on the adequacy of these steps to date to ensure that patients and prescribing physicians are aware of the study results and treatment options other than Iressa while allowing the drug to be available to patients who may be benefiting from it.

Thank you.

DR. MARTINO: Thank you, Dr. Pazdur.

A new member has joined us. Dr. Temple, if you would be so kind as to introduce yourself.

DR. TEMPLE: Good morning. Bob Temple, Office Director.

DR. MARTINO: Thank you. For the

audience, as well as the committee, I want to remind everyone that this morning's purpose is not to decide the fate of this drug, so those of you who are here thinking that that is what we are going to do, please relax, that is not the point.

The point this morning is realizing that there is some new information that needs to be properly disseminated to the public, both the medical public as well as the lay public, has that process taken place and what is that process.

So, those really are the issues before this committee.

At this point, I would like AstraZeneca to approach the podium and introduce your speakers, as well as give us some understanding of what they will be speaking on please.

Sponsor Presentation - AstraZeneca L.P.

Introduction and Regulatory History

DR. SCOTT: Thank you, Dr. Martino.

My name is Mark Scott and I am the U.S. Development Leader for Iressa.

As Dr. Pazdur just mentioned, Iressa was granted an accelerated approval under Subpart H in May of 2003 to treat advanced non-small cell lung cancer after failure of two types of chemotherapy.

Subsequent to Iressa's approval, this committee has discussed in general the terms of the Subpart H approval guidelines and the need for rapid completion by sponsors of their post-marketing trials that are required as part of such an approval.

During these discussions, an important question was raised by ODAC, what should be done if a confirmatory trial does not meet its primary objective. The ODAC discussion at the time acknowledged that there would probably be no quick and easy answer if this situation were to arise.

We are here today because this hypothetical situation is now real and it applies to Iressa. The study we are here to discuss is Trial 709, one of the confirmatory trials for

Iressa which did not achieve statistical significance for its primary endpoint of overall survival.

We will describe for you the actions AstraZeneca has undertaken to communicate the results of Trial 709 to physicians, so that informed decisions can be made regarding the clinical use of Iressa.

Today, we will describe important findings from Trial 709, how the data from Trial 709 is actually quite similar to prior clinical data on Iressa and additional analyses, and clinical trials that are being conducted or planned to better understand which patients are most likely to benefit from Iressa.

We will also outline the timings of availability for data for FDA review, what has occurred and the future direction for Iressa, provide important lessons about drug development, and accelerated approval in the era of targeted oncology therapies.

After I cover a brief regulatory history,

Mr. Kevin Carroll will speak more on Trial 709, then, Dr. Judy Ochs will present the actions AstraZeneca has taken to inform the oncology community and the implications for the development of Iressa. I will then review the timelines that we have to provide data to FDA.

As posed to the committee by FDA, we look forward to hearing the Committee's thoughts on the appropriateness of the communications taken regarding Trial 709.

Today, we have two experts on lung cancer, Howard Burris from Sarah Cannon and Mark Kris from Memorial Sloan- Kettering, and they will be supporting the AstraZeneca staff here to answer any questions the Committee may have.

Lung cancer is the most common cancer and the leading cause of cancer mortality in both men and women with over 170,000 new patients being seen each year in the United States.

The disease is complex, most patients are diagnosed with advanced disease, symptoms are common, and the prognosis is poor.

Standard first line therapy for advanced disease was, and continues to be, platinum-based doublet chemotherapy. Prior to 2003, after failure

of first line therapy, only docetaxel had been demonstrated to improve overall survival. No therapy had been approved for use after failure of both first and second line therapy.

Standard chemotherapies do offer benefits, but with significant toxicity. Therefore, there are many lung cancer patients who cannot tolerate any chemotherapy.

There was a great demand for new, active, less toxic agents for non-small cell lung cancer. Now, Iressa is a small molecule inhibitor of the epidermal growth factor inhibitor tyrosine kinase. EGFR expression plays a role in angiogenesis, apoptosis, proliferation in many tumors. Iressa is thought to mitigate against these factors.

The Iressa Phase I program began in 1998 and doses up to 1,000 mg/day were studied. Among the 289 subjects enrolled, the most common toxicities were low-grade diarrhea and rash, and

the dose-limiting toxicity was reversible Grade 3 diarrhea, and this dose-limiting toxicity occurred at doses beyond 800 mg/day.

Marked anti-tumor activity was seen in non-small cell lung cancer population that participated in the Phase I program, and there were actually 10 of 100 patients where responses were noted, and these responses occurred across the dose range.

Because of the safety findings and the activity findings in Phase I, we chose the doses of 250 and 500 mg/day to be further investigated in the third line monotherapy setting, as well as in first line trials in combination with platinum-based chemotherapy.

I will now focus on the data relevant to the accelerated approval of Iressa.

IDEAL I and II were trials conducted among patients where chemotherapy had failed. Both trials randomized patients between 250 mg and 500 mg of Iressa per day. The primary endpoint in each trial was objective response, the requirement for

response was at least a 50 percent reduction in measurable tumor area, or significant reduction in non-measurable disease, and these decreases needed to persist for at least one month.

Across doses, response rates seen in IDEAL I and IDEAL II were 19 and 10.6 percent. Responses were durable with ranges of 13 months and 7 months for IDEAL I and II respectively.

Also of note was the variability that was seen in response across some subgroups. Higher rates were seen in females, never smokers, those with adenocarcinoma histology, and of those of Asian ethnicity.

As you will see in a few minutes, this same variability in response is suggested for survival, as well, when Trial 709 was further analyzed. There were no differences in efficacy between the two doses, and the survival curves are presented on this slide where we have collapsed IDEAL I and II together and looked at 250 versus 500, and the survival curves were completely overlapping.

As for safety, the most drug-related adverse events were of low grade, while the most common adverse events were rash and diarrhea.

There were a greater number of events at the 500 mg dose. On the basis of these data, the 250 mg dose was chosen on the basis of its efficacy and tolerability as part of our application for accelerated approval as a monotherapy in refractory disease.

As Dr. Pazdur mentioned, Iressa was the subject of the ODAC in September of 2002. These response rate and safety data were reviewed, and the committee voted in favor of accelerated approval.

The FDA granted accelerated approval in May of 2003 in patients refractory to both docetaxel and a platinum-containing regimen. The post-approval commitment trial started in July of 2003.

We agreed to conduct and analyze and report on three additional clinical trials, to examine the effects of Iressa as a monotherapy in

patient with advanced non-small cell lung cancer where chemotherapy had failed.

These included Trial 709 where an improvement in survival was sought, and the preliminary results will be the focus of Mr. Carroll's presentation today.

Trial 721 examines whether the survival seen with Iressa is not inferior to survival seen with docetaxel. There is a planned interim analysis of this trial with complete data for this to be available in June of this year, and with survival data from this trial available in November of next year. The results from this trial can confirm the effectiveness of Iressa.

Trial 710, the third Subpart H commitment, was a placebo-controlled trial where an improvement in symptoms was sought. However, the early availability of results from Trial 709 in December of last year compromised the ability to recruit patients.

As a consequence, the independent Data Safety Monitoring Committee recommended that

further recruitment was not justified because the trial was unlikely to be completed. In agreement with FDA, this trial was stopped in September of last year.

Two other trials featured as additional commitments that were not linked to the accelerated approval, we were asked to provide reports on the SWOG 0023 and BR19 trials.

These placebo-controlled trials seek to demonstrate a survival improvement for Iressa after definitive therapy in two settings of non-small cell lung cancer. Both trials continue to recruit.

In summary, there were three Subpart H confirmatory trials and two additional trials. One has been closed, three are ongoing, and I will like to ask Mr. Kevin Carroll, the statistician for Iressa, to come and share with you the fifth trial, Trial 709.

Trial 709

MR. CARROLL: Thank you, Mark.

Today, I will be presenting to you preliminary data from Trial 709, which is a large

randomized Phase III trial comparing Iressa to placebo in advanced chemotherapy-failed non-small cell lung cancer.

The data I will be sharing with you today are as we saw them for the first time on December 16, 2004, and so are consistent with the materials in your briefing document.

Since then, the data have been further validated, in fact, were finalized on the 2nd of February 2005. There have been few changes to these data and none that materially affect the results I will be showing you today.

In Trial 709, 1,692 patients were randomized to Iressa or placebo on a 2 to 1 basis in 210 centers across 28 countries. In light of the approval of Iressa in the U.S.A. in May 2003, no U.S. sites were included in this trial, as randomization to placebo was considered infeasible.

Further, to ensure balance between the treatments at baseline, the randomization was stratified for histology, gender, reason for failure to prior chemotherapy, and smoking history.

In terms of key eligibility criteria, the patients randomized into Trial 709 had advanced non-small cell lung cancer and had failed 1 to 2

prior chemotherapy regimens.

Furthermore, the patient population entered into Trial 709 was highly refractory since the patients had either to be intolerant to their most recent chemotherapy or had to have progressed on or within 90 days of their last chemotherapy cycle.

In Trial 709, as has been said, the primary endpoint was overall survival. As stated in the protocol, the primary analysis method was a stratified log-rank test. As is common in oncology trials, the protocol also stated that a supportive Cox regression analysis would be conducted.

There were 2 co-primary populations for analysis, the overall population and a subset of patients with adenocarcinoma histology. At least 900 deaths were required overall to provide 90 percent power.

The secondary endpoints are listed on this

slide, being time to treatment failure, objective response, quality of life, symptoms, and safety.

Several subgroup analyses were pre-planned with the aim being to examine outcomes in relation to important clinical and biologic factors, such as EGFR expression and EGFR mutations, and my colleague, Dr. Ochs, will say more about this later in our presentation.

The data I will be presenting today are all those that accrued up to and including the end of October 2004. This date was chosen because it was estimated by this time the 900 deaths we needed for analysis would have occurred on the database.

So, following data collection, preliminary data became available for the first time in mid-December 2004. At this time, median follow up was 7 months, and we knew of 969 patient deaths.

As can be seen on this slide, patients in Trial 709 were recruited mainly from Central and Eastern Europe and then Asia. As I mentioned before, there were no U.S. sites in Trial 709, and due to the approval of Iressa in December 2003,

only 1 percent of patients were recruited in Canada.

This slide shows the baseline characteristics of the patients in Trial 709. The median age was 62 years, about two-thirds were male, one-fifth were never smokers, one-fifth were of Asian descent, about half had adenocarcinoma histology, and about half had received one prior chemotherapy.

In line with our intent to recruit a highly refractory patient population, 90 percent of the patients in 709 had progressed on or within 90 days of their most recent chemotherapy. Finally, as you would expect in a large randomized clinical trial, the treatment groups were well balanced at baseline.

I would like to move on now to look at survival in the overall population. As you can see, there was some improvement in overall survival in Iressa-treated patients with the Kaplan-Meier curves separating after about 4 months. However, the magnitude of that improvement was not

sufficient to reach statistical significance in the primary stratified log-rank test, however, the supportive Cox regression analysis did suggest statistical significance.

Here are the survival curves for the co-primary population of patients with adenocarcinoma histology. Again, there was some improvement in overall survival in Iressa-treated patients, but the magnitude of that improvement was not sufficient to reach statistical significance on the primary stratified log-rank test.

Again, here, the supportive Cox regression analysis did suggest statistical significance.

Moving on now to secondary endpoint data, tumor shrinkage in terms of response rates was significantly greater in Iressa-treated patients compared to placebo.

In terms of the time to treatment failure being the time from randomization to the first event that led to the cessation of randomized treatment, there was a statistically significant difference between the treatments with the risk of

treatment failure being 18 percent lower in Iressa-treated patients compared to placebo.

The reasons for treatment failure are shown on this slide. As can be seen, the primary driver for treatment failure was progression be it either symptomatic or radiographic, with approximately 56 percent progressing on Iressa compared to 70 percent progressing on placebo.

As you would expect, Iressa failed more often due to adverse events than placebo, and Other on this slide refers to a number of items including lost to follow-up, noncompliance, and withdrawal of consent. As you can see, there was no difference between the two treatments in this regard.

Turning now to quality-of-life data, the analyses of these data is currently ongoing, but I can share with you some initial results. As you can see, the primary quality of life endpoints being symptoms, overall quality of life, and trial outcome index, all tended to favor Iressa-treated patients although the treatment differences were relatively small.

As I mentioned before, several subgroup analyses were pre-planned. Now, before I run through these data with you, it is important to

emphasize that these analyses are not retrospective, nor are they data driven.

The subsets were identified in advance based on what we saw in our Phase II trials and based upon findings on other drugs in the same class.

Furthermore, in analyzing these subsets, we have applied a rigorous statistical approach whereby we looked first for evidence of a subset by treatment interaction to give us confidence that the subsets are truly behaving differently, and if evidence exists, then, we go on to look at detail at the subsets.

It is important to recognize that this is a harder test to pass than simply having a list of subsets and looking for p less than 0.05. So, if we do see differences in Trial 709, we can be reasonably confident that they are more likely due to a real drug effect than due to chance alone.

This is the first of two slides that show subset analyses. For each subset analyzed, you can see the hazard ratio and its confidence limits and the response rate in Iressa-treated patients.

As you will recall, the hazard ratio measures the risk of death on Iressa-treated

patients to placebo-treated patients, and therefore, a hazard ratio of less than 1 to the left of the vertical line shows a treatment effect in favor of Iressa, and a hazard ratio to the right of the vertical line shows a treatment effect in favor of placebo.

So, now while no subgroup favored placebo, there was clearly some variability in survival outcome. This was most marked in terms of smoking history where outcomes in never smokers was statistically different than outcomes in ever smokers.

This is the second slide showing data in subsets, the same format as the previous slide. Again, you can see there was variability in outcomes with, in this instance, it being most

marked in terms of ethnicity where patients of Asian ethnic origin have statistically different outcomes to patients of non-Asian ethnic origin.

Now, while the credibility of subset analyses is always a matter of debate in any clinical trial, in 709, the rigorous approach we have taken provides us with confidence that the differences we have seen are most likely due to a real effect of the drug, and less likely due to chance.

So, the findings we have seen in Asians and on smokers are therefore supported statistically by the presence of subset by treatment interactions and also clinically by prior Phase II data that have consistently shown increased response rates in these populations.

Furthermore, Trial 709 is internally consistent with respect to these subsets, with better time to treatment failure and a two-fold improvement in quality of life in Iressa-treated patients.

This slide shows survival curves for never

and ever smokers. As you can see, there was a 33 percent reduction in the risk of death in never smoking patients treated with Iressa compared to placebo. There was no significant difference in ever smokers.

Similarly, this slide shows survival curves by ethnic origin. Again, you can see there was a 34 percent reduction in the risk of death in Asian patients treated with Iressa compared to placebo, and there was no significant difference in non-Asian patients.

I would like to move on now to look briefly at the safety data in Trial 709. I should note these data have become available since we compiled the briefing document, so they won't be in your papers.

The adverse event profile in Trial 709 is consistent with the established safety profile for Iressa with the most common adverse events being rash and diarrhea.

Notably, there was little difference between the treatments in terms of serious adverse

events, adverse events leading to withdrawal, and the incidence of interstitial lung disease.

Here is a summary of the most common adverse events in the trial ordered from highest to lowest frequency in Iressa-treated subjects.

As you can see, with the exception of rash and diarrhea, which I just mentioned, there is little difference between Iressa and placebo-treated patients in terms of the adverse event reporting. In particular, there were relatively few Grade 3/4 adverse events in Iressa-treated subjects.

This list of adverse events continues on this slide where again it can be seen there is little difference between Iressa and placebo-treated subjects.

As I mentioned at the outset, the preliminary data we saw on December 16th were validated and finalized as of the 2nd of February 2005. These final data confirmed a total of 976 deaths occurring on or before the October 2004 data cutoff. With only 7 additional deaths, it is

obviously not surprising that the findings based on the preliminary data remain unchanged.

On reviewing the data in December, the Independent Data Monitoring Committee recommended that further follow-up of Trial 709 should be obtained. Having seen somewhat late separation in the Kaplan-Meier curve, they were unwilling to rule out that further separation could occur with more follow-up.

Hence, survival data were updated as of the end of January, which provided for a further 3 months of follow-up, taking median follow-up to 10 months and overall mortality in the trial to 70 percent.

As you can see, these further data are consistent with the planned protocol analysis, and despite increased crossover in the placebo arm to Iressa, variability in survival outcomes continues to be seen.

To briefly summarize what we have shared today, the data seen on December 16 showed some improvement in survival in Iressa-treated patients,

but the magnitude of that improvement was not sufficient to reach statistical significance in the primary stratified log-rank test.

Overall, however, considering both primary and secondary endpoints, these data showed that Iressa was efficacious in the population study, but there was marked variability in survival outcomes.

So, with that, I would like to thank you for your attention and hand over to my colleague, Dr. Ochs. Judy.

Clinical Actions and Implications

DR. OCHS: Thank you, Kevin.

In this part of our presentation, I would like to briefly summarize AstraZeneca's actions to communicate the results of Trial 709 to the oncology community. Following this, I would like to give an overview of the clinical implications of the Trial 709 data, review some of the immediately relevant emerging science, and conclude with our proposed or ongoing development proposals.

In agreement with the FDA, AstraZeneca concluded that it was in the best interest of

patients that the information on Trial 709 be rapidly, extensively, and clearly communicated.

On December 17th, a Dear Doctor letter approved by the FDA was distributed by AstraZeneca. This communication provided physicians with the needed information to enable them to make the most appropriate treatment decisions. The expectation was that this communication would greatly reduce the number of patients receiving Iressa for the first time.

In addition, AstraZeneca would provide to the FDA, prescription data every two weeks to be able to assess the continuing impact of the communications.

It was also agreed that a key goal was to maintain Iressa availability to those patients already benefiting who would wish to continue and had concerns about possible Iressa availability.

A commitment was given to the FDA that AstraZeneca would rapidly provide them with all of the data as it became available to allow them a thorough and informed analysis.

Upon public release of the top line Trial 709 survival results a series of extensive communications were simultaneously begun and are

listed on this slide, and were previously mentioned by Dr. Pazdur.

Taken as a whole these actions were designed to ensure that relevant physicians would be aware of the results and be reminded that alternative therapeutic options with proven survival benefits should be considered.

On January 6, the FDA and AstraZeneca met and agreed upon the following steps for continuing communication of the Trial 709 data. A public disclosure of the then available results would be made at the first available scheduled ODAC meeting, today, acknowledging that the further trial data would still be pending.

Ongoing communication of the Dear Doctor letter was to be done using journal placement and the full clinical data would be submitted and presented at scientific meetings and published in refereed scientific journals as soon as possible.

Abstracts have been submitted to the AACR meeting, as well as the World Lung Cancer Conference. A full publication submission is planed in the May-June time frame.

Here is a copy of the Dear Doctor letter, which I realize you cannot read. The letter,

however, does include the survival results in the overall and adenocarcinoma subpopulation along with median survival and respective hazard ratios.

The sentence highlighted in red above is included in the body of the letter and urges physicians to consider other treatment options. This is how the letter is being displayed in the 10 most widely read oncology journals, and a list of these journals is shown in the next slide.

The impact on Iressa usage has been marked in the 10 weeks since the Dear Doctor letter was first sent out. There has already been a significant reduction in the prescriptions written for Iressa, and our internal AZ usage data also indicates marked reduction.

Market research, that we have just

obtained from 100 community oncologists, indicates that the great majority are aware of the data contained in the Dear Doctor letter and have modified their treatment practice accordingly.

Thus, all of the agreed upon communication actions have been set in motion, and the available information suggests that the oncology community is aware of and acting on the information.

The larger question is now being asked: What are the clinical implications of the Trial 709 data, and what are the next steps? These are clearly important questions for oncologists and patients since Iressa possesses significant durable anti-tumor activity which has greatly benefited some patients and some patient subsets.

Yet, in Trial 709, Iressa did not meet the statistically defined survival endpoint in an unselected patient population.

Advances in understanding of the molecular biology in this area of EGFR inhibition, as well as in the area of non-small cell lung cancer, are occurring rapidly and have the potential to better

select or predict those patients who would benefit beyond, or in addition to, clinical characteristics.

What are the questions that we are asking as we seek to understand the Trial 709 outcomes, and not wrongly or prematurely make conclusions about the actual role or place of Iressa, an agent with anti-tumor activity in the treatment of a disease with a continuing poor prognosis? Why did this result occur?

How does this result compare with our other data on Iressa in non-small cell? Were the findings in our trial due to play of chance? Was the dose selection appropriate? Were there methodologic issues, such as the trial population and where the trial was conducted of any potential impact on the findings?

What biologic data may be available now and in the future to help better understand the clinical outcomes, and what further relevant clinical data in the recurrent non-small cell lung cancer setting are expected?

Firstly, how does the survival outcome seen in Trial 709 compare to other data with Iressa? As was previously mentioned by Dr. Scott

in our Phase II program, a striking and unanticipated finding was the apparent high rate of response in patients with certain clinical characteristics.

It can be seen if one compares these Phase II response rates with those in Trial 709, and the Phase II results are in the right-hand column in yellow, and the 709 results in the middle column in white, that the same patient groups continued to show higher response rates.

In addition to these higher response rates, the subgroups having the highest response rates experienced the greatest benefit in survival. The patient subgroup with the highest response rate were the never smokers, and as previously noted, the survival in this subgroup was significantly increased.

Similar trend, although not of the same magnitude, of survival benefit was seen in women

and with the adenocarcinoma group.

Continuing with this line of inquiry, higher response rates and statistically significant survival results and benefit were seen in those patients of Asian descent.

Could chance have played a role as the defined survival endpoint was so narrowly missed? Trial 709 and the erlotinib trial BR21 are the only two Phase III survival trials which compare an oral EGFR inhibitor with placebo in the recurrent non-small cell lung cancer patient population.

Both Iressa and erlotinib have similar overall response rates as can be seen in the right-hand portion of the slide. The erlotinib trial did reach statistical significance for the overall population.

Juxtaposing overall survival hazard ratios as we have done in this slide shows that while the point estimates differ, there is a high degree of overlap in the confidence intervals. The small confidence interval in Trial 709 reflects the larger trial size in 709, which is almost twice

that of the BR21 trial.

Dose selection. Since there appears to be a difference in magnitude of survival benefit in BR21 compared to Trial 709, questions about the adequacy of the Iressa dose have arisen irrespective of the data used to support its use in this trial.

The erlotinib dose used was at the maximal tolerated dose, while the Iressa dose is one-third the maximal tolerated dose, reflecting different development strategies.

As you might guess, we have gone back and re-evaluated our prior experience in light of the current data. Our extensive Phase I program had 280 patients, and these patients received doses ranging from 50 mg to 1,000 mg.

Responses and durable stable disease first were seen at the 150 mg dose level. There was no dose response evident from 150 mg through 1,000 mg with respect to partial response rates, partial response rates plus stable disease rates, or the duration on Iressa therapy.

In our Phase II trials, as previously mentioned, we formally compared the 250 and 500 mg dosage. 250 mg was chosen as it was above the 150

minimum dose that we saw responses and stable disease at, and 500 mg dose was chosen in part because of minimizing the amount of patient interruptions of therapy due to toxicity.

We found no difference in efficacy including survival although the adverse events and therapy interruptions were more frequent at the higher 500 mg dose.

Admittedly, however, we have not rigorously evaluated doses above 500 mg, and it is unknown if doses above 500 mg would achieve better overall or patient subset survival outcomes. Due to the lack of data, we cannot rule this out entirely.

Speculatively, can the inability to achieve statistically significant survival be explained by too few patients likely to benefit based on their advanced disease status with refractoriness as specified in our patient

inclusion criteria.

Another area to further explore are the impact of environmental factors, such as smoking, as it relates to various geographic regions where the trial was conducted.

As Mr. Carroll showed, over one-third of the patients on Trial 709 were from Eastern Europe where the median pack year exposure was very high. Patients with the highest smoking exposure appear less likely to benefit from EGFR inhibitor therapy.

We have looked at our data and found a continuous spectrum in terms of survival benefit, with the greatest survival benefit appearing in never smokings, but it continues with the amount of exposure to smoke.

So, what can we conclude at this point? Iressa is an active agent, the response data are consistent in our Phase II and III trials. The patients most likely to benefit are those patients who never smoked and those of Asian ethnicity.

With these consistent findings, using an agent that inhibits a specific receptor and

pathway, it is logical to assume that there is an underlying biologic basis. In the last 10 months, two areas of translational research have been fruitful and may be useful in better understanding the clinical data in our Phase III program in Trial 709, as well as guide therapy in our future development.

The two biomarkers of most promise currently are EGFR expression and the EGFR mutations. Published Iressa Phase II data did not appear to show definitive correlation of EGFR expression with response, but tumor samples were not available from all patients, and the trials were not controlled.

Recently, however, results relating EGFR expression to survival outcomes were included in the erlotinib label.

The second promising biomarker are activating mutations. These were first described approximately 10 months ago in responding Iressa patients. There are other promising, but more exploratory biomarkers that are included in the

Iressa science program including gene copy number and dimerization patients, but again these remain more exploratory.

What I would like to do now is show you from the erlotinib label--and I have included the three graphs they have relating to EGFR expression--and to ensure perfect synchronicity and accuracy, I am going to read the portion for you for all of those of you who can't read the lower right-hand column.

What we see here are three graphs. The graph to the upper far left is the graph of the patients who had positive EGFR expression in their tumors, with the lower part of the Kaplan-Meier showing the patients treated with placebo.

The graph to your far right, on the upperhand side is the patients who were EGFR expression-negative compared to placebo. The lower lefthand is those patients that they did not have EGFR expression data on.

As stated in the label, Tarceva prolonged survival in the EGFR-positive subgroup and the

subgroup whose EGFR status was unmeasured, but did not appear to have an effect on survival in the EGFR-negative subgroup. However, the confidence intervals for the EGFR-positive, negative, and unmeasured subgroups are wide and overlap, so that a survival benefit due to Tarceva in the EGFR-negative subgroup cannot be excluded.

It needs to be said that a positive EGFR expression status in this study was defined as having at least 10 percent of cells staining positive for EGFR in contrast to the 1 percent cutoff specified in the DAKO EGFR pharmDx kit instructions.

The use of the pharmDx kit has not been validated for use in non-small cell. Accordingly, the data to date are inconclusive, but tantalizing as to the predictive nature of EGFR testing.

In this trial, as in Trial 709, the tumor sample collection was not mandatory, and thus the number of samples is less than the number of enrolled patients.

This is a busy slide and summarizes a very

busy area of research in the 10 months since mutations were first described. As noted on this slide, mutation appears to occur almost exclusively in non-small cell lung cancer. The mutation is activating and in the ATP-binding site, which is where Iressa's activity occurs.

I mentioned that the mutation was first described in patients with rapid, dramatic and prolonged responses to Iressa. The increased frequency of the mutation occurs in patient subsets where Iressa responses are most frequent and where the survival benefit is most likely to be seen, that is, those patients who were never smokers, patients of Asian descent, women, and adenocarcinoma histology.

There are actually two papers out this week looking at smoking status in relationship to the presence of these activating mutations, and depending on the paper, a minimum of 25 percent to 75 percent of patients in different geographic regions who were never smokers have the mutation present.

While patients whose tumors possess this type of somatic mutation appeared to be much more likely to have a response, all patients with

mutations do not have a response. We have recently looked at our IDEAL II data, and in the small subset with 14 mutations that we detected, 6 of these patients had prolonged partial responses.

Again, where are we? EGFR expression appears to be associated with increased survival. EGFR mutations appear to explain some, but not all, of the responses to Iressa.

Outcomes in Trial 709, comparing Iressa to placebo, will be explored in terms of EGFR expression, activating mutation, and other biomarkers.

We anticipate that this data will be available in June 2005. We have collected close to 600 tumor samples. Approximately 400 of them we estimated based on our past experience will be fully evaluable for EGFR expression, and 200 for mutation status.

It is hoped that these results may provide

further insight into the clinical outcomes that we have seen in Trial 709.

Thus, with these current clinical and translational data, what prospective studies are underway or could be considered?

One proposal would be to evaluate patients with metastatic disease and compare the outcomes of Iressa with chemotherapy. Mandatory tissue collection is an obvious requirement to evaluate the utility of biomarkers with respect to both outcomes in both the chemotherapy-treated patients and in patients with EGFR expression or overexpression.

Targeted studies in patient populations is another obvious way to proceed. We have an ongoing Phase II trial which is enrolling patients who are mutation-positive, another trial that is a trial that should be considered is that in patients who are never smokers.

Never smokers represent 20 percent of the U.S. population of non-small cell lung cancer patients.

Finally, specific trials in the Asian populations to define the role of Iressa in the first line setting appear warranted. Here, too,

translational studies would be integral to the trial. There are already several trials being conducted in Asia, as you might anticipate.

A clinical question of increasing relevance that hasn't been answered to date is that of comparing both survival outcome and toxicities of Iressa or any EGFR inhibitor with single agent chemotherapy.

Trial 721, as previously noted by Dr. Scott, is a randomized Phase III post-approval commitment trial which compares Iressa to docetaxel. This trial will complete patient enrollment by the end of the summer, and an interim survival analysis is expected this May or June.

Trial 721's principal investigators and steering committees have reviewed the Trial 709 data and continue to support this trial. Another similar trial is being conducted entirely in Japan.

Some clinical support to continue at this

dose is mature Phase II data in a Caucasian and Hispanic patient population, which has recently matured and become available. In addition to showing comparability with the primary symptom endpoint, comparable outcomes were seen with response rates, time to progression, and overall survival.

The next slide is a Kaplan-Meier survival curve from this trial, and it is easy to see the comparability of these trial results. With a median follow-up of 9 months and 55 percent overall mortality, there are no differences between Iressa and docetaxel.

The overall survival with docetaxel is consistent with that previously reported with this agent and in this clinical setting. Although the trial is small, if Iressa was behaving as a placebo, then, one would have expected Iressa to have performed substantially worse in both time to progression, as well as overall survival.

Back to our original question: Where are we now?

Well tolerated agents in the EGFR inhibitor class of agents are now an accepted addition to the therapeutic armamentarium of

practicing oncologists and clinical trial investigators.

Clinical and translational data are pointing the way to the most appropriate and optimal use of Iressa. AstraZeneca and our clinical investigators remain committed to this and other biologically targeted agents as the way to the future.

Thank you.

DR. PAZDUR: Silvana, I am sorry, I didn't realize there was more from AstraZeneca, but if we want to have some discussion or clarification before the open public hearing, that would be appropriate.

Summary

DR. SCOTT: Thank you, Dr. Ochs.

As you have heard from both Mr. Carroll and Dr. Ochs, there is a lot of work ongoing to fully understand Trial 709, and there are other

trials, such as Trial 503, that provide supportive information, and Trial 721, which is also part of our Subpart H commitment to the FDA.

This slide summarizes some key milestones that will be occurring. It is expected that the complete data from Trial 709 and Trial 503 will be with the FDA in June for their review. After that time, we expect to discuss labeling updates as appropriate based on the final data findings.

It is expected that the Subpart H commitment trial, Trial 721, will deliver its final survival data in November of 2006.

While the drug development road for Iressa has not been straightforward or without its surprises, the development program for this agent has provided a great deal of valuable information about non-small cell lung cancer and the EGFR target.

Iressa is an active and well tolerated agent, and the lung cancer community has urged us to continue the development of this drug, and we are committed to doing so.

Trial 709 has provided important patient selection information in a controlled randomized setting that may in the future help us write

appropriate labeling to guide the clinical use of Iressa.

You have also heard today the critical information regarding EGFR expression and mutation status is yet to be delivered from this trial.

Trial 721, the head-to-head trial versus docetaxel can provide confirmatory evidence of the effectiveness of Iressa. As outlined, the development program for Iressa will help in identifying those patients who are most likely to benefit from Iressa.

AstraZeneca rapidly and thoroughly disseminated information to oncologists about Trial 709 to ensure informed treatment decisions would be made while further analysis were underway.

As the patients responsive to Iressa will tell us, and their physicians will support, Iressa remains an important treatment option for non-small cell lung cancer.

We thank the committee for their attention and welcome any questions at this time.

Committee Questions

DR. MARTINO: Dr. Ochs, do one thing for me before you leave. A slide was shown by--Dr. Ochs actually had the slide up--where you

demonstrated what has been done to disseminate this information, if you would just flash that one more time.

I will allow the committee to ask questions. We actually have no time allotted for that, so please keep your questions pertinent to today's issue, which really is has this information been appropriately disseminated.

The slide that I want you all to just notice are the things that they have, in fact, done to disseminate this information. Rick, can you simultaneously just remind the group what the FDA has done from its side in terms of disseminating the information, so that everyone is sort of up to date.

DR. PAZDUR: We have notified shortly when

we were in receipt of this information, an e-mail went out from the FDA to ASCO members notifying them on that day that we received the information of the study results and alternative treatment.

We have a letter posted on our website that is included in your packet.

DR. MARTINO: So, then, from the FDA's side, the information has gone out to physicians primarily, as well as the website.

DR. PAZDUR: Correct.

DR. MARTINO: And from AstraZeneca, information has been provided to physicians, as well as to the lay public.

DR. OCHS: Yes.

DR. MARTINO: At this point, I will take some questions, but please keep them brief and succinct.

Dr. Hussain, you are first.

DR. HUSSAIN: It is a question to either Dr. Mark or Dr. Ochs. When you pointed out that you are possibly thinking about targeted population, I saw that there were no women

mentioned and no adenocarcinoma.

Does that mean if you were a smoker and a woman, that the smoker component takes over as far as your potential benefit, or that if you are an Asian and a smoker, then, the smoker takes over?

DR. OCHS: I think I will let Dr. Carroll discuss that particular issue since there is a lot of interconnection and interplay.

MR. CARROLL: Thank you for your question. Of course, it is very important, I mean it is one that we need to look at more closely, what is the interplay between the factors of interest, be they Asians, be adenocarcinoma, gender.

The data, as I said, were finalized only--I am not sure--four or so weeks ago, and that kind of analysis requires multivariate analysis to actually see which factors are contributing, which are the ones that are predicting the treatment effect.

That is something that we do plan to do in the next coming weeks and months to provide that data to the FDA, so we can answer the very

important question that you have raised, because I am not sure we have the answer to that today.

DR. MARTINO: Dr. Perry.

DR. PERRY: I am not sure who gets this question, but I have been under the impression that in Europe particularly, the incidence of squamous cell carcinoma was considerably higher than in the United States, so I am somewhat surprised of a 48 percent incidence of adenocarcinoma histology worldwide, particularly when two-thirds of the patients seem to be from Europe.

How do you know that these are adenocarcinomas, is this the local pathologist's interpretation, and are they inclined to overread them as adenocarcinomas rather than as non-small cell carcinomas not otherwise specified?

DR. SCOTT: I will ask Dr. Alan Barge to come and speak to that point.

DR. BARGE: Thank you. Alan Barge, AstraZeneca.

We have not done central pathology review. All of the diagnoses were the ones that were

confirmed by the hospital pathologists, so we couldn't answer your question directly, I am afraid.

DR. MARTINO: Dr. Rodriguez.

DR. RODRIGUEZ: I just wanted some clarification about the actual trial design, and just have a few questions which might be relevant because this was done by a variety of cultural groups.

Were the patients and the investigators both blinded to the assignment to placebo?

DR. SCOTT: Yes, it was a randomized double-blind trial.

DR. RODRIGUEZ: How was compliance confirmed in the participants?

DR. SCOTT: Nick Botwood will come to the stand.

DR. BOTWOOD: Thank you. Nick Botwood, AstraZeneca. We did look at compliance on this trial and found that over 90 percent of the patients were compliant and had taken at least 95 percent of their medication.

This was based primarily on data that we collected in the CRF in terms of any documented dose interruptions for whatever reason, and then we

went on to further validate that, to actually look at the number of tablets that were returned and looked at the number of tablets that had actually been prescribed to validate that what was in the CRF was actually the correct information.

DR. RODRIGUEZ: Along those lines, was there a required or concurrent diarrhea prophylaxis program, and was compliance to that also monitored?

DR. BOTWOOD: That wasn't, no.

DR. RODRIGUEZ: It is interesting because your failure to treatment has a significantly different profile with regards to symptoms and adverse events. It seems that the patients on the Iressa arm, a higher proportion were taken off study because of those problems, is that correct? That is what your bar graph seemed to show.

DR. BOTWOOD: Kevin Carroll can answer that question, please.

MR. CARROLL: If I am correct, you are

asking whether there was a difference in withdrawal due to--

DR. RODRIGUEZ: Yes, side effects.

MR. CARROLL: Side effects. As I showed when we went through the adverse event data, there was very little difference between the two treatments in terms of withdrawal due to adverse events, and in terms of the data that we obtained on time to treatment failure, there were, in fact, fewer--Iressa failed fewer patients due to progression than placebo, so I don't think the difference was there in the way that perhaps you think.

DR. MARTINO: Dr. Levine.

DR. LEVINE: I also have several questions. First, you mentioned crossover. How many of these placebo patients did cross over to Iressa?

DR. SCOTT: Dr. Botwood.

DR. BOTWOOD: Yes, thank you. The rate of crossover from placebo to Iressa in this trial was only 3 percent.

DR. LEVINE: Three. Do you have data on other treatment beyond, you know, crossover to anything?

DR. BOTWOOD: Yes, we do. The number of patients that went on to receive any subsequent chemotherapy was 10 percent, and this was balanced between the Iressa and placebo arm.

DR. LEVINE: Just to further that a little bit, even complementary therapies in Asia, and so forth, do you have data on that, green tea?

DR. BOTWOOD: It was extremely small.

DR. LEVINE: My other question related to the concept of secondary smoke. In Eastern Europe and in Asia, where so many of the population smoke, even individuals who say that they weren't smokers may have been exposed, and therefore, did you look at cotinine levels or anything? That might be something to explore, or did you look at that?

DR. BARGE: I am afraid we haven't looked at that. When we looked at the smoking demography of the patients from Eastern Europe, approximately 85 percent of the patients from Eastern Europe were

heavy smokers, and they had a higher median year exposure than the patients from other regions, but that is as far as we got, I am afraid.

DR. MARTINO: Dr. D'Agostino?

DR. D'AGOSTINO: Yes. I am having a hard time keeping my questions solely to the material that has been circulated as opposed to asking a million questions about the study, but the question I do have in terms of the reporting of the data, you may have said it, and I am sorry if I missed it, you did have the expected number of deaths, you wanted 690 or whatever, 960, and you got more.

I understand that the study did run its course, and then you did an analysis with unclean data or not completely clean data, and then later on had clean data, or was the analysis you are reporting an interim analysis?

DR. SCOTT: The analysis that we reported on in December was not an interim analysis. It was based on final survival data, but it had been yet to be validated.

DR. D'AGOSTINO: Okay. So, it was the

validation. Thank you.

DR. MARTINO: Dr. Proschan.

DR. PROSCHAN: You mentioned that the Phase II trials identified subgroups, and ethnicity was one of them. I am wondering if, at that time, you specifically decided to break it into Asian versus non-Asian, and why do you think there is a difference?

DR. SCOTT: We can have Mr. Carroll talk about the rationale behind the subgroups that we planned for Trial 709, and then perhaps have Alan Barge talk about why we think so.

MR. CARROLL: The subsets that we have looked at in Trial 709, all of them we have shared with you today, I have not shared a subset of the subsets, of course, and they were determined primarily by what we saw in our Phase II data, and also information that came out in June of this year on the BR21 trial, as described by Dr. Ochs.

There, there was an evaluation of Asians and non-Asians, and that, in addition to our findings in the IDEAL trials where our Japanese

patients had a much higher response rate was a motivation to look at that subset amongst others that were deemed to be clinically relevant.

Perhaps I can now turn to my colleague, Dr. Barge, to answer the second part of your question.

DR. BARGE: Yes, thank you. There is a good deal of speculation as to why patients of Asian ethnic origin appear to do better on this class of drug. There have been some quite interesting publications very recently. In fact, this week there was a publication from Dr. Gazda [ph] at UT-Southwestern. His group showed that the frequency of activating mutations of the kind that Dr. Ochs described is much higher in Asian populations, particularly female Asians, and particularly female Asians with adenocarcinoma.

The Phase II studies that we conducted in various Asian countries all show that the frequency of responses are much higher in those populations, and we have seen response rates as high as 60 or even 80 percent in selected populations of Asian

nonsmoking females.

Whether or not that is all driven by activating mutations we don't know, but that is certainly a very strong hypothesis at the moment.

DR. MARTINO: Mrs. Ross.

MRS. ROSS: Thank you, Madam Chair.

If I understand correctly, the primary purpose of this hearing is to evaluate or just to discuss the transparency of the post-approval process and the adequacy of the notifications.

In that regard, I would like to advise the rest of the panel of other steps that were indeed taken by both AstraZeneca and the FDA, and I would like to thank Dr. Pazdur in particular for his help on this.

As the only lung cancer advocacy organization nationwide, we started receiving many phone calls from patients who were somewhat panicked when they heard the news in the press that Iressa might be pulled. The press always leaps to the worst possible conclusion, as you all know.

These people were discussing stockpiling

drugs, buying them in Japan. There was a lot of panic out there. Dr. Pazdur responded, and AstraZeneca did, by helping us draft more information, more plain English information to put up on our website and to tell people over the phone when they called in a state of panic about Iressa.

I think that should be noted. I think that overall, the process was extraordinarily transparent and more than adequate in dealing with the situation. Again, I would just like to thank FDA and AstraZeneca for all they did.

DR. MARTINO: Dr. Temple, did you want to make a comment?

DR. TEMPLE: Just one question. We certainly never at any time thought that someone who had apparently responded to the drug should lose access to it. That was never in doubt.

But I wanted to ask you about where AstraZeneca is at the moment. This was, shall we say, an optimistic presentation. The study, after all, failed. You had opportunities to identify subsets before the study that would be your primary

analysis, but you didn't think that they were good enough to do that.

So, these are now--it's an important distinction, Ralph may want to comment more--these are after-the-fact subset analyses in a study that did not win. That is different from subset analyses in a study that did win.

But what I really want to know is where do you come out on the question of new patients with non-small cell lung cancer being started on Iressa now. The material you put out says you should consider other drugs. Fine.

But would it be your view that at the present time, optimism about the future and data that might come forward notwithstanding, a person with this disease should really not be started on Iressa, would that be your view, or is that not your view anymore?

DR. SCOTT: Our view is that what was stated in the Dear Doctor letter then is what is today, that physicians should consider other options armed with the information from this

particular trial.

If I could ask Dr. Kris to come up and talk about how this has played out in his practice, maybe Dr. Burris, as well.

DR. KRIS: To answer your question, Dr. Temple, I think the most important thing is to put this into a context of what is available for a patient with advanced non-small cell lung cancer particularly after the failure of initial therapy.

I think that the information that we have today is that there are some patients, those with an EGFR mutation, that have, and the literature today says that they have an 89 percent chance of having a response, and in those patients, when you look at their duration of response and survival, it is clearly prolonged. In the trials that looked at survival in mutation positive and negative people being treated, it is much better with treatment.

So, as a clinician, my first point is to find those people that have that extraordinary chance of benefit, that is, mutation-positive people, and the two surrogates for positive

mutation we have today, that is, never smoking status for U.S. population and worldwide, is probably Asian, and it is not simply Japanese. There are reports now from Taiwan, from China, Singapore.

DR. TEMPLE: Let me be clear, though. You are looking at the mutation status of the people in--some of the people anyway, about 200 you said--in the trial, and maybe that will be overwhelming and knock everybody's eyes out.

But at the moment you have no prospective data on that subgroup for survival.

DR. KRIS: The only prospective data that exists on the treatment of mutation-positive patients is, frankly, an extrapolation to the never smoking patients.

DR. TEMPLE: I understand.

DR. KRIS: But those are placebo-controlled trials.

DR. TEMPLE: But what I am really asking is what you really mean, and we will probably have to have subsequent discussions, one might say that

you should use the drug with very similar properties, similar mechanism, et cetera, that has actually been shown to improve survival.

Are you saying something to the contrary or not? I don't think it is clear yet. I sort of thought it was clear, but from your presentation, I don't.

DR. KRIS: Well, I frankly think that the most critical slide there was looking at the hazard ratios for the two substances, for gefitinib and erlotinib. I am putting my clinician hat on, it is not an AstraZeneca hat right now, and that clinician's hat is that there is effect there.

You can argue the p value of 0.04 versus 0.07, and there are people here that can do that much better than I, but from the clinician standpoint, you have to make that choice. But you must remember that this isn't--you also have a patient, you have a man with a squamous cancer sitting in your office that is smoking today, and his likelihood of benefit by the literature is extraordinarily small, well under 5 percent.

So, for that patient, you are going to make another choice, so that the choice for the patient is not going to be decided by this trial as

a clinician.

DR. TEMPLE: I am really asking about what is your view now, is on a person who is a candidate for an EGFR order of treatment now based on available data. I actually thought you thought that for the moment, one should use the drug that actually won, but I no longer perceive that in your presentation.

DR. KRIS: I am talking about from a clinician's standpoint, and I interpret the whole of the data as unbelievably consistent. I mean I think it is extraordinary that when you look at the mutations, when you look at the response rates across country, across drug, it is how consistent it is, particularly the smoking observation.

DR. TEMPLE: The pattern may be the same. It may just be that this drug doesn't work as well as the other one even though the pattern is the same. It is possible.

DR. KRIS: Again, I can't rule out that possibility, but you can't look at any one piece of data in my estimation, and this is one piece of data today.

DR. PAZDUR: But Mark, you pointed out that you may look at the mutational status in

making a decision, but really, in the United States, only a small number of people really have that available to them.

DR. KRIS: Rick, from a practical standpoint, I don't look at the mutation status. We can do that at our institution, but it is a very limited availability right now. The decision is made on clinical grounds, and the surrogates for mutation we have today, and they are two. They are never smoking status and Asian birth, and that is how we make our decision.

DR. PAZDUR: I have another question for AstraZeneca. In your presentation, you noted a decrease in new prescriptions. Could you tell us what you mean by new prescriptions for Iressa, does that mean new patients or simply renewal of

prescriptions of existing patients that are already on it, or can you distinguish between that?

DR. SCOTT: The new prescriptions are not new patients, they are a mixture of patients that are getting a refill of prescriptions, because every time a new script is written, it could be for a patient that didn't have a refill, and it could be for new patients, but I will ask Carolyn Fitzsimons to talk about that data, how we are interpreting it with the availability of other information that is indicative of most--

DR. PAZDUR: Because we are very much interested, following up on Bob's question, how many new patients--

DR. SCOTT: Right, and I will ask Carolyn Fitzsimons to come and speak to that.

MS. FITZSIMONS: Thank you. Carolyn Fitzsimons, AstraZeneca.

If I can just show the slide as to what is happening with the prescription data and try and answer your question, Dr. Pazdur, in terms of specifically new patients.

We have not been able to secure a source to actually define new patients, so we have to take the new prescription data as indicative of what is

happening in the marketplace.

The new prescription data, as Mark has just explained, is not wholly attributed for by new patients. It encompasses every time a new prescription is written, so a repeat prescription.

From the data that we have and is shown here, on the significant decrease that we have seen in new prescriptions, a 58 percent decrease since the announcements of Trial 709.

It is our belief, based upon the duration of therapy of an Iressa patient who is currently receiving the product, that the majority of these prescriptions are now being written for patients who were prescribed Iressa prior to the announcements of Trial 709, and are receiving ongoing therapy from consultations with their physician, therefore, we assume they are deemed to be benefiting.

We have conducted some market research

earlier in February to try and further establish what is happening with new patients, and from that data, we have established that physicians are aware of the Trial 709 results, and are not longer choosing Iressa as their EGFR inhibitor of choice, they are choosing erlotinib, and 86 percent of them indicated that from the market research.

DR. SCOTT: If I could ask Skip Burris to come up and talk about what has happened at Tennessee Oncology. Although it is an n of 1, it is reflective.

DR. BURRIS: Thank you, Mark. It is an n of 1, but it is a large group of 36 practicing oncologists, and it gets to Dr. Temple's questions, and he and Mark were certainly talking about one issue, but we felt the need to issue some guidelines.

Certainly those guidelines were that those patients that were being treated with Iressa, should be continued on Iressa, that those patients who fit into a class where it is felt it appropriate that an EGFR inhibitor should be

utilized, that erlotinib or Tarceva would, in fact, be the preferred agent in the short term, that there should be consideration given based on the data between the two agents, that, in fact, if patients were intolerant of one or the other, to switch to the other in the class. If fact, that has occurred in at least several patients.

Lastly, and maybe most importantly, is the fact that as a conscious decision, analyzing the data within our group, we have continued to accrue and randomize patients on a count done quickly yesterday, 9 patients, in fact, randomized to Iressa in a controlled Phase III trial in patients with refractory lung cancer.

So, the believe of the group, as Mark alluded to, certainly subsets that will benefit, but we have continued to accrue to trials comparing a new agent with Iressa in this setting, so that accounts for some of the new prescriptions written in our group, as well.

While the comment, and I certainly agree with most of what Dr. Temple said, I mean we don't

have a winner here in the sense that there is not randomized data between erlotinib and gefitinib to date, so I think for many of us, the direction of this class is heading into what subsets will benefit, and for now we don't know direct head to head the differences in the two.

Certainly there are small differences in terms of mechanism of action, pharmacology and toxicity.

DR. MARTINO: Mrs. Ross, you will have the last comment, and then I am going to turn to the public forum.

MRS. ROSS: Thank you very much, Madam Chair.

I just had a quick question actually for Dr. Pazdur and Dr. Temple. You are not suggesting, are you, that doctors should not be allowed to write new prescriptions for Iressa?

DR. TEMPLE: Well, no. First of all, we don't control what doctors write, but there isn't any doubt that--I don't know what you mean by a new prescription--a new prescription for Iressa in

someone who is already on the drug and responding to it is not an issue.

MRS. ROSS: New patient new to the drug.

DR. TEMPLE: I am more worried about what AstraZeneca is telling people. I thought it was fairly clear they thought, given a choice, for someone who wants that mechanism, they would use the drug that actually showed a benefit, not the drug that didn't.

I no longer am clear that that is their goal after this presentation today. It sounds much more ambiguous than that, and I am just trying to find out what it is. I thought the comment about what is being done in Tennessee makes a lot of sense, if you think that therapy is appropriate, use the drug that won.

Look, we have been pushing, if anything, the idea that there are subsets of the population that are more likely to respond than others, and that has been I think apparent from the earliest data with Iressa. There undoubtedly are differences among subsets of the population.

But Ralph can comment on this. All of those differences in a trial are much more credible when the trial wins overall or when you have

specified that as the primary endpoint. It remains somewhat after the fact, not implausible given the other data, that people who never smoked, you know, are much more likely to respond.

All those things are probably true, but still, given a choice of two drugs now, one of which has a quite successful overall clinical result, and the other of which doesn't, most of the time people would suggest that you use the one that actually had the favorable result.

I thought that was the direction AstraZeneca was urging people to go. I am not as sure of that after hearing the presentation today.

DR. SCOTT: Could I--

DR. MARTINO: I am sorry, I need to ask a question here.

Has the FDA had the opportunity to review the materials that have been prepared by AstraZeneca?

DR. TEMPLE: Yes.

DR. MARTINO: You have. So, you have seen, in fact, the written materials?

DR. PAZDUR: The written materials, yes.

DR. MARTINO: Okay. And can I trust that since they are in the public media now, that, in

fact, you have agreed or approved, or in some way decided that they are okay with you? I understand--

DR. TEMPLE: We did. I am now slightly nervous about them.

DR. MARTINO: I understand the concept of what is their intent, however, I think what we, as a committee, can judge is the steps that they have taken, the material that they have supplied, and the content, the written content in that material, is it fair, appropriate, and informative.

What their intent might be in their gut and in their heart, in all fairness, I think I understand your question, but it is not really what this committee can deal with.

DR. D'AGOSTINO: Can I go to Bob's

question? I mean I thought that what we were looking at was basically this letter, and that I think is fine, and I think it reflects what the data shows.

I am bothered by the presentation that if--are they also, are they putting this letter out and then showing this presentation, because the presentation has a completely different bent to it, and my question was going to be, what is their presentation to the field, is it just this letter, or are they throwing this--now, that is different than the people who are running the studies.

The ones who are running the studies obviously have to see this, but what is the collection of M.D.'s being told?

DR. MARTINO: That is an important question, that, I would like the company to answer to.

DR. SCOTT: If I could respond first and have Judy Ochs talk about the intent of the letter. Again, the intent of the letter in December is the intent today, and I will have Judy Ochs talk about

the intent, please.

DR. OCHS: Yes, I did send the letter, and my signature is on it, and I stand by it. That was the letter that we sent out. What we said in that letter is true. It is no less true today.

The presentation today, however, reflects some time, now that we have the full totality of the data, we are beginning to look at it, it will be submitted to you. The FDA will review it. Again, many times when one goes through protocols and through data, there will be the data, there may be some aspects to the interpretation.

The bottom line, that the trial did not meet statistical significance has not changed.

DR. MARTINO: One more question and then I will turn to the open forum, please.

DR. REAMAN: You did show data today about a particular subgroup or subgroups that do appear to potentially have more of a benefit than others, the corollary being that there is a large group that don't appear to have any benefit.

Is that data that has only been made

available to you since the letter went out in December, and, if not, why wasn't there any mention of that in the communication?

DR. OCHS: When the letter went out, that is all we had. We didn't have the rest of the data to a large degree. We hadn't had any opportunity to look at it. We literally saw the data, about 10 people, on Tuesday, and the data went out Friday morning, it was that quick a happening.

Again, I think as we are looking at the data ourselves, it is clear. The one thing I would say is that as Kevin presented in his presentation, all of the patients, if you look at the hazard ratios, it is to the left in terms of potential benefit for Iressa.

There obviously are, as Kevin pointed out, variability, but nonetheless, we are looking at a trial that barely missed reaching statistical significance, so it is not like there wasn't benefit, it did not meet a statistically defined endpoint to which we all agree, and to which we would not change our recommendation to physicians

that solely based on the data, but I think that Dr. Kris and Dr. Burris have brought up other things, other data that is out there, other information.

And I think one of the things that has happened is that Iressa has been around for a while, people have had some experience, so people will be looking at the literature. Certainly, the first opportunity for the data as a whole to be seen is today.

We submitted it to a scientific forum where it will be presented. There will be questions asked. It will be questioned, and it will be submitted to peer-reviewed journals.

Open Public Hearing

DR. MARTINO: Thank you. We will continue this in a few moments, but at this point I do want to turn to the open public hearing. There are several of you that have asked to speak, so the microphone that you will be using is in the center of the room.

Allow me to read the following in anticipation of your presentations.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decisionmaking. To

ensure such transparency at the open public hearing session of the Advisory Committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, 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 products, and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, the 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 this issue of financial relationship at the beginning of your

statement, it will not preclude you from speaking.

Ms. Clifford, if you will announce our speakers, please.

MS. CLIFFORD: Peter Lurie is our first speaker.

DR. LURIE: Good morning. Peter Lurie with Public Citizens Health Research Group. I am a physician. I have no conflicts of interest to disclose. We take no money from government or industry.

As the members of the committee will I hope have noticed by now, this morning Public Citizen filed a petition with the FDA to remove Iressa from the market on the grounds that no less than three mortality studies have now proved negative.

We, instead, ask that for those patients who remain on the drug, and completing courses of therapy, that they can receive the drug through IND status.

You will notice, too, that in Europe, the marketing application for Iressa has been withdrawn

and that in Japan, the Ministry is giving serious consideration to removing the drug from the market.

As you all know, Subpart H is the mechanism through which this drug was approved, and to emphasize, that accelerated approval law makes clear that the FDA may withdraw approval of a fast track product "if a post-marketing clinical study fails to verify clinical benefit." That is certainly the case over here.

In fact, even prior to approval, there were a couple of studies that showed lack of clinical benefit, and the two instant studies were, in the words of the FDA medical officer, "unambiguously negative," and the medical officer made the observation that "the FDA has never received a cancer drug application for accelerated approval when definitive data in another related setting showed a lack of efficacy."

Those were first line therapy trials, which were both negative with respect to mortality, and the drug on the market for third line therapy, of course, we will acknowledge the principle in

oncology is that a drug is most likely to work as first line therapy rather than third line therapy, and, of course, in the end, that is exactly what the ISEL has confirmed.

So, we have these two negative mortality studies even going into the approval of this drug. Now we have the ISEL study, which shows a very small survival difference, 27 versus 22 percent, but not statistically significant under the primary data analysis.

As you will notice from the slides presented by AstraZeneca this morning, the overall quality of life was also not benefited by Iressa.

Instead, what we have seen, you have all heard of rescue chemotherapy, I think what we have seen here is rescue biostatistics. A number of subanalyses that have been done, some of them aren't clearly post-hoc, especially the Asian one. You will notice from your briefing materials that some subanalyses are described as prespecified, but the second table is one that implicitly are not prespecified. The Asian group is among them.

How many of these subanalyses have been done? Why is it that the rather simple to conduct multivariate analysis has not been done, and why is

it that conveniently none of them are ready for this meeting?

In response, we have seen the FDA put out a letter. We have seen another letter from AstraZeneca, which in effect are telling patients to think about not to take the drug. I mean what kind of public health approach is this to have a letter from a drug company that, in effect, suggests that patients not take their drug?

That doesn't seem like an adequate public health response to us, and, in fact, patients are still taking the drug, 331 new prescriptions in the week of February 18th. The company may claim that these are not new patients, but there is no evidence for that either.

The fact is that there is a drug on the market which has clear, proven mortality benefit, and patients can easily be diverted from the effective therapy to this one for which there is no

benefit.

As Dr. Temple said, if there are two drugs that are available, why not use the one that won.

There are also dangers from this drug, and we have outlined these in prior letters to FDA, particularly in the area of interstitial lung disease, 588 deaths now in Japan, and our analysis of the adverse drug reaction data from FDA show 144 reports of interstitial lung disease including 87 deaths in this country just since the time that the drug was approved.

What really we are seeing over here is an elaborate dragging out of this process, a drug that probably should not have been approved in the first place, and now, even while empowered by Subpart H to remove the drug from the market, it still hasn't happened.

How ironic this is. A company gets a drug on the market through an accelerated approval process and then when the data turn out to be negative, suddenly it goes slow - let's wait for the EGFR data, let's wait for the easy-to-do

multivariate analysis that we haven't done, and the EGFR data will be ready, would you believe it, in two to three weeks from now, it couldn't be ready in time for this meeting.

These EGFR analyses should be thought about in the following context. In the Phase II trial, there was no relationship between the expression of EGFR and outcomes. There is no calculation of a positive predictive value for these mutations.

Clearly, people without them are responding and vice versa. We really don't know the positive predictive value, and as was also pointed out, this is a research tool. It is not something--and even AstraZeneca admits this--that can be used to distinguish patients at present, and therefore, decide whether or not to provide them with therapy.

If this is important enough a question, it should be researched, and the IND is the appropriate mechanism to do that.

Finally, to close, with Subpart H, if ever

there was a drug that was slated for and eligible for removal from the market under Subpart H, this is it, a drug, which even for the indirect--sorry--for the surrogate marker had minimal benefit in the Phase II uncontrolled, non-placebo-controlled, even unblinded trial, minimal benefit on the surrogate markers, clear dangers, proven effective therapy in terms of reducing mortality, and now patients continue to be placed on the drug, and three negative mortality studies.

If this drug is not taken off the market on these grounds, it will make an absolutely mockery of Subpart H.

Thank you.

MS. CLIFFORD: Thank you, Mr. Lurie.

Our next speaker is Laurie Fenton.

MS. FENTON: Good morning. I am Laurie Fenton and I am President of The Lung Cancer Alliance, the only national organization that is dedicated exclusively to advocating on behalf of lung cancer patients and their caregivers and

survivors.

DR. PERRY: We can't hear you very well.

MS. FENTON: Okay. How is that?

Again, Laurie Fenton, the President of The Lung Cancer Alliance. We are the only national organization that is dedicated exclusively to advocating on behalf of lung cancer patients, their caregivers and survivors.

I believe you have my statement, so I will condense what I would like to present today.

AstraZeneca has provided grants in the past for educational programs, but they have not compensated me in any way today to present what we are here to share.

The Lung Cancer Alliance understands that the FDA is required by statute to evaluate drugs by looking at safety and efficacy data in large populations of patients to determine whether benefits outweigh the risks.

Interestingly, we have discovered that Iressa does not fit neatly into this protocol, and while Iressa's current clinical trial data has not

revealed dramatic survival benefits overall, it has shown striking benefits for a small subset of the larger population, with less side effects and quicker response rates.

As was shared earlier, we received many phone calls from patients who were extremely concerned that Iressa could be pulled from the market, particularly a drug that had helped them so dramatically.

Patients spoke of stockpiling the drug and beginning to take Iressa every other day to make their supply last longer, and I am glad you will be able to hear from patients directly on this point.

The reality is that we have an unmet public health need. Lung cancer's mortality statistics can no longer be ignored. Beyond demanding that government redirect its own resources to effect change, we as advocates also want to nurture responsible drug development to help in our fight to eradicate this number one cancer killer.

Alimta and Tarceva, recently approved for

the treatment of lung cancer, are important arrows in our treatment quiver, but Iressa must also be recognized as an important weapon in this battle.

Even if unable to meet the broad population standard, we cannot ignore the fact that Iressa has shown striking benefits within a subset of the population, and to this effect, lung cancer patients and their doctors need all, not limited, choices now.

It is our hope that both the FDA and AstraZeneca find a way to allow doctors and lung cancer patients access to Iressa while, at the same time, agreeing upon a way to further study and evaluate the drug.

It could provide a window of opportunity to better understand the horrible disease that lung cancer is, who will benefit most from the drug treatments and why.

I again thank you for allowing us to be represented here today.

MS. CLIFFORD: Thank you for your comments, Ms. Fenton.

Our next speaker is Selma Schimmel.

MS. SCHIMMEL: Good morning. My name is Selma Schimmel. I am the CEO and founder of Vital

Options International. It is a nonprofit cancer communications and advocacy organization that also produces the Group Room Cancer talk radio show, which weekly gives me an opportunity to speak with a great many cancer patients.

While I am not a lung cancer survivor, I have survived both breast and ovarian cancer. I want to clarify that I have no financial interest, investment, or gain associated with my presence here today, but I am here to help lung cancer patients, their loved ones dealing with non-small cell lung cancer, and because I really believe that we are at a crossroads and a convergence of technology that necessitates a new dialogue and opportunity for positive change.

Patients and medical consumers deserve choice, but most importantly, they need and expect full disclosure and rational explanations to help them make informed choices, and what patients

especially need are adequate safeguards to protect them from erroneous choice.

As advocates, we thank and rely upon our partners at the FDA and the NCI. We also applaud AstraZeneca's prompt and open disclosure regarding its top line Iressa data results on December 17th, 2004. It was a respected and valued action and of particular importance at a time when the general public has such a lack of trust and expresses hostility towards the pharmaceutical industry and the regulatory and approval process.

So, I bring a question to the forefront, because it is really at the core of today's proceedings, and because the process and the course of action being taken now sets a tone and a precedent for our future.

How am I to respond to the man who tells me that he has read that Iressa has no survival advantage, that it is not being used in Europe, yet he will begin receiving it here? I find I have no reasonable and satisfactory answer.

But what the patient is really asking is

how many patients are being harmed by not receiving the most effective and safest product for their disease. How can patients advocate for themselves when they are receiving conflicting information and double messages?

Finally, how can patients trust the system? While Iressa should remain available to a defined patient population who might benefit, as well as for the subset of patients who are already responding favorably or for whom there is no other option, a labeling change is needed now, not months from now, to reflect the current indications and information, so patients are not mistakenly deprived of their best treatment option and to avoid further patient confusion and misperceptions, a labeling change allows for the full circle of information disclosure to be complete, as well as implemented.

Iressa has paved the way for a deeper understanding of the differences between EGFR agents. There is much yet to be understood about Iressa and the scope of who may and may not

benefit, as well as which patient groups may derive comparable or perhaps even greater benefit from Iressa than other proven therapies.

One of the great hopes is the development of proper screening assays, but since none have been scientifically validated, patients are in need of additional security and safeguards.

So, as we face a new world in medical technology, we must also try to bridge the communication and comprehension gap between patients and providers. It is hoped the decisions coming out of this meeting are made in context to today's fragmented medical culture and evaluated in its entirety for the much broader and significant implications that will impact the oncology community in general, color public perception and attitudes associated with clinical trials, confidence when trials are negative or halted early, and drugs that are developed under an FDA fast track application.

Advancing and widening technology requires a mechanism to teach the public and to instill

trust.

Thank you very much. I have copies of my statement at request.

MS. CLIFFORD: Thank you, Ms. Schimmel.

Our next speaker is Rosalind Brannigan.

MS. BRANNIGAN: Good morning. My name is Rosalind Brannigan and I have no financial relationship with AstraZeneca except that I am buying its drug.

Recently I have had two profound shocks.

First, in November of 2003, I broke my arm at my health club and was diagnosed with Stage IV non-small cell lung cancer. This was a major shock to someone who had not smoked in 38 years, who exercised an hour a day, and who has spent their life working in public health.

I underwent six months of weekly chemotherapy, platinum and Taxotere. Three months later, my cancer had come back and had metastasized to my liver, and I was put back on weekly chemotherapy.

Shortly after that, I learned from the

Massachusetts General Hospital that I had the genetic mutation to be a candidate for Iressa, and I was put on Iressa in October of 2004.

By December, when I had a PET and CT scan, it showed that my tumor in my lung and my liver had both reduced significantly in size and that my CEA tumor marker had plummeted by 90 percent.

However, this good news was immediately followed by having me open the New York Times on December 20th and to read that FDA was reviewing its approval of Iressa and that it might take this drug off the market.

Just last Friday I had another PET/CT scan, and it showed that the tumors in my liver are completely gone, and that the tumor in my lung continues to shrink.

Iressa is working for me. When I asked my oncologist if I should switch to Tarceva, he said, "Absolutely not." He was adamant that I stay on Iressa because it's working for me, and he thinks it's a wonderful drug for all of his patients in his practice who are responding to the drug.

Iressa should remain available.

Thank you very much.

MS. CLIFFORD: Thank you, Ms. Brannigan.

DR. MARTINO: Thank you, ladies and gentlemen.

Committee Discussion

We will now return to the committee's proceedings in terms of if there are additional questions, but as I let you do that, let me read for you the questions that I really want you to discuss and to think about.

1. Discuss whether the content of the information communicated by the FDA and AstraZeneca on Iressa is satisfactory. Should any other information be communicated?

2. Further, discuss whether the target audience and the selected means of communication are satisfactory. Should any other audiences or means of communication be used?

Now, in your packet, you each have a letter from the FDA, and there is also the Dear Doctor letter that AstraZeneca has provided. What

I, myself, have not seen is what has been provided to the lay public. It sounds like there has been information provided in various magazines, et cetera.

Can someone from the company review that for us and tell us what the content of that information is, because providing information to physicians is critical, but with this drug I am concerned that unless we communicate properly to the lay population, we may be confusing them rather than helping them as I think our last speaker made clear to us.

DR. SCOTT: I will ask Carolyn Fitzsimons to come and talk about the patient communications.

MS. FITZSIMONS: Thank you. Can I just clarify the question you are asking, you want to know about the content of the communications directly to patients and the public?

DR. MARTINO: Correct.

MS. FITZSIMONS: On December the 17th, as was shown on the original presentation by Dr. Ochs, we immediately informed the patient advocate

groups. We had a teleconference with them, gave them the information about the top line results with the guidance that should they have any concerns, that they should go at their first opportunity to consult with their physicians about what the most appropriate treatment options would be.

We did say that they should not stop taking their Iressa until they had spoken to their physicians and deemed what was the most appropriate action in consultation with their physicians.

We also put out similar information on the AstraZeneca website and also on the specific Iressa websites also.

Subsequent to December 17th, we then went back to our own records where we had got information from patients who had contacted AstraZeneca directly to gain information about Iressa or were on our patient assistance program for Iressa.

So, any known patients to AstraZeneca, we went out a mailing, either postal or on e-mail to

inform them of the information, provide them with the Dear Doctor letter, and give them the guidance that at the first opportunity, they should consult with their physicians about their ongoing treatments and what would be the best choices for them.

DR. MARTINO: Has the FDA seen any of the written material for the public, and are you satisfied with it? Is that a yes or a no?

DR. PAZDUR: Yes.

DR. MARTINO: Generally yes? Okay.

Dr. Hussain, you had a question?

DR. HUSSAIN: I want to thank the members of the public that presented, and I thought that their comments were very thoughtful, to be honest with you. It kind of encapsulated everything that this committee is facing at this moment.

But I want to go back to the presentation that Ms. Schimmel had done and Ms. Brannigan. Before coming here I talked to my lung colleagues who deal with lung cancer and have worked with Iressa and Tarceva, and a variety of other agents.

I have myself not used it in the setting of lung cancer.

What I was impressed by is their impression from their own patients that there is clearly subsets of patients that benefit, and I think Ms. Brannigan is a perfect example of that. So, there is no question as doctors, ethically, it is going to be very hard to say to a patient who is on it and is responding, or is likely to respond when there is nothing else that you can't get it. That, to me, doesn't make a lot of sense.

On the other hand, I think it is also unethical to keep it available for people who we know are not likely to benefit and to allow that part to happen, because there is an ethical issue of side effects and cost, and these things are not cheap, and there may be, by giving them something of this sort, will take them away from stuff that works.

I have to get back to the clinicians in the group, and I do agree with Dr. Temple, when you are starting a new patient and you have two drugs,

one that stood the test, and the other one did not stand the test, to me, it, from a clinical sense, doesn't make sense to use a drug that didn't stand the test when you are starting a new patient, but that is where the art of medicine comes in, and I am not sure that I could argue that way too much.

So, my point is to go back to Ms. Schimmel's recommendation, which I think the package insert and the labeling has to change, reflecting the fact that the definitive trial did not work, and that perhaps--and I don't know if that is allowed--that there are some subsets that seem to benefit, and that if one is to use the drug, perhaps they could consider using them in that subset to give some guidance to the physicians.

The other thing, to the patients, I think that considering that industry uses the media to advertise their drugs, perhaps to ensure that every patient had heard about it, is to use the media to indirectly say something, so that they can contact their doctors as another means of assuring that

people have heard about it.

The other concern I had, had to do with the labeling of people as Asian. We live in the United States and have certain definition of ethnicity, which I am not sure that are clear. I, myself, was born in Baghdad. I consider myself Asian. So, does that drug apply to me?

I think when we talk about benefits in general, and I wouldn't consider a Japanese person equal to Vietnamese, equal to Chinese, equal to Indian, Pakistan, Afghanistan, and on. I think those populations have to be very clearly defined beyond this Asian ethnicity thing, because I don't really know what it means.

DR. TEMPLE: It's actually, I mean I am not saying this is fully worked out, it's actually non-Caucasian who seem to do best. It is not entirely--it was actually some mixture of Japanese, some mixture of other people, but non-Caucasian was the subgroup.

DR. HUSSAIN: I think we get wrapped up in these ethnicity race issues. To be honest with

you, I don't even know what I would even describe myself, so we have to be very clear about those definitions.

DR. TEMPLE: You are right, and it is totally after the fact, and I doubt if you probed, you would always get a good answer on who it was. I do want to remind everybody that the same subsets that seemed to be responding better here are the same subsets that respond better to Tarceva, too, except there you have some EGFR data that helps shed light on it.

DR. PAZDUR: Perhaps that's an area that I would like to focus on in the discussion and get several people's opinion on, in this fact of new patients, and that is what we feel very uncomfortable with here, basically, what should be the option for new patients that would be looking at an EGFR receptor drug.

Here again, you have two drugs here, very similar, similar response rates, similar facts, that if you take a look at their development program, they have had failed trials in first line

settings when combined with chemotherapy, however, in the Registration study for Tarceva, there was a survival advantage seen and secondary endpoints were positive in this trial, so we are quite comfortable that that was a win for this drug.

Given the information, given the fact that there are similar subsets also that we see in the patients between Iressa and Tarceva, and remember the Iressa data is somewhat subject to questions about these subsets, because they did not win on their primary endpoint, so looking at these subsets could be statistically ambiguous or criticized.

Given that fact, given a new patient, what should be the treatment option if you are looking at a EGFR receptor drug?

DR. MARTINO: I am having a hard time with all of this, Rick, which is we are now getting to issues of as a physician in my own office, okay, how do I practice medicine, and I practice medicine based on everything that I know at that moment, so any of you, be it the drug company, be it the FDA, be it anyone, the only thing that you can do is

provide me the opportunity for me to know something. That is all you can do for me.

You cannot be in a position where you are looking over my shoulder saying, but, Dr. Martino, did you actually consider that your patient was male or female, that they were Asian, whatever in the hell--excuse me--that means. That is not the position that I think either of you can take.

The issue at hand, as I think I understand it, is have both sides communicated that there is a problem with this drug, and that people have to recognize that there are alternatives, the alternatives are not unknown, so it is not for you to do anything more than I think to make people aware, that you are reminding them that there are alternatives, and that you are reminding them that they have to think.

I kind of have the feeling like now we are moving into, you know, how do you sit in my office and look over my shoulder. I don't mean to be unkind, but that is what I am sensing here, and I don't know that any of you can do that on either

side of this table.

DR. TEMPLE: There is labeling that, for one reason or another, sometimes suggests that another drug be used before this drug. There is a calcium channel blocker called deprenyl that has pronounced effects on the Q-T interval. It is recommended for people who don't respond to other calcium channel blockers for angina.

So, labeling can do that if there is a good case for it. This isn't done lightly, of course. That doesn't force the doctor to do that, it encourages them, shall we say. Clozapine, a granulocytosis-causing antipsychotic drug is explicitly second line therapy because it is thought that you should fail first on something that doesn't have that liability.

So, there are examples of that if that is appropriate. I should emphasize we don't do that lightly because, you know, you are not in the office, you don't know the exact circumstances, that is fair, but sometimes you can conclude, and the sponsor concludes with us, that the right

recommendation is this should be reserved for someone who fails on the other one, or you should try that one first.

That is something labeling does sometimes say.

DR. MARTINO: But that is an issue whether you are ready now to change the labeling, and I don't know that that is again the discussion from today's meeting. I appreciate you have that responsibility.

Who is next on my list here? Dr. Mortimer.

DR. MORTIMER: I think the issue from an evidence-based standpoint, in answer to the FDA, is clearly that the data support the use of erlotinib as first line therapy.

I think where the gray zone happens is a statistical one, and what do we do when there are overlapping confidence limits, when the difference in response is 8 and 9 percent, but the confidence limits overlap.

I think the third issue that is concerning

that we don't know the answer to until crossover data is available, is are the same patients responding to Tarceva, the same patients that respond to erlotinib, and I guess we don't know that yet. So, the statistical question I think is at the heart of this.

DR. D'AGOSTINO: I guess I just didn't think we were going to be talking statistics, I thought we were going to be talking what is the material that is being presented, and I am very concerned that we have an accelerated approval product here, it has been approved, and you can't ask the sponsor to sit on the data, and not get it out in the literature.

So, what I am concerned about is that I think these letters are fine, and I understand the letters for the public seems to be fine, but if tomorrow we go to professional meetings and we start hearing a lot about these subsets, then, I think there is going to be an awful lot of confusion.

So, maybe we need an accelerated review of

this material, so that we can have the statistics question, because again I did not come here thinking we were going to have a statistics review, but rather is the public being made aware of the fact that the study was negative on the overall, and then what else might be needed, and I think what needs to be needed is a quick review of the actual data, so we can answer your question.

DR. MARTINO: Dr. Proschan.

DR. PROSCHAN: I think the statistical issues, it is not clear cut. I mean this trial really is about as close to being a positive one as you can get in the sense that if they had used a Cox model, which people feel is fine, you know, they would have gotten a significant effect, so it is not just the subgroups, it's other issues as well.

I had problems with some of the presentation. In particular, the graph showing the comparison of Iressa to docetaxel, you know, and the claim that, well, we are not seeing much of a difference there, and we would have if it were a

placebo. I have a problem with that.

That is a small sample size and I am not convinced at all that there is not a difference there that would be seen with a larger sample size. So, I have problems with some of the presentation this morning, but it is very thorny.

I disagree with the classification that this is a negative trial. There is negative and there is negative. This is a negative trial, but there are extenuating circumstances, as well.

DR. D'AGOSTINO: But, again, we don't really want to get into this, but the Cox analysis has some assumptions carry to it. These curves are sticking together and then they separate, so the assumption may not be met of proportionality, and I am not going to say another word about statistics.

[Laughter.]

DR. MARTINO: Thank you. Dr. Perry.

DR. PERRY: I would like to point out that during the brief time I have been on the committee, the FDA has approved several drugs without my help, and I am sure they have also turned down several

without my help, so it seems to me that the only things that come before this committee are those that are bathed in shades of gray.

So, I think it is clear that we have varying viewpoints, that we have very different interpretations of the evidence before us, and I expect that is why we are here, and so I don't expect that we are going to walk away with a clear black or white decision.

When I raised my hand half an hour ago, I was trying to address--

DR. MARTINO: I do apologize.

DR. PERRY: Yes, I understand. You are doing a wonderful job in a difficult circumstance, particularly when all of us love to hear our own voices, they resonate so well.

I was going to address Question No. 2, which is whether target audiences have been addressed selectively. I have to say, to give credit to AstraZeneca, I have got more notice about this drug than I have credit card applications, so they have clearly done a good job in saturating the

medical community, at least the lung cancer doctors.

I can't speak to the lay public, but they have clearly I think gone over and above their obligation to communicate with doctors. I can't think of another time in which, in my practice, I have been so inundated with information about the adverse effects of a drug.

DR. MARTINO: I do apologize officially and personally, and thank you.

Dr. Brawley.

DR. BRAWLEY: Run down your list, Madam Chairman. My first thought is I must say to the advocates I appreciate all four of their comments this morning, because so frequently--well, let's just leave it that I got something positive and something to think about from every advocate's statement this morning.

I wonder why so many patients were concerned that Iressa might be pulled, and was there some press, did anyone do something to frighten patients into believing that this drug

that they are on is going to be pulled away from them.

Next, going into Questions 3 and 4, and actually addressing the advocates and the survivors, I think we all owe them an apology because the development of this drug has been mishandled. It has been mishandled by AstraZeneca, it has been mishandled by this committee.

I, myself, take some blame for that, because I voted for approval of it two years ago. The fact remains that this drug has been available for 7 years, and we still haven't figured out exactly how this drug should be used in the treatment of lung cancer.

Perhaps if we had held off in getting it available to people two, three years ago, those studies would have been done. There are a number of studies that have done a number of subset analysis, and I have made my career, by the way, by saying we should not do subset analysis based on race, because race or ethnicity is not a biological categorization of populations, it's non-scientific.

I actually think I was quoted in the press when I voted for this drug two years ago saying that this is lung cancer's tamoxifen in search of

its estrogen receptor. Unfortunately, the failure to totally find and totally categorize that estrogen receptor is the reason why we are in the pickle that we are in today.

It may very well be that people--Asian is a way of racial profiling, and the best way to politically--I am sorry--the best way to scientifically profile is people who happen to have that receptor, which may very well be of a higher prevalence in people who were originally born in Japan or China, or maybe even Iraq.

That is what we have got to start doing, and we have got to be much more scientific. Now, in partial defense of everybody who mishandled the development of this drug, including myself, this is one of the first of the targeted therapies to come along, and none of us really had developed target therapies a lot before this one came along, so we need to learn from our mistakes and go forward.

With that, I will relinquish the microphone.

DR. MARTINO: Dr. Levine.

DR. LEVINE: Several comments. First, I will agree, I mean there is not winning and not winning, and this is on the edge, and I don't

honestly believe in my soul that there is no efficacy of this drug. I think the company have shown data to suggest that there may be something there.

The other thing that bothers me a little, I wasn't on the committee either for Tarceva or Iressa, and I don't know the data, but we are hearing or I am hearing that Tarceva is a "better" drug.

So, my question is, by chance, how many women were on that trial, how many non-Caucasians, how many non-smokers, and I don't know if it is fair to compare one drug to another when those very important issues have not been presented to us, and I know we aren't asked to do that, but that is a comment I have. I feel disquiet about it.

The second is an administrative question. The company was asked, after accelerated approval, to do three studies. One study was agreed upon that should be dropped, but my question to the FDA is, if you are going to base everything on one study out of two, why were they asked to do two or three, and what is the administrative concept here, if the company is asked to do two or three studies, aren't we, in fact, obligated to look at all of

them in making our decisions.

That's it.

DR. MARTINO: Dr. Temple, Rick, you want to comment on that?

DR. TEMPLE: Rick has to remind me what the second study is, but I think the short answer is this was a very large study. You would expect it to be able to detect an overall survival effect if there was one, and the fact that it didn't tells you something.

It absolutely, as people have said, it doesn't prove the negative. A negative study never proves the negative almost. Maybe if it's

significantly worse than no treatment, but that hardly ever happens, but it doesn't support the positive.

Not to get too far apart, but we are learning in more and more cases that there are subsets of the overall population that respond, and if the subset is too small, you will not have an overall effect on survival, that is inevitable. That doesn't mean the drug is useless.

So, there are obviously people who respond dramatically, and if you could identify them ahead of time, you might be able to show there is a survival benefit in that subset we were sort of talking about this yesterday, but this is a developing area and we don't yet quite know how to do that.

Just for what it's worth, in the Tarceva data, there are some very intriguing things. For example, if you look at the subsets of people who do particularly well, like nonsmokers, it's the nonsmokers who are EGFR-positive who do spectacularly well, it's not the nonsmokers who are

EGFR-negative who do spectacularly well, and that is true for women and all those subsets.

So, you know, we are not declaring any of that definitive, the number of patients in the negative subsets are too small to be definitive, and the confidence intervals overlap, but you are starting to get the impression that these data are telling you something, but it is still early.

But one of my problems with survival data in general is that if the response rate is low enough, you can't bring the whole study along unless you have a population of a million or something, and that doesn't mean it doesn't work, so we have got to get better at identifying who the potential responders are, so you can study them and identify them as the people to be responders.

Anyway, the new study even without the additional study, gives you more information than you had before, and I think the view would generally be that that should be reflected in labeling, and if you learn something else in addition, you add that.

DR. PAZDUR: We generally do ask for other than just one confirmatory trial. We are interested for the development of the drug, and we

are realistic that a trial can fail, in quotes, by chance alone obviously.

Given the fact there are other trials, the docetaxel trial, it was a difficult trial, and we brought this same question to the committee several months ago when we looked at Alimta.

One cannot do a non-inferiority trial here, they have to beat this drug. A non-inferiority is impossible to do in this setting and we had lengthy discussions, which I won't bore you with, on this whole issue of non-inferiority with docetaxel.

But there are problems here, and that was specifically stated by us, had to be a superiority trial. This is a placebo-controlled trial. It is about as clean as you could get here, and obviously, this is bothersome or we wouldn't be here to bring this to people's attention.

DR. MARTINO: Mrs. Ross.

MRS. ROSS: Thank you, Madam Chair.

First, just an administrative technical question and then one other question. I didn't hear properly the start of the testimony of Ralph Nader's group. Did they file a financial disclaimer on this, or were they testifying on

behalf of someone?

DR. TEMPLE: He stated that he had no conflict.

MR. LURIE: I made it perfectly clear that we have no conflict of interest whatsoever. We take no money from AstraZeneca or any other drug company, or any other corporation, nor from the government.

MRS. ROSS: Thank you. I just wanted to clarify, I didn't hear that.

To Dr. Brawley's comments, I was in the audience the day you voted in favor of accelerated approval, and frankly, I am so glad you did. I know that Dr. Pazdur was not in favor, and other members from FDA, however--

DR. PAZDUR: You don't know that, you do

not know that, ma'am, you are not a mind reader.

MRS. ROSS: In any event, it was approved, we don't erase that, but I think we have to look at the benefits that have come from this. First of all, and let's not forget this, there are a significant number of people who have, in fact, benefited from Iressa. Their quality of life, as the study done by Dr. Joan Shold [ph] at the University of Wisconsin, was greatly improved.

Now, they might not be living five years out, we don't even know that. I don't even know what the data is from Japan on longer term survival with Iressa, but the fact is that there are people surviving.

Secondly, the other enormous benefit to come from this is that it is focusing attention, large populations, on these targeted therapies, and who knows, maybe Iressa in combination with a VEGF, or in combination with something else, might be the real answer to a lot of these recalcitrant late stage lung cancer, but please, please keep in mind it has opened, like Laurie says, it has opened a

window, we have another place to go to look and help these late stage lung cancer patients.

Late stage lung cancer patients only have a 5 percent chance of survival. We can't cut down on what is available to them to survive, and it is not just that it is not fair. I wholly agree with you that we need to do more research on these receptors, in determining who will respond to these drugs, and we will do anything we can to support that research.

Perhaps if this committee makes a clamor for that, we might get the attention of other government agencies who are charged with that research and get them talking, too.

DR. MARTINO: Ladies and gentlemen, this meeting is coming to a close. I need to remind the group that you have gotten off track here. Okay? Even though I keep reminding you, the point today is not whether this drug dies or lives, that is not the issue here, and some of you refuse to understand that.

The issue here was have we sufficiently

informed the necessary people. So, I realize there is no vote to be taken, but I, for my own satisfaction, would like to hear an answer to that question, and I am going to start with Dr. Doroshow. Are you satisfied that the public and the physicians have been appropriately informed or not?

DR. DOROSHOW: Yes.

DR. BRAWLEY: No.

DR. D'AGOSTINO: Yes, but I am concerned that we have to move, the FDA, the sponsor has to move quickly on making a resolution about this particular study, but I think they are informed.

DR. PROSCHAN: Yes.

DR. GRILLO-LOPEZ: I don't have a vote, but I do have an opinion, and I would say yes, because as a physician, I have been receiving the same number of communications by e-mail, letters, et cetera, that Dr. Perry has.

DR. MORTIMER: Yes, on the basis of the e-mails and mail.

DR. PERRY: Yes.

DR. HUSSAIN: Yes.

DR. MARTINO: Yes.

DR. REAMAN: I will give a conditional yes

for the constituency of the medical community, but I don't think we have actually seen anything that has gone to the public, so I don't know how we can be asked to comment or vote on something that we have never seen.

DR. MARTINO: I actually think that is a very fair statement. I mean we have been told that the FDA has seen what has been put in the public media, and it is to their satisfaction, so I guess right now we have to kind of trust that.

DR. BRAWLEY: Madam Chairman--

DR. PAZDUR: We have examples in your packet of the letter and their ad.

DR. REAMAN: The only thing I have in my packet is a copy of the Dear Doctor letter.

DR. WILLIAMS: But I do think we should mention it has been limited, I believe, to the patients AstraZeneca has access to, which represents a subset, and I don't know if there is

another way to reach those others. Certainly, the advocates have been helpful.

DR. REAMAN: We heard that there is announcements on websites. We have not seen that, we could have seen that, that could have been provided, and it wasn't.

DR. BRAWLEY: Madam Chairman, the basis of my no vote is I do think the physicians have been well informed, but I am concerned when I hear advocates say they are afraid that they are going to run out of their drug, and it is going to be taken away from them while they are on therapy.

DR. RODRIGUEZ: I concur with the previously stated comments. I actually don't know what the public has heard. Obviously, the public heard some negative statements from the press, otherwise, there would not have been this fear in the patients about the drug being removed, which isn't even an issue at this stage, as I understand.

DR. MARTINO: Perhaps we can infer the very fact that the public was so concerned that the drug is coming off of the market, that, in fact,

the word that the results are negative must have gotten out.

That really is the issue here, isn't it? For them to be worried, that is the message that they heard, however they heard it.

DR. LEVINE: I agree that the medical community has been well informed, and I am respectful for the company of having done a very good job in that regard, but I am unclear as to what the committee is asking them to do as far as the patient community.

I don't think we are saying that they should be going out there and saying don't worry, this is all wonderful, the drug is available. We can't go in that direction.

I would be in favor of a label change, and I would also say to the company, in all fairness, and I don't know whether they did, if the company has directly advertised to the community of patients on TV and radio, they should be asked to directly advertise that the drug has difficulties here. If they have not done that, then, fine.

MS. HAYLOCK: I am an oncology nurse and a member of the Oncology Nursing Society, and I would just like to add that the Oncology Nursing Society

was involved in distribution of information, and we have a membership of over 30,000 nurses.

So, I think the nursing community, and for those of you who have been through treatment, I think you realize that the oncology nurses are the ones who are oftentimes involved in informed consent and also patient and family information, and teaching, and for caregivers, as well.

So, I think the nursing community was also involved in the dissemination of information to recipients and patients and caregivers.

DR. PAZDUR: In fact, the e-mail that we sent out to ASCO simultaneously goes out to ONS membership, as well as is put on the NCI website.

MRS. ROSS: Yes, we are quite satisfied with the information disseminated to the patients and particularly in the follow-up, as I mentioned before, we did speak with FDA regarding the calls we were getting, and Dr. Pazdur was very helpful in

crafting a statement that we could put on our website that would allay people's fears.

Their main concern was they were afraid the drug was going to be pulled immediately, and that came about because of the press and certain other citizens organizations that were crying wolf.

Also, there is a vast network, an on-line e-mail list among patients, sub rosa, so to speak, and we, at the Lung Cancer Alliance, immediately notified every other lung cancer group we knew plus got Dr. Pazdur's statement up on those e-mail lists, so I think it was a very widespread net.

DR. MARTINO: Last question from me to Dr. Temple and Dr. Pazdur, at this point, are you considering revising the package insert, or where are you in that process?

DR. PAZDUR: Yes, we will be discussing that internally.

DR. MARTINO: Ladies and gentlemen, that is the end of this morning's meeting. There is a second topic and I am going to ask you to return here at 20 to 11:00, please, to start the second

part of this meeting.

[Break.]

Call to Order and Introductions

DR. MARTINO: Good morning, ladies and gentlemen.

The topic for this morning's meeting and discussion relates to a safety concern with the agents Aredia and Zometa, specifically osteonecrosis of the jaw.

Before we start into the topic, I would like the committee members, as well as the members from the FDA, to introduce themselves, and I think we will start on my right, Dr. Doroshow, if you would introduce yourself, please.

DR. DOROSHOW: Jim Doroshow, NCI.

DR. BRAWLEY: Otis Brawley, Medical Oncology and Epidemiology, Emory University.

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

DR. PROSCHAN: Mike Proschan, Statistician, National Heart, Lung, and Blood Institute.

DR. GRILLO-LOPEZ: Antonio Grillo-Lopez, Industry Representative.

DR. MORTIMER: Joanne Mortimer, Medical Oncology, University of California at San Diego.

DR. PERRY: Michael Perry, Medical

Oncology, University of Missouri, Ellis Fischel Cancer Center.

DR. HUSSAIN: Maha Hussain, Medical Oncology, University of Michigan.

DR. MARTINO: Silvana Martino, Medical Oncology, Cancer Institute Medical Group, Santa Monica.

DR. REAMAN: Gregory Reaman, Pediatric Oncology, George Washington University.

DR. RODRIGUEZ: Maria Rodriguez, Medical Oncology, M.D. Anderson Cancer Center.

DR. LEVINE: Alexandra Levine, Hematology/Oncology, University of Southern California.

MS. HAYLOCK: Pam Haylock, Oncology Nurse, University of Texas Medical Branch in Galveston, and I am the Consumer Representative.

DR. IBRAHIM: Amna Ibrahim, Medical Officer, FDA.

DR. SCHER: Nancy Scher, Medical Officer, FDA.

DR. COLMAN: Eric Colman, Medical Officer, FDA.

DR. AVIGAN: Mark Avigan, Office of Drug Safety.

DR. TEMPLE: Bob Temple, Office Director, OD-I.

DR. PAZDUR: Richard Pazdur, FDA.

DR. MARTINO: Thank you.

Next, the Conflict of Interest Statement by Ms. Clifford.

Conflict of Interest Statement

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

Based on the submitted agenda and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug

Evaluation and Research present no potential for appearance of a conflict of interest with the following exceptions:

In accordance with 18 U.S.C. 208(b)(3), full waivers have been granted for the following participants. Please note that the following interests waived are unrelated to Zometa, Aredia, and its competing products.

Dr. Otis Brawley has been granted waivers under 208(b)(3) and 21 U.S.C. 505(n) for owning stock in a competitor, valued between 25,000 and 50,000 per firm.

Dr. Michael Perry has been granted a waiver under 21 U.S.C. 505(n) for owning stock in two competitors, valued between 5,001 to $25,000. Because his stock interests fall below the de minimis exception allowed under 5 CFR 2640.202(b)(2), a waiver under 18 U.S.C. 208 is not required.

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

of the Parklawn Building.

With respect to the FDA's invited industry representative, we would like to disclose that Dr. Antonio Grillo-Lopez is participating in this meeting as an acting industry representative acting on behalf of regulated industry. Dr. Grillo-Lopez is employed by Neoplastic and Autoimmune Disease Research.

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

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

Thank you.

DR. MARTINO: Thank you.

Dr. Pazdur will now address the group and

give us some guidance as to the nature of this problem and what our agenda is.

Opening Remarks

DR. PAZDUR: Pamidronate and Zometa are potent intravenous bisphosphonates. Aredia received approval for hypercalcemia malignancy in 1991, for multiple myeloma in 1995, and for osteolytic bone metastases from breast cancer in 1996. Zometa was approved for hypercalcemia malignancy in August of 2001 and for a broad bone metastasis indication in February of 2002.

In 2002, the FDA received 9 spontaneous reports for osteonecrosis of the jaw in patients with malignancy whose treatment regimens included intravenous bisphosphonates.

In 2003, the first published reports of ONJ in patients treated with intravenous bisphosphonates appeared in the literature.

In a high proportion of cases, there was an association with a recent dental procedure. These patients had no history of radiation therapy to the head and neck.

The Zometa package insert was updated in September 2003 to include information about osteonecrosis of the jaw in the Adverse Events

section. The Aredia package insert was also updated in November of 2003.

In August 2004, changes were made to the Precautions section of the Zometa label, followed by a parallel change to the Aredia label, regarding osteonecrosis of the jaw. Novartis issued a Dear Doctor letter in September 2004 regarding osteonecrosis of the jaw.

The purpose of bringing to ODAC the problem of osteonecrosis of the jaw in association with intravenous bisphosphonates is to highlight a drug safety issue in oncology and stimulate consideration of how post-marketing safety issues in oncology should be addressed.

Although there have been anecdotal reports of ONJ in association with oral bisphosphonates administered for osteoporosis, we wish to limit today's discussion to osteonecrosis of the jaw in association with Zometa and pamidronate. Less data

is available for the oral bisphosphonates, and the risk-benefit considerations are different for patients with malignancy compared to patients being treated for benign bone diseases.

Thank you.

DR. MARTINO: Thank you, Dr. Pazdur.

Dr. Nancy Scher will now describe the history of Zometa and Aredia and its regulatory process.

FDA Presentation

Regulatory History of Zometa and Aredia

DR. SCHER: Good morning. I shall provide an overview of the regulatory history of the approval of Zometa and Aredia, and also provide some chronology regarding the recognition of an unusual adverse event occurring in some patients treated with intravenous bisphosphonates.

Aredia is approved for treatment of patients with osteolytic bone metastases of breast cancer and osteolytic lesions of multiple myeloma in conjunction with standard antineoplastic therapy.

It is also approved for hypercalcemia of malignancy and Paget's Disease of bone.

You have heard the Aredia approval dates.

Again, in 1995, there was an approval for osteolytic lesions of multiple myeloma, and in 1996, for breast cancer.

The approval of Aredia represents a regulatory precedent. Skeletal related events, or SRE, were defined and used as a basis for the approvals in the bone metastases indications for Aredia and subsequently for Zometa.

This slide shows you the four components that define that composite endpoint - pathologic fractures, radiation therapy to bone, surgery to bone, and spinal cord compression.

The multiple myeloma indication for Aredia was based on a single double-blind, randomized, placebo-controlled trial, where Aredia 90 mg monthly intravenously was given for 9 months.

Aredia demonstrated superiority to placebo for several SRE endpoints.

For breast cancer, there were two

licensing trials for Aredia. They were double-blind, randomized, placebo-controlled, Aredia 90 mg IV every 3 to 4 weeks was given for 24 months.

Patients were required to have at least 1 osteolytic lesion. In one study, patients were receiving chemotherapy, and in the other study, patients were receiving hormonal therapy.

Together, the trial results supported the indication for Aredia in patients with metastatic breast cancer.

Zometa is approved for treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy. Zometa is also approved for hypercalcemia of malignancy.

Zometa was approved for hypercalcemia of malignancy in August of 2001. At that time, Novartis submitted a supplemental NDA for the bone

metastases indications to FDA. FDA reviewed this application as a priority NDA.

In February 2002, Zometa was approved for the bone metastases indications. This approval for Zometa expanded the indications for bisphosphonates.

Zometa was approved for a broad range of solid tumors, not limited to breast cancer as Aredia had been. Furthermore the lesion type was not limited to osteolytic lesions. However, the optimal duration of therapy could not be defined from the trial design.

The oncology indication for Zometa was based on 3 randomized trials. The multiple myeloma/metastatic breast cancer trial randomized patients to an active control of Aredia 90 mg, for Zometa 4 mg.

The remaining 2 trials were placebo-controlled, 1 in prostate cancer and 1 in other solid tumors.

The primary endpoints were time to first SRE and proportion of patients with SRE.

This slide provides some additional detail about the Zometa registration trials. You can see the multiple myeloma/breast cancer trial was

relative large, greater than 1,600-patient trial, and it had a non-inferiority design.

Time to first SRE was the preferred FDA endpoint. You see information about that presented. For prostate cancer and other solid tumors, Zometa 4 mg demonstrated superiority to placebo. For multiple myeloma or breast cancer, Zometa 4 mg was non-inferior to Aredia 90 mg.

This slide shows the number of cases of osteonecrosis of the jaw reported to the FDA by year. In 2001, there were no such reports. In 2002, there were 9 cases reported of patients with osteonecrosis of the jaw who were receiving intravenous bisphosphonates as part of their treatment regimen.

There were additional cases in 2003, and more cases in the first half of May of 2004. These numbers were provided to me by the Office of Drug Safety. As of this time, as you will hear in

subsequent presentations, the number of reports is in excess of 600.

This slide lists a fairly comprehensive review of the literature of reports of osteonecrosis of the jaw associated with bisphosphonates. You will see the chronology is somewhat similar to the chronology of the adverse events reported to the FDA.

I want to point out that this literature pretty much starts in 2003. Most of the reports are abstracts or very brief reports, and particularly earlier on, we are limited to the oral surgery literature.

The most detailed report that I am aware of was Dr. Ruggiero's paper in May of 2004, reporting 63 cases of osteonecrosis of the jaw in patients taking bisphosphonates. Again, this was in the oral surgery literature.

Subsequent speakers will provide you with details of the clinical manifestations of this adverse event. This is just a very brief and limited description of some of the features

characterizing these patients.

The patients with ONJ had diagnoses of malignancy. They had not received head and neck radiotherapy. Their treatment regimens included intravenous bisphosphonates. A high proportion of these patients had recent invasive dental procedures.

In response to reports of ONJ in cancer patients treated with IV bisphosphonates, changes were made to the labels of Zometa and Aredia.

The Adverse Events section was updated to include ONJ in September of 2003 for Zometa, and then Aredia in October. The Precautions section for both drugs were updated in August 2004.

The next two slides paraphrase the contents of the current Zometa label. For reference, the actual language from these sections of the labels is included in the document which contains discussion points distributed this morning, and it was also in the Committee's background documents if you would like to refer to the label information.

I think I need to go back.

The Adverse Events section reported that ONJ had been seen in patients treated with

bisphosphonates. The majority of cases were associated with a recent invasive dental procedure. It stated there were multiple risk factors for ONJ, including cancer, chemotherapy, radiotherapy, corticosteroids, et cetera.

It stated that although causality cannot be determined, it would be prudent to avoid dental surgery as recovery may be prolonged.

The Precautions section reiterates some of the previous information, is placed in a more prominent section of the label, and provides some new information, as well.

Osteonecrosis of the jaw is seen in cancer patients, many of whom were also receiving chemotherapy and corticosteroids, the majority of cases associated with dental procedures. Many patients had signs of local infection including osteomyelitis.

Baseline dental exam should be considered

if there are risk factors such as cancer, chemotherapy, corticosteroids, poor oral hygiene.

While on treatment, avoid invasive dental procedures. If a dental procedure is required, there is no data to say if discontinuing therapy reduces the risk of ONJ.

In summary, Zometa and Aredia are effective drugs for the bone metastasis indication.

An unusual adverse event has been identified in some patients treated with intravenous bisphosphonates.

The true incidence of osteonecrosis of the jaw is unknown.

Thank you very much for your attention, and you will hear a lot more about this from subsequent speakers.

DR. MARTINO: Thank you, Dr. Scher.

Our next speaker is Ms. Carol Pamer from the Office of Drug Safety. She will speak on Post-Marketing Safety Assessment of Osteonecrosis of the Jaw with Pamidronate and Zoledronic Acid.

Post-Marketing Safety Assessment of Osteonecrosis of the Jaw: Pamidronate and Zoledronic Acid

MS. PAMER: Good morning. My name is Carol Pamer and I am a safety evaluator in the

Office of Drug Safety.

I will be presenting a brief overview of the FDA's spontaneous reporting system named AERS, including its strengths and limitations. I also will provide a high-level summary of case reports of ONJ that have been reported with pamidronate and Zometa.

I am going to discuss specific difficulties in assessing the case reports, and finally, our epidemiologist, Carolyn McCloskey, has prepared some comments concerning the epidemiological issues concerning the study of this event, and I will present those remarks on her behalf.

Generally speaking, a spontaneous reporting system is a mechanism for clinicians and patients to report adverse events that occur after a drug has been marketed in a larger and more diverse group of patients after the clinical trials

are over.

In the U.S., these case reports are known as Med Watch reports, and the database which houses them is the AERS database. FDA has maintained a reporting system since 1969. Over time, modifications have been made to the system and the database primarily as computer capabilities have increased.

There are a number of factors which affect reporting patterns and quality of case reports that FDA receives. Some types of adverse events are more or less likely to be reported than others, and some examples of that are cases with a fatal outcome or severe outcome, special populations, such as children, or adverse events that are usually suspected to be related to drug use.

The type of product and condition for use can affect reporting. Prescription drug products require patient interaction with the health care system, so those events related to the products may be detected more frequently.

Reporting for a drug tends to be heaviest

in the first few years after marketing, and then it tapers off over time. Media attention or medical publishing will affect that. Finally, the quality and extent of reporting varies by pharmaceutical company, and regulations affect that directly, as well.

AERS is an uncontrolled means for gathering information about a marketed drug, so some case reports are better documented and more convincing of a possible relationship than others.

Critical elements of a case report, which are evaluated, include the time to onset or temporal relationship of the adverse event to the drug, assessment of whether the patient has any symptoms of the adverse event prior to starting a product, and a baseline health status can help in documenting that.

Evaluating drug dechallenge is drug safety jargon for evaluating whether the symptoms of the adverse event went away after the drug is stopped.

Drug rechallenge refers to testing whether the adverse event recurs if the drug is restarted.

If both dechallenge and rechallenge are positive, that can be a pretty strong indicator that an adverse event is related to a drug.

Another critical issue in evaluating the strength of a case report is determining whether there are other explanations for the events. Typically, these are other medical conditions or other drugs.

The other items, consistency with pharmacologic effects, known effects in the class, and controlled trials attempt to make an argument that the drug caused the events rather than they were simply associated with it.

There are some limitations of using spontaneous reports for investigating drug safety. The system is passive or voluntary in the U.S., so in many cases, are not reported. This will also vary from drug to drug and over time.

Reporting bias exists in that some events are more likely to be reported than others. The quality of cases is highly variable. You have many reporters and reports are often incomplete.

Duplicated cases can be submitted and this requires a case review to sort those out.

Very importantly, we don't know what proportion of the true number of cases of an adverse event in the population are reported to AERS, which is the numerator of an incidence rate, and we don't know the true counts of how many people take the drug. That is usually estimated by drug usage data at this point and that is the denominator of an incidence rate.

So, with these limitations in mind, there are adverse events for which AERS is best applied. Its best functionality is for detecting safety signals, the early warnings that there might be a problem with the drug.

The best documented convincing cases can be used to develop a descriptive case series. The more well established a diagnosis is for an adverse event, the more likely it will be noted by a clinician and also be readily identified in AERS.

Events with a low background rate in the general population or that are rare can be more

readily detected with AERS, and events with a shorter latency period lend themselves to detect signal detection more readily.

Now, I will just present a quick summary of the reports of osteonecrosis and osteomyelitis that have been reported for the two IV bisphosphonates.

An in-depth review of 139 cases was previously conducted by Jenny Chang of the Office of Drug Safety, and a copy of that review was included in the background package for this meeting, and my tables just provide a brief status update to that review, which my numbers are cumulative though.

Novartis Pharmaceuticals will be presenting a more detailed overview of the cases.

This slide lists the details of the search used for this update, and there are two important differences to point out. The case series by Jenny Chang included cases of osteonecrosis at other sites, although most cases involved the jaw, and the Novartis data differ due to slight differences

in search terms, different cutoff date, and they don't have reports from other manufacturers.

It is probably not very visible all the way back there, so I will go through it.

This slide summarizes which of the two drugs was indicated as being prescribed in the reports. There are a total of 654 in which the two drugs are mentioned. The first listing is pamidronate only, which was 136 or 21 percent of the reports.

Pamidronate or Zometa, its sequential use was defined in this way as any history of use primarily to keep the solo use cleaner and the drugs persist in bone, so it was just neater to keep solo therapies separate, and then if there was any mention of a history of the two, then, this is in this category, and that constituted 28 percent of these reports.

Then, zoledronic acid were 49 percent, and then one of the two drugs, oral history again of another bisphosphonate, that was about 2 percent of the 654. The numbers just grossly seem to be in

proportion to the use of the products.

This table summarizes the primary indication for use listed in the report. Most patients were being treated for cancer. Multiple myeloma was approximately 34 percent either with or without another. Most of them were alone. Some mentioned a history of other cancer, so those were just tallied separately. Breast cancer, approximately 27 percent if you consider other cancers mentioned. Prostate cancer, around 7 percent.

There were 16 percent cancer unspecified or other type. Most of those were unspecified. Osteoporosis, osteopenia, and osteolysis, which is probably a cancer, that was 1 percent, and then 15 percent of the cases didn't have an indication listed at this point.

At this point, I will discuss specific difficulties encountered in evaluating these cases reported with the two drugs.

One of these is the increased rate of reporting due to publicity makes the assessment of

the usual pattern of reporting difficult. Confounding factors were present in many of the cases.

Assessment of drug dechallenge is confounded. I will explain that later. Establishing a pattern in the time to onset after the drug was started is also difficult.

Confounding factors were present in many of the case reports primarily due to the nature of the underlying disease being treated.

This list includes the various drugs, procedures, and medical conditions which theoretically could have some effect on bone and increase the risk of ONJ.

Spontaneous reports, as frequently happens, had missing information, which was also true in this case series.

A clear assessment of the drug dechallenge was limited by the fact that these drugs persist in bone, and the duration of action is prolonged, so even though the drug is stopped, the actions persist, and a prolonged period would be required

to determine whether the patient completely recovered.

Many patients required therapeutic interventions, so this confounds evaluating whether the only factor in the patient recovering was, in fact, stopping the drug.

Time to onset was also difficult to evaluate in that the detection of ONJ was often at a later stage, for example, when a dental extraction was conducted, but failed to heal.

We didn't search for cases where possible early symptoms were present, such as jaw pain or tooth loss, but no definitive diagnosis had been made. That was beyond the scope of the search. Information on the early symptoms was missing in a number of cases.

Now, I will present Carolyn's remarks on the epidemiological perspective of studying this condition.

Studying osteonecrosis of the jaw is the challenge and even more so with these drugs. It is a rare event and obtaining a population background

rate for comparison is difficult, and it is especially difficult for multiple myeloma and breast cancer patients.

The difficulty in identifying ONJ cases in existing databases is that ONJ does not have a specific code for searching a database. For example, there is no specific ICD-9 code for ONJ.

It is also difficult to determine an accurate number of patients exposed to IV bisphosphonates due to the fact that many are given in free-standing clinics.

Finally, it will be difficult to identify an equivalent cancer control or comparison group for study of ONJ associated with the IV bisphosphonates.

Some potential sources of data include oncology clinics, which could provide a cohort of patients exposed to IV bisphosphonates. A potential source for determining a more accurate count of cases could be dentists and oral surgeons. Dentists could provide cases of dental or jaw infections, jaw pain, or osteomyelitis of the jaw

regardless of drug exposure.

A national registry could provide a means to collect all cases of ONJ identified in different settings.

To summarize the epi perspective, there are limitations in identifying and capturing cases and quantifying IV bisphosphonate exposure in electronic, pharmacoepidemiological and post-marketing surveillance data including HMOs and passive reporting databases.

Chart review studies at major medical or cancer centers have their own limitations in capturing all ONJ cases with these products.

Obviously, a randomized, controlled clinical trial would be superior to studying this in currently available databases, however, there are limitations to controlled clinical trials especially since this condition is rare.

A national registry of ONJ cases should be considered.

To conclude, in spite of the limitations of the available drug safety tools, we believe that

these cases present a highly plausible safety signal. Some of the reasons for this are most of the cases that have been reported affect the jaw, lending plausibility to a specific or common mechanism.

A large number of reports of a generally rare event have been received. The duration of use of the drug relative to diagnosis of a chronic condition is fairly short, and serious adverse event reports tend to be captured well in AERS.

We would suggest that other studies be conducted to attempt to identify which patients may be most susceptible or if modification to treatment regimens would reduce the risk.

Thank you.

DR. MARTINO: Ms. Pamer, on behalf of the committee, I need to ask you to clarify some things for me.

Can you give me a better understanding of who tends to report or who has the ability to report toxicities to the FDA system? I am assuming it's patients, I am assuming it's physicians. Are

pharmaceutical data also incorporated into that?

MS. PAMER: Many of the reports we received are reports that have come to the company, and then the company is required to send those to FDA, and patients, there are means through the Internet. You can also report directly to FDA through Med Watch. So, this is the Med Watch data collection system.

DR. MARTINO: So, anyone is able to access the system. In general, where does most of the information come from, is it physicians, is it pharmaceuticals, or is it individual patients? In general, I am asking you, not specific to this toxicity.

MS. PAMER: Most of reports are, and in this case series, most of them were dentists, M.D.'s, or oral surgeons. They might have reported first to the company, but they come to us, but they are mostly health care providers.

DR. MARTINO: So, a patient would be the least likely person to report directly to you, do I understand that correctly?

MS. PAMER: Less frequently they do, but it depends. There are some issues where they report a lot through the Internet.

DR. MARTINO: So, once someone initiates a report, I am assuming that there is information that is requested from them, that gives you certain details. Is there any human interaction to then get additional data, or what is the extent of what is obtained from such a report?

MS. PAMER: Probably the company could give you an idea of how they collect the information on how their system works.

DR. MARTINO: My question--I may ask the same question of them--but my question of you is, the FDA system is really the one I am interested in, once I, as a human being, report that I have had a toxicity, I am assuming there is some questions I will be asked to answer, who are you--

DR. AVIGAN: Can I just participate?

DR. MARTINO: Can someone help me?

DR. AVIGAN: Yes.

DR. MARTINO: Thank you.

DR. AVIGAN: We actually have a number of avenues by which we can address those issues, when a signal is seen and there are questions that are raised that require follow-up, we have the opportunity to ask the manufacturer, the company, to go and do sort of specified follow-ups through

discussions that we would have with them.

Another approach is that on particular issues, we can contact the reporter, the reporters are listed in our Med Watch form, and get direct follow-ups from them. So, I would say that there are a number of possibilities, and these are generally conceived of based on the case at hand.

The retrospective look at safety problems typically is limited, because you don't get information in real time, and there is a general problem of getting a full plate of information on particular cases when you are going retrospectively to cases that have been reported about previous events.

DR. MARTINO: That does answer my question. Help me to understand what would

stimulate the system to recognize that there is a potential problem. I am assuming that all kinds of things get reported to you and somehow someone has to sift through what is noise and what do you sort of focus in on. Answer that for me, please.

DR. AVIGAN: Right. It really is on a case-by-case basis, and I think Carol has outlined some of the points that would raise our concerns about a signal being truly linked to a risk and a causally related event.

Some of the points are that the event that is being reported has a low background rate or would not be necessarily expected to occur in the kind of cluster that it is being reported at. So the background effect, the temporal association, and then the quality of the cases themselves.

In addition to the counting of the total aggregate of cases, we actually with specificity look at individual cases, and some cases based upon the information that is provided allow us to create a kind of probability analysis of causality, so that it is a different dimension of looking at the

question of is the drug going to the specific adverse event.

In this case, one of the features of this particular adverse event is that the anatomical site specificities are quite striking, that is, the osteonecrosis search is not anatomically specific, but when we pull the cases and look at what these reports are, they are very, very strongly, well, biased.

Most of the cases actually are of the jaw, which would be different than, let's say, an osteonecrosis search for the general background population or for other medications. As an example, that would point towards a signal, for example.

DR. MARTINO: Thank you.

Next, Dr. Brian Durie from Cedars-Sinai will discuss Osteonecrosis of the Jaw in Myeloma: Time Dependent Correlation with Zometa and Zometa Use.

Osteonecrosis of the Jaw in Myeloma: Time Dependent Correlation with Zometa and Zometa Use

DR. DURIE: Members of the Committee, ladies and gentlemen, I appreciate the opportunity to present these data to you today. These data

were presented at the American Society of Hematology in oral session in December and will be published shortly.

The basis for these studies feeds in exactly with the discussion that was just being held. This is a study that was conducted as a collaboration between the International Myeloma Foundation, which is a nonprofit entity based in California, and Cancer and Research and Biostatistics, which is the research entity run by John Crowley. Many of you will know that that is the stat center for the Southwest Oncology Group.

So, this is a collaboration between the IMF and a rather well-known statistical group.

The International Myeloma Foundation provides a number of functions. One of them relates to patients, and that is an educational function, and that is serviced by an 800 hot line, and it is serviced by a variety of seminars that

are held across the country, as well as help to support groups.

So, in terms of receiving a signal, if something unusual is happening, and patients want to find out, they are quite likely to call our 800 number. So, we are one of the first people who might hear about a new problem that is emerging.

In this particular study, I would like to emphasize one other point, and that is that the purpose here was to try to identify individuals with osteonecrosis of the jaw, and so we could evaluate and understand these cases.

We were not in a position to evaluate the denominator for these studies, so this is not a study related to the incidence. It is a study related to an analysis of patients who actually have this problem.

So, just to show you visually, well, what is osteonecrosis of the jaw, and these pictures on the left were provided by Sal Ruggiero, who is present here today on my right, and was the first person to report a case series of 63 patients in

the Journal of Oral and Maxillofacial Surgery.

So, it covers a spectrum. The first part of the spectrum is exposed bones, bone spicules. The end of the spectrum is where there has been significant underlying osteonecrosis of the jaw, which can indeed be a substantial problem which involves poor healing, secondary infection, and loss of teeth, and in some cases, significant parts of the jaw.

There are several mechanisms that have been proposed linked in with this related to the disruption of the bone remodeling cycle.

So, how frequent is osteonecrosis? As you have heard, we do not really know the true incidence of this except that it was rare in the past, and it is very clear that it was rare in the past and now we are seeing it.

Our 800 number is ringing. Patients are coming in to see dentists and oral surgeons. This was not happening before for myeloma patients. Dr. Marx reported his first 36 cases in 2003. Dr. Ruggiero, who is right here, reported his patients

in 2004. Those were 63 patients that were diagnosed between 2001, February, and 2003.

Of note, there are two aspects about his patients. They did include some patients that had been treated with oral bisphosphonates, the majority with IV bisphosphonates. They did include a few patients who did not have cancer, patient who had osteoporosis only.

Here, more recently, in myeloma groups around the country, clearly, we are seeing many more of those patients. At the patient seminars that I mentioned earlier, these are seminars where 1- or 200 patients would be present at a time.

Consistently now, there are 5, 10, sometimes more patients in the audience who have osteonecrosis, and this translates in that setting to maybe 2 to 5 percent of the people who are in that setting. How that translates to the wider population, I don't know.

For me, this was a very important opportunity because it allowed me to structure the questionnaire that I am going to show you today. I

had met a lot of patients who had osteonecrosis of the jaw. I understood how it had come to attention, how it manifested.

I knew, for example, that most of them knew that they did, in fact, have osteonecrosis of the jaw. They had seen a dentist, they had seen an oral surgeon. They knew what that was, so they could answer that question yes or no.

So, was this a diagnosis missed prior to 2001? I think not. Certainly from the bottom picture that I showed you, this is not something that would go unnoticed.

What has caused the increased frequency? Well, both Dr. Marx and Dr. Ruggiero certainly drew attention to the bisphosphonates.

So, what are the questions right now? From our perspective in this questionnaire, we looked at is the likelihood of osteonecrosis ONJ linked to the use of the Aredia and Zometa in the patients that responded to our survey, to what extent were other therapies impacting the frequency and the likelihood, were there identifiable risk

factors, what was the magnitude or severity of the problem, and what we thought was quite important was is this a problem confined to myeloma, is it more common in myeloma versus, for example, breast cancer.

So, we surveyed both myeloma patients and breast cancer patients, which is important in one particular aspect, and that is that the treatment, the other treatments for breast cancer and myeloma are obviously quite different. For example breast cancer patients are not frequently treated with thalidomide and high-dose dexamethasone.

So, this was an anonymous web-based survey that was conducted in August of 2004. It included 1,203 patients, of which 904 had myeloma, 299 had breast cancer. They were recruited by a variety of electronic means - through the IMF web site, through ACOR, but also through a number of established listservs, Nexcura and Y-Me, National Breast Cancer Organization.

A number of very, very specific questions were asked with pop-downs where it was possible to

select a variety of answers.

The setting for this, in structuring the questions, was the treatments that are available for myeloma. The therapies have mostly been available for several decades, and you can see here, starting at the bottom, Melphalen and prednisone, radiation therapy including sometimes to the head and neck available for a long time. Steroids have been used for several decades, stem cell for two, three decades now.

At the top here, you see really three types of agents that have been available more recently: the bisphosphonates, thalidomide, and Valcade. Valcade has been available sufficiently recently that it is not really an issue. So, we focused on thalidomide, bisphosphonates, and steroids primarily as potential risk factors, but we looked at all of these therapies.

Of 1,203 patients, 904 myeloma, there were 62 myeloma patients who had osteonecrosis of the jaw. There were 54 who, in addition, these are 54 additional patients who had suspicious findings.

These were patients who had not been given a diagnosis of osteonecrosis of the jaw, but had suspicious findings that we identified as bone erosions, bone spurs, or exposed bone. These were specific questions that were asked.

For breast cancer, 13 with a diagnosis of osteonecrosis, 23 with 1 or more of the suspicious findings.

The first thing that we noticed was that it was more likely for osteonecrosis to occur over time. In this case, it was from the time of diagnosis. You will see I used different time markers here. This one is time from diagnosis. We also looked at the time from the start of bisphosphonate therapy, for example.

You will see this curve has got two parts to it, a very shallow curve here, and then a sharper part to the curve here. So, this is what we decided to investigate in more detail.

The first thing that we looked at was the time frequency over the last few years, 57 patients where we had data. These are the number of cases

in 2004, 321. There were cases in the past. There were patients related to head and neck irradiation. The same pattern for breast cancer. You can see a striking increase in the last 2 1/2, 3 years.

This shows you the frequency of use of other therapies in addition to the bisphosphonates. You can see here the 62 patients, myeloma, osteonecrosis of the jaw, 57 had been taking bisphosphonates, 3 had head and neck irradiation, so there are actually 2 patients who had not had head and neck irradiation or were taking bisphosphonates.

You can see there was a pattern of Aredia and Zometa use as listed here. We are going to go into that in more detail. A majority of patients had obviously used steroids, some prednisone, some dexamethasone, and about half the patients had taken thalidomide at some point.

This shows you the increasing incidence of osteonecrosis among the respondents from the date of diagnosis, looking at the use of Zometa, Aredia alone, patients who had been taking Aredia, but

switched over to Zometa when it became available, and those who had not taken any bisphosphonate.

You can see the little blue one over here. We are going to look at that in more detail. That is Zometa, which represented 22 percent of the patients, 28 percent to Aredia alone, 45 percent had actually switched over from Aredia to Zometa. So, interestingly, this occurred more frequently in this series and patients who had switched from Aredia to Zometa.

We were quite interested in the time to the onset in the two major groups there, and this was quite striking. Patients who had been taking Zometa, the average time, the mean time 18 months to the onset of osteonecrosis, 19 months to the onset of suspicious findings. Aredia, 6 years, 72 months, somewhat shorter, to the onset of suspicious findings.

Now, obviously, we realized that these drugs have not been on the market the same length of time, so we have done some corrections related to that, that you will see in a moment. This is

obviously statistically different.

This just shows you visually, the blue is Zometa, the red is Aredia, for myeloma and for breast cancer. The patients were more frequently either taking Zometa or switched over to Zometa at the time that they developed the osteonecrosis or the suspicious findings.

In this case, we looked at the exact length of the treatment with Aredia or Zometa with respect to the likelihood of getting osteonecrosis of the jaw. Again, you can see there is a difference related to Zometa or those who switched from Aredia to Zometa versus Aredia alone.

In all three cases, obviously, it is going up over time, of course.

Now, to compensate for the fact that the Zometa has only been on the market for three years at the time of our study, we censored the data at three years and compared Aredia with Zometa with three-year censoring and looked at the log rank p value estimates at 36 months.

Zometa is in blue, and you can see here

that it occurred more frequently. I think that what caught our attention, and our concern actually, was this is 12 months right here. You can see that there were clearly patients having osteonecrosis of the jaw within the first year of therapy, the mean value was 18 months but certainly cases occurring within the first 6 to 12 months.

We looked at other factors. This compares patients who had been taking prednisone and not taking prednisone. You can see that these are the events here. No difference in the likelihood with and without prednisone, although in a variety of other studies, there was some increased risk in patients concomitantly taking steroids, but this did not play out over time.

We also looked at thalidomide and dexamethasone, and again there were some suggestions that patients taking thalidomide and dexamethasone were at higher risk, however, this did not play out in the time dependent regression analyses, so that both for thalidomide and dexamethasone, there was no difference using the

log rank method.

So, what suddenly occurred to me was, well, why did we start to see this problem in 2001, and I suddenly realized when I was looking at the statistics that 6 years is the average time to the onset with Aredia, well, 6 years is the time since Aredia came on the market, 18 months is the time for Zometa. Well, that is the time since Zometa has been on the market.

So, there is a coincidence of time frames here related to the time since these agents have been in the marketplace.

There is one other very important point, and that is that 6 years of Aredia, how many patients with myeloma are alive and could be taking Aredia for 6 years. Well, obviously, that is less than 20 percent of the patients. So, the number of patients at risk taking Aredia at 6 years is much, much lower.

Just to compare the data with myeloma and breast cancer, since the therapies are so much different, there was no difference in the

likelihood with censoring at 3 years between the breast cancer patients who responded and the myeloma patients who responded.

However, if you looked at Zometa and Aredia, the difference persisted. It was much more likely that Zometa could be associated with osteonecrosis or suspicious findings early in both myeloma and breast cancer.

What were predisposing factors? It was quite striking and has been emphasized by several speakers that the predisposing factor is prior dental problems including surgery and all kinds of dental issues, and here a very striking difference. Patients likely to get this problem are highly more likely, with myeloma and breast cancer, to have had underlying dental problems.

So, among the respondents, duration of therapy is clearly an increased risk factor. With the 36-month estimates, Zometa is more likely than Aredia to be associated with osteonecrosis.

None of the other therapies in the time dependent analyses impacted this likelihood.

Patients with prior dental problems were much more likely to develop osteonecrosis of the jaw.

Our preliminary working conclusions, and people are going to be able to discuss elements that might derive from this, but clearly, precautions related to dental care could impact the likelihood of this disease, and obviously, precautions related to bisphosphonates could impact the likelihood of this problem.

I would like to thank the groups and individuals who participated in this project, particularly the organizations who contributed patients, the statistical center, and particularly Vanessa Bolejack, who did the statistical analysis.

Thank you.

DR. MARTINO: Thank you, Dr. Durie.

I would now like to turn to Novartis and ask Dr. Young to present their data.

Sponsor Presentation - Novartis Pharmaceuticals

ONJ Reported in Bisphosphonates Treated Patients - An Overview

DR. YOUNG: Good morning. I am Dr. Diane

Young, Vice President of Clinical Development-Oncology at Novartis. I am an oncologist by training.

I would like to start by thanking the Chair, ODAC panel members, as well as the FDA today for the opportunity to share our current understanding of an important clinical entity, osteonecrosis of the jaw. There has been an recent increase in awareness and interest in this condition due in part to the efforts of Drs. Ruggiero, Marx, and Durie, as well as the FDA and Novartis.

In this presentation, I will provide an overview of the ONJ cases reported in bisphosphonate-treated patients. This will be followed by a perspective on the benefit-risk of bisphosphonates in patients with metastatic bone disease by Dr. James Berenson.

Allow me to recognize the advisors that are here with us today to help answer questions that may come up during the discussion. It is important to note that while these external

advisors have been invited by Novartis, the views that they express here are their own views, and not those of the company.

Dr. Ana Hoff from the M.D. Anderson Cancer Center is the principal investigator on a chart review that is ongoing in cases of ONJ in bisphosphonate-treated patients. Dr. James Berenson from the Institute for Myeloma and Bone Cancer Research.

Dr. Regina Landesberg, Assistant Professor of Oral and Maxillofacial Surgery at Columbia University. Dr. Lloyd Fisher, Professor Emeritus of Biostatistics from the University of Washington. Dr. Salvatore Ruggiero, Chief, Division of Oral and Maxillofacial Surgery at Long Island Jewish Medical Center.

This is an overview of my presentation. Importantly, Zometa and Aredia have delivered significant benefits for patients with multiple myeloma and metastatic disease from solid tumors, reducing significant morbidity from the serious complications that these patients experience

related to bone involvement from their tumors.

Novartis has actively examined cases of osteonecrosis of the jaw since we received the first spontaneous reports in December of 2002.

In spite of this, ONJ remains a poorly understood entity. Frequency estimates vary wide, however, based on available data it appears to be infrequent in cancer patients on bisphosphonates.

Additionally, the anecdotal and limited nature of the available data makes it hard to draw conclusions about causation or any difference between Aredia and Zometa.

Novartis takes reports of ONJ very seriously and we are committed to ensuring patient safety. We will do this through conducting further studies to increase our understanding of the condition, communicating our findings, and identifying strategies to prevent and optimally manage this problem.

The benefits of Zometa and Aredia in reducing the significant morbidity associated with complications of bone disease in cancer patients

remain highly favorable when considering the risk of ONJ.

As the panelists are aware, metastatic bone involvement by cancer is a prevalent condition and causes serious consequences for patients with advanced cancer. The complications of bone metastases cause considerable morbidity including pain, impaired mobility, pathologic fracture, spinal cord or nerve compression, and hypercalcemia of malignancy.

Zometa and Aredia help people living with cancer avoid or delay painful and debilitating complications of metastatic bone disease. As Dr. Scher noted in her presentation, Aredia and Zometa have been both shown to be effective in the treatment of bone metastases in multiple myeloma and breast cancer.

Zometa has been further shown to be effective in prostate cancer, where Aredia was not effective, and in other solid tumors, such as lung, renal, colorectal, and bladder cancer. The benefit-risk of IV bisphosphonates is well

established. Risk of renal impairment is manageable in most cases by monitoring creatinine.

Based on this profile, Zometa and Aredia have become the standard of care and are recommended in ASCO guidelines for the management of multiple myeloma and metastatic breast cancer patients with bone lesions.

I will begin my review with osteonecrosis as a general clinical condition before focusing on the jaw. Osteonecrosis is a better known clinical entity most commonly seen in the hip. The etiology and pathogenesis are not well understood.

The common precedent is impaired blood supply leading to ischemia of bone. Osteonecrosis has been associated with a variety of risk factors, and is generally felt to be a multifactorial process. Cancer patients are at particular risk of developing osteonecrosis.

In a search of the general practice research database in the UK, the incidence of osteonecrosis in cancer patients was 4 times higher than in the general population. Coagulopathy is

another risk factor as are treatments, such as corticosteroids, radiation therapy, and chemotherapy.

Interestingly, there are preclinical data and clinical data to suggest a role for bisphosphonates in treatment of osteonecrosis of long bones. There is a series of 16 patients with osteonecrosis of the hip who had improvement after 12 weeks of alendronate by Agarwala, et al.

Osteonecrosis of the jaw has been less frequently described and the incidence in the general population is not known. The pathogenesis is not well understood, although similar risk factors to osteonecrosis have been suggested in the literature.

It is important to note that there may be risk factors that are specific to jaw bones that may play a role of pathogenesis of osteonecrosis of the jaw. Exposure to the external environment and particularly infectious agents through the teeth is one issue. In addition, there is repeated trauma from dental procedures, and lastly, the oral cavity

is an area where the bone is covered by a relatively thin mucosal layer, which is subject to trauma.

ONJ in cancer patients is a condition of which there is limited awareness until recently. The incidence of ONJ in cancer patients is unknown.

There were a few case reports of ONJ in cancer patients that occurred with chemotherapy, and not with bisphosphonates, in the literature prior to 2003. Another condition, osteoradionecrosis, related to head and neck radiation has been frequently described with a reported incidence rate of 8.2 percent.

Novartis received the first spontaneous report of ONJ in an IV bisphosphonate-treated cancer patient in December 2002. The first series of such cases were published in 2003 by oral surgeons who were treating these patients.

Since these reports, we have been investigating these cases to better understand this clinical problem.

There are four data sources available

regarding ONJ that I will briefly review today - the Novartis clinical trials, spontaneous reports that have been made to Novartis, literature, and a retrospective chart review that is ongoing at M.D. Anderson.

Before reviewing the data, I want to point out that there are significant limitations in these data sets which make it difficult to draw conclusions about many aspects of ONJ.

Controlled clinical trials offer generally reliable, quality assured, source verified data. The Novartis clinical trials which I will discuss were conducted prior to 2001, at a time when there was little awareness of ONJ. In addition, the median follow-up for these trials is about 5 to 13 months, and we plan to update this follow-up as part of the investigation.

The spontaneous report database, as expected and as explained well by Dr. Pamer, may have incomplete information, as well as diagnostic selection and reporting biases.

The existing literature is mostly case

series. In many cases, the data are incomplete. In addition, there was the web-based survey presented today, which does have some methodologic limitations which I will discuss later.

The M.D. Anderson Cancer Center study is a retrospective chart review of over 4,000 charts of patients who have received bisphosphonate therapy, looking for cases of ONJ at a single center. It is ongoing at the present time.

In addition, there are a number of issues which may confound interpretation of all these data sets. The impact of a recent increase in awareness may affect the numbers and types of reports received, the lack of consistency across these data sets in terms of case definition, and there have been other changes in treatment of cancers that may have a possible impact during the same time period.

Let us look first at our clinical trials. We did a retrospective search of the clinical trial database to identify cases of ONJ, since this had not been identified as any sort of adverse event that we noticed during the study conduct.

The lack of clear definition of ONJ poses a challenge to identifying these cases in a clinical trial database. This shows the process

that Novartis uses to identify potential cases of ONJ from the clinical trials database and the spontaneous reports database.

There is no current MedDRA term for ONJ, so in order to screen for potential ONJ cases, Novartis used a wide net of 18 MedDRA terms as shown. Cases that resulted from this screening were medically reviewed to identify cases of ONJ.

This is the current working definition that Novartis uses to identify potential ONJ cases, any of the findings shown here with a suggestion of maxillofacial area involvement. This is a fairly broad range of terms because we want to err on the conservative side and attempt to capture as many cases as we can.

The next two slides show, in summary, pivotal trials that have been screened for ONJ, and also shows the trials where the ONJ cases were identified, because we actually did identify 6

cases consistent with this definition in this search.

The first 3 trials are the placebo-controlled Aredia trials in the bone metastases indication. The median duration of follow-up for these trials was 10 to 18 months. One case was identified in the multiple myeloma trial on an Aredia arm.

007 was a dose-finding study for Zometa in bone metastases that had an extension phase--I am sorry, that is with Aredia. Two cases of ONJ were identified in the study in multiple myeloma patients, one in the Zometa arm and one in the Aredia arm.

036 and 037 were hypercalcemia malignancy studies comparing Zometa to Aredia. A single case was identified in this study on the Zometa arm.

Study 10, 11, and 39 were the pivotal bone metastases studies for Zometa. The median follow-up was 5 to 14 months in these studies. 10 was the study that was mentioned, a non-inferiority study in breast cancer and myeloma comparing Zometa

to Aredia. A single case was identified in the Zometa 4 mg arm of the study.

704 was a placebo-controlled study evaluating prevention of metastases in hormone-refractory prostate cancer without bone metastases. A single case of possible ONJ was identified in the Zometa arm.

The 6 cases are for simplicity displayed by treatment received. Please note that the dose groups shown reflected the trials previously. It is a variety of trials with different follow-up periods, and these are not balanced per se for tumor type or indication on bone mets versus hypercalcemia, but, in general, if we are looking at it, we did not see any cases in 1,347 patients treated with placebo.

We saw 2 cases of ONJ out of 1,334 patients treated with Aredia, and 4 cases of ONJ out of 2,730 patients treated with Zometa. It is important to note that all of these cases were described as non-serious by the investigators.

The next two slides show clinical findings

in these 6 cases. In the first column, we show the tumor type, and then the diagnosis, and the site, as well as the year that the case occurred, the drug, the time to event, risk factors, and the severity grade and outcome.

Note that when we look at the case description, that 2 cases were called osteomyelitis and 1 was aseptic necrosis. Because of lack of definition, it is really not clear if all the time these represent the same clinical entity, but we capture all these cases.

Interestingly, there were clearly cases similar to ONJ that occurred prior to 2002 in these clinical trials, one in 1992, 1999, so they are rare, but I mean there were cases that were similar that did occur.

The 2 Aredia cases shown here had a time to onset to ONJ of 28 months and 14 months. The time to onset of Zometa cases shown here and on the following slide were 14, 22, and 22 months.

Also noted is that spectrum of severity is seen in these cases. All events were initially

graded mild to moderate. Two cases of out of these 6 progressed to Grade 3 and had more severe outcomes, such as mandibular fracture and a mandibular excision reported on the next page.

The others were listed as stable or unknown at the end of the study.

Case No. 4 is a head and neck patient who reportedly developed ONJ 13 days after a single dose of Zometa for hypercalcemia malignancy. These was no information in the case report on whether this patient had radiotherapy, but that is something that we are looking into since it seems likely given the history of this patient.

We used the same method described to search all completed trials for cases of ONJ. We did not identify any cases in 3,217 patients treated with Zometa or any cases in 1,214 patients treated with Aredia. There are more than 10,000 patients enrolled in ongoing studies, and to date, 4 cases of ONJ have been reported in these trials, all with a dose of 4 mg of Zometa. These cases are shown on the next slide.

These cases have occurred in 2 patients with breast cancer, 1 patient with prostate cancer, and 1 patient with multiple myeloma. All of these

cases reported pre-existing dental problems including pre-existing osteomyelitis of the jaw.

The next data category we will review is from the spontaneous reports received by Novartis. These are the total number of spontaneous reports that Novartis had received as of the cutoff date for our report of December 7, 2004, at the top.

These include both cases that have been reported, as well as the reportable cases from the literature, and there can be duplication at times. As of the December 7th cutoff, there were 610 cases, 119 in Aredia-treated patients, 248 in Zometa-treated patients, and 243 who were treated with both agents, generally Aredia followed by Zometa.

Most of these cases have been reported in the U.S. There have been 218 reports in multiple myeloma patients, and 125 reports in breast cancer patients. To put these numbers into context, there

have been 1.9 million patients treated with Aredia since 1991 and 1 million patients treated with Zometa since 2001.

It should be noted that almost no Aredia is currently used in the U.S., having been replaced largely by pamidronate generic, and also the Zometa use has been increasing recently since the approval.

All analyses that are subsequently presented are related to the 610 cases. For completeness, we wanted to include the current number of case reports as of February 22nd, which number 875.

We believe that the increase in cases is due to the increased awareness related to communications on ONJ during the fourth quarter last year, such as the Dear Doctor letter, there was press coverage. There were reports at scientific meetings, and we believe that is what this is related to, but we have to watch the pattern closely.

We looked at all these cases. This is the

610 cases for known risk factors of osteonecrosis. While available data can be limited in many of these case reports, 74 percent reported at least 1 risk factor in addition to cancer diagnosis, corticosteroids in 38 percent, chemotherapy in 52 percent, thalidomide in 15 percent.

Twenty-eight cases had radiotherapy to the head and neck area, and probably have osteoradionecrosis instead of this condition of ONJ. Three cases had reported herpesvirus infection of the maxillofacial area, a reported cause of ONJ in non-bisphosphonate treated patients in the literature, and 4 percent of reports had documented actinomyces infection.

In 50 percent of the cases, dental events were reported to precede the diagnosis of ONJ, with tooth extraction being the most common. Many of the reports were incomplete for this kind of information.

This shows the limited information that is available from the spontaneous report database regarding reported outcomes of ONJ, and relates

this to whether or not the patient continued bisphosphonate therapy. I present this although it really is difficult to draw conclusions from this data.

There were only 224 cases which had sufficient information. If you look at the last column, which is the total number of accessible cases, about 20 percent of these cases are reported as recovered or improved. Forty-one percent are reported as no change, 8 percent reported as deteriorated, with 30 percent being unknown, a category which includes recovered with sequelae.

When we look at the impact of changes in bisphosphonate therapy, whether it is continued or discontinued, there are really not major differences in the groups that stand out. Of those who continued bisphosphonates, 26 percent were reported to have recovered and 14 percent had worsened, while for those who had discontinued bisphosphonate, 18 percent recovered, and 6 percent deteriorated.

Unfortunately, this data does not really

allow us to conclude whether continuing bisphosphonate therapy has an impact on the course of ONJ, and further study of this question will be needed.

In the spontaneous report database, it appears that the mean time of onset, defined as the time from initiation of bisphosphonate therapy until the onset of ONJ, is longer for Aredia than for Zometa.

We believe that a direct comparison of the time to onset for Zometa and Aredia is not feasible in this data set. Some of the problems have been talked about already. We don't have a common definition of ONJ or onset of ONJ.

There is this different pattern of product usage. Aredia has been available for a much longer time, while Zometa has only been available for 2001.

The utilization of Aredia has declined significantly, while utilization of Zometa is increasing, and the recent increase in awareness could have accelerated the diagnosis of ONJ. In

addition, concurrent therapy has changed significantly over time with the contribution of this unknown.

I will now comment on literature reports of ONJ. This chart summarizes the reports of ONJ that have appeared in the literature and which Dr. Scher has already mentioned. I just wanted to highlight two of these reports.

First, as Dr. Ruggiero has the largest series of these cases reported, I wanted to briefly mention his findings. He describes 63 cases of patients who had received bisphosphonate therapy and developed osteonecrosis of the jaw.

His results as far as a description of these cases are generally consistent with what I have reported from the spontaneous report database in terms of demographics and reported risk factors.

The bisphosphonate use reported in his series was 57 percent Aredia, 31 percent Zometa, and 12 percent others, which included 7 alendronate, and 1 resedronate. The majority of his cases required surgical removal of involved

bone in this series.

I also wanted to comment on the study by Dr. Durie and his colleagues which was presented today. This was a web-based survey, which has underscored the clinical issue of ONJ in patients taking bisphosphonate, and raised a number of interesting questions.

There are a number of methodologic issues inherent in the type of survey which limit the ability to draw conclusions. First, the survey participants were anonymous and therefore data cannot be source verified.

In addition, there are biases with the survey methodology. Patients who have an event are more likely to respond as are patients with more recent events, and lastly, as discussed with our own post-marketing database, calendar time is really a confounding factor because of the different durations that Aredia and Zometa have been on the market.

The analyses were not adjusted for calendar time, so caution needs to be used in

interpreting these.

Lastly, I would like to review early data from the M.D. Anderson Cancer Center chart review. To obtain more information about the incidence, clinical features, and natural history of ONJ, Novartis is supporting a retrospective chart review at M.D. Anderson Cancer Center with Dr. Ana Hoff as the principal investigator, and Dr. Hoff is with us today.

M.D. Anderson Cancer Center is a large institution with access to complete pharmacy, clinical and dental records. In this study, all IV bisphosphonate users have been identified by the pharmacy, as well as all charts with a diagnostic code consistent with ONJ in the past 10 years, 4,032 charts have been identified.

Dr. Hoff provided us with the results of the review of the first 25 percent of the charts because we were coming to this meeting today, and this was non-random review at this time.

Because of the way that the charts were sorted by the pharmacy, patients with the greatest

number of bisphosphonate infusions were reviewed first, and, in addition, there were 7 cases that were reviewed out of sequence because they were suspected to have ONJ.

There were 18 cases of ONJ identified in the first 963 charts reviewed. Out of 631 patients with breast cancer, 11 ONJ cases were identified. ONJ cases were identified in 6 out of 148 of charts with multiple myeloma. Another case was seen in a medullary thyroid cancer patient.

The time from the first bisphosphonate to ONJ was a broad range, from 4 months, which was an Aredia-treated patient, to 57 months, Aredia followed by Zometa in this case.

In these 18 cases, 4 patients received Aredia only, 3 received Zometa only, 1 received alendronate followed by Zometa, and 10 received Aredia followed by Zometa.

We look forward to getting additional results of this study, and Dr. Hoff may be able to comment on her opinions of the findings.

We wanted to look at what is the frequency

of ONJ, what do we know about this right now. The background incidence of ONJ in bisphosphonate-treated patients is not know, nor is the incidence in cancer-treated patients in general.

The estimates of frequency from the various data sets vary significantly, and as we have discussed, there are many caveats, so we really don't know what the incidence is. The spontaneous report database, which is certainly underreported, provides a reporting rate of 0.03 percent if we consider the current patient numbers. This is certainly an underestimate.

At the other extreme is the web-based survey, which is most likely an overestimate in which 6.2 percent reportedly had ONJ.

In the controlled clinical trials, 0.15 percent of patients had suspected ONJ cases. The median follow-up of these trials is 5 to 18 months, and they were conducted in a time when there was no awareness of ONJ.

It is too early to assess the incidence

from the M.D. Anderson study as the review is not yet complete, but in the current data, the rate is 1.9 percent.

ONJ and bisphosphonate-treated patients is not yet well understood due to the significant limitations in the data sets that are available. There is no common definition of ONJ in the various reports, nor are there common staging or severity measures to allow objective evaluation across different series of cases. Diagnostic criteria are not yet established, and information on the natural history of disease is not available.

It would be very interesting to know how long it takes the clinical picture to develop, are there any early changes that precede the development of ONJ that could guide prevention strategies. These are really critical questions.

There is no common treatment algorithm either how to manage ONJ or what to do with the bisphosphonate therapy, and lastly, we do not have an understanding of what factors are causing this to happen in a small number of cancer patients

receiving bisphosphonates. Further investigation is needed to answer these questions.

Novartis has taken these reports seriously, and we have undertaken a number of initiatives to better understand ONJ and to communicate findings to physicians and patients.

This slide summarizes activities since the first spontaneous reports were received. Our activities have focused in three areas. First, was to ensure patient safety by making sure that the package insert reflected the evolving information on this newly-described event. The first update to the label occurred in August 03, a second update in March 04, and the precaution was added in September of 2004.

Secondly, it was to learn more about the cases. We have actively followed up on many of the cases that have come into the spontaneous report data set. We can talk about our methodology, if you like, and we have been actively trying to collect additional information.

This is extremely challenging as many of

the cases are recognized and treated and reported by oral surgeons and dentists, while some of the patient records with information about cancer and therapies are with the oncologists. This is critical for this type of adverse event.

We have also initiated two multi-disciplinary advisory boards to evaluate these cases and to make some preliminary recommendations on management. We also initiated the M.D. Anderson Cancer Center to try and get more detailed information on frequency and characteristics of ONJ.

Our third goal was to communicate the new information. We distributed a Dear Doctor letter describing the label changes to over 17,000 hematologists, oncologists, urologists who treat prostate cancer, and oral surgeons.

The results of our advisory panels have been distributed as a white paper beginning at the ASCO meeting last year, and this information is planned to be submitted for publication.

We have also worked with patient advocacy

groups, both to share information and to discuss patient education initiatives.

This summarizes some of the key findings of the advisory panel that met regarding the care of patients with ONJ that are reflected in the white paper that has been distributed.

This describes some of the recommendations related to diagnosis and treatment of ONJ, an important learning from the oral surgeons who have cared for these patients is that aggressive surgery can often exacerbate the condition and that conservative management approaches are recommended.

Some patients can be managed with topical treatments, rinses, and antimicrobial treatments.

Most critical is to understand strategies to prevent ONJ, and there were a number of recommendations from the panel. Routine dental exams were recommended prior to bisphosphonate therapy, particularly to identify dental problems that should be addressed.

Patient education regarding good dental hygiene was considered very important and good

communication between dentists and oral surgeons and oncologists was thought to be essential to manage these patients.

We have incorporated the recommendations of this panel into the recent package insert in the Precaution section that you are reviewing today.

Novartis has also reached out to patient advocacy groups to share information about ONJ and to discuss patient education initiatives. We intend to meet regularly with these groups as they represent an important way to communicate with the patients that have these diseases.

We have developed and made available a patient education brochure starting in August of 04, and have distributed 65,000 copies to our field representatives. Physicians and nurses can use these materials to educate patients who are receiving bisphosphonate therapy.

This brochure describes ONJ, instructs patients on good dental hygiene practices while undergoing cancer treatment, and urges patients to talk to their dentists and their oncologists if

symptoms arise.

We are also currently implementing clinical programs to learn more about ONJ. Critical as a first step is to develop a consistent case definition, staging system, and severity assessment. We are in the process of developing consensus definitions with experts.

In addition, we will obtain additional information from our pivotal trials by attempting to follow up on completed clinical studies to see if any cases of ONJ have occurred beyond the study period.

We also plan to capture specific data on ONJ in ongoing and planned studies. We plan several new studies. We are going to do a retrospective chart review specifically in myeloma patients at the University of Arkansas.

We also plan to incorporate ONJ assessments into trials that have been planned for other reasons, to try and get some other information. We, in particular, are planning a large randomized prospective study, which includes

breast cancer and myeloma patients, and will being the fourth quarter of this year.

In addition, an ONJ assessment is going to be incorporated into a study that is under discussion and being planned by SWOG in adjuvant breast cancer patients, and the details are under discussion.

We would also like to initiate a prospective study to understand the natural history of ONJ in patients newly receiving bisphosphonates. We are considering whether we should do a natural history study or some sort of registry study.

This shows our large randomized study that we are planning to conduct. The objective of this study is actually to look at therapy with Zometa beyond the one-year treatment period, and looks at Zometa 4 mg weekly every 3 months and placebo.

This is a large study in 3,500 patients, and we are going to incorporate ONJ assessment in this study.

This is the SWOG study design. This is a 6,000 patient study randomized to three arms with

different bisphosphonates, and this again is a very large study where we could look, incorporate ONJ assessment, and get some additional information.

This just shows the ONJ surveillance plan that is incorporated into the SWOG study.

This is our current proposal for ONJ monitoring in our clinical trials going forward. This is being discussed with experts. It includes physical evaluation and dental evaluation, as well as imaging with panoramic radiographs, and we plan to develop specific CRFs to capture details of dental exam and ONJ assessment including criteria for staging and severity. We will evaluate at a minimum of every 6 months.

In conclusion, Zometa and Aredia are important medications which have significant benefits for patients with multiple myeloma and metastatic disease from solid tumors, reducing the morbidity from the serious complications that these patients have related to bone involvement of tumors.

Novartis has actively investigated cases

of ONJ since we received the first reports, and we continue to investigate, however, ONJ remains a poorly understood entity. Frequency estimates are variable. Based on available data, it appears to be infrequent in cancer patients, but we need additional information.

There is insufficient evidence to demonstrate a difference between Aredia and Zometa in terms of risk of ONJ at this time.

Novartis takes these cases seriously and we are committed to ensuring patient safety, to increasing our understanding, communicating our findings, and identifying strategies to prevent and manage this problem.

The clear benefits of Zometa and Aredia in reducing the significant morbidity associated with complications of bone disease in cancer patients remain highly favorable when considering the risk of ONJ.

DR. MARTINO: Thank you, Doctor.

I now have a bit of a problem, which is that we are going to run overtime, and I want to

give as much time as possible to the questions and dealing with the issues amongst the committee.

Dr. Berenson, where are you? Now, with all kindness and love from me to you, can you summarize what you are going to say in a few moments? I would be most grateful. Thank you.

Clinical Benefit of Bisphosphonates in Cancer Patients with Metastatic Bone Disease

DR. BERENSON: I guess that is why my mother made me take impromptu speech in high school.

Let me be brief. What I want to do is summarize the benefit of bisphosphonates for cancer patients with metastatic bone disease.

This is an extremely common problem. More than 500,000 Americans are afflicted with it. Most myeloma patients develop metastatic bone disease or myelomatous bone disease, most patients with breast, prostate, and a significant number of lung cancer, as well.

The median survival importantly of these patients is measured in years, unlike other

metastatic sites in which patients succumb often within weeks to months. These have major clinical consequences, not only for the patient, the families, but society in general, and the reason for that is shown here.

That is because these lead to consequences, and in the top four, in yellow, you see where they care considered skeletal-related events from the studies that have been done by Novartis with Aredia and Zometa.

These are the placebo arms. Commonly, patients fracture. These are the number of patients or percentage of patients per year who develop these complications. Less commonly they develop cord compression of collapse, often leading to the requirement for radiotherapy or surgery to bone, hypercalcemia less common, bone pain frequent before bisphosphonates, often leading to the use of analgesics with quality of life effects, of course, ultimately impacting the patient's survival.

Now, here is the overall results of bisphosphonates that have been done. First, in the

nineties, that we did with Aredia, that is, the myeloma trial showing a marked reduction, as you see, in both the percentage of patients with an event by 21 percent, the endpoint, and more impressive on the right side is halving from 2 to 1 of the number of events per year.

Similar data from the breast cancer data led by Hortobagyi shows a nice reduction in both the percentage of patients with an event and about a third reduction in the number of events per year.

As one can see in the trials that have been similarly conducted with prostate cancer, Kohno, a recent Japanese study, and Lee Rosen's study, marked reductions not only in the percentage of patients with an event, but impressive and important, the number of events per year is halved, from a third to a half, huge reductions when one thinks about the 500,000 of Americans who have this problem.

Now, the only head-to-head comparison of Zometa and Aredia, which led to the approval of this drug, as you know, for breast and myeloma,

this was a non-inferiority comparison trial, of course, but one can see the four major endpoints all favored Zometa, less patients with an event, a delay in time to first event, reducing the number of events per year by approximately a third, and on the right side, the multiple event analysis taking into account not only the time to first event, but time between subsequent events, a 16 percent relative risk reduction and statistically significant in favor of Zometa.

So, what does this all mean? Well, first of all, it means that Aredia has been shown to definitively reduce skeletal complications in breast and cancer patients with lytic disease only.

Two studies showed it to be ineffective in prostate cancer that were randomized I did not mention. It has not been evaluated in other tumor types. In addition to breast cancer and myeloma, Zometa has been shown to dramatically reduce the skeletal complications in patients with prostate cancer, that is, metastatic to bone, as well as other solid tumors that are metastatic to bone.

Data I did not present, these drugs have been shown to markedly reduce bone pain and the requirement for analgesics, and, indeed, in trials

done with both Zometa and in the past with Aredia, preventing the deterioration in the quality of life, most important to our patients with metastatic cancer to bone.

In our own experience, we have had 6 cases of ONJ, and by the way, we have had more than that number of patients who were referring to our oral surgeon with a presumptive diagnosis from the dentist who did not have it.

There has been an important range of severity. Three patients required only intermittent antibiotics were on Aredia and Zometa in one case, and Zometa only in the other two. They remain on ongoing bisphosphonate treatment, and their symptoms have all improved.

One patient was only diagnosed last month. She remains on treatment, her symptoms largely resolved with several weeks of clarithromycin orally. Two other patients, one on Aredia followed

by Zometa, one on long-term Zometa on a clinical trial initially, discontinued bisphosphonates secondary to significant effects on chewing. Importantly, both of these patients have markedly improved by being off the bisphosphonate and are chewing normally in one case, and almost normally in the other.

Equally importantly is the bottom bullet, the status of these patients' myeloma. One of these patients has had a skeletal-related event, 3 are in long-term complete remission, 1 following a transplant, 1 simply on VAD alone, and 1 on thalidomide alone.

One is in near complete remission, and impressive to me is the last sub-bullet. Two patients on long-term therapy are still indolent, and both patients have received no other treatment, and, in fact, 1 patient had a 40 percent reduction in M-protein, which is ongoing 5 years later.

So, skeletal complications have profound effects on the lives of patients with metastatic bone. We have seen data that shows that the IV

bisphosphonates markedly reduce the risk of bony complications.

Both then number of events per year are reduced by about a third to a half, and the percent of patients with any event by 15 to 40 percent. These drugs have profoundly reduced bone pain, the requirement for pain medication, and prevented the deterioration in the quality of life.

As you have seen, patients receiving IV bisphosphonates may infrequently develop ONJ. What the frequency is, we don't know. We have seen a range of numbers I put up here. Equally important is the severity, it varies markedly, and in all of our cases, it has improved even on patients who continue on therapy with oral antibiotics and Peridex washes.

Thus, the risk of ONJ is a minor one, it is rarely clinically significant in our own practice compared with the major problems that would result if patients did not continue these important medications. That is the high risk of fracture you have seen that is reduced, the risk of

cord compression, the requirement for radiotherapy or surgery to bone.

Thus, the benefits, the reduction in fractures, the requirement for radiotherapy, reduction in bone pain, and ultimately the impact on quality of life far outweigh the putative small risk of ONJ and the renal deterioration that infrequently occurs, and with good management, is even less frequent, and I will stop there. Thank you.

DR. MARTINO: Thank you, Doctor, I most appreciate your succinctness.

Open Public Hearing

The next part is the public portion of our program. There are several of you that have asked to address this committee. The microphone you are going to use is the one that is in the center of the room, and as you get ready for that, I need to read a statement to you that relates to your presentations.

Both the Food and Drug Administration and the public believe in a transparent process for

information gathering and decisionmaking. To ensure such transparency at the 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, the 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 today's meeting.

Likewise, the 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 this issue of financial relationship at the beginning of your statement, it will not preclude you from speaking.

MS. CLIFFORD: Felice.

DR. O'RYAN: Felice O'Ryan. I am an oral and maxillofacial surgeon at Kaiser Permanente in Northern California, and after hearing in 2003, Dr.

Sal Ruggiero's wonderful presentation about osteonecrosis in bisphosphonate patients, I finally found what I thought was at least some sort of beginning answer to what I had been seeing.

In Kaiser Permanente, we have 3.2 million members in Northern California, and 4 million members in Southern California, therefore, we have a huge and well-documented database.

My colleagues in Southern California have also noticed some of the problems we have been seeing and after looking at some of the clinical problems, I am looking to you today to present some cases, show you the spectrum. I do not consider these problems minor or insignificant, nor do my patients, and to ask for guidance.

I also feel that the FDA and Novartis has done a very poor job of informing people about this potential risk. I have informed our oncologists at Kaiser Permanente via e-mails and attached clinical

photos about the risk of this.

Unfortunately, the oncologists are not particularly comfortable doing oral exams, and so some of this has been missed.

I won't go through the pathophysiology, I think that is pretty well known to people. I am just going to show you the spectrum of cases that I see from what I would consider minor and insignificant.

This is a 65-year-old woman with breast cancer. She has been on--all my patients have been on, first, Aredia, followed by Zometa. The earliest has been 6 months after the initiation of Zometa treatment.

I have at least 30 patients, and these are unsolicited patients, in other words, patients that have been referred to me with this complaint.

She did undergo a dental extraction and on your right you can see that she has teeth, and just behind the teeth, around the mucosa, is a small bone defect that has been chronically present, not responsive to oral antibiotic therapy, nor oral

rinses.

This is another patient of mine, a 68-year-old male, multiple myeloma, been on both Aredia and Zometa. He does have some bad teeth, I admit it.

However, unfortunately, you can't see this particularly well. The necrotic areas in his mandible are up on the right corner and look like some food debris. That is not food, that's his jaw. These are how my patients have all begun.

The tissue on the lingual surface of the mandible initially sloughs off, and then, like the jaw is on fire, it continues, at least in my small patient group, from the back end of the mandible up to the front end, and can involve teeth.

The majority of my patients have not had dental extractions, dental trauma, dental treatment before presenting.

Again, this is not responsive to antibiotics or local oral therapy.

This case concerns me the very most. She is a 60-year-old delightful woman with multiple

myeloma, been on both Aredia and Zometa, thalidomide, and, of course, all these patients have been on corticosteroids.

She came to me with a small lesion in her mandible that began as the size of maybe a small split pea in the back. What you are looking at is 6 months or progression. This is her mandible. This is dead bone. She has had a draining fistula on the outside of her face that now she has been--I have had her on a PIC line, I have had for hyperbaric oxygen.

It is continuing to spread. I have nothing to offer her. I have no treatment. I can't resect this because the rest of the bone is dead and there is nothing normal to resect to. She is looking at a possible free fibula flap, which is a 20-hour operation, and a really hard hit for these people who are already medically compromised.

So, I don't think anybody can stand here and tell me that that is an insignificant problem. These patients are in pain, they smell bad, they can't eat, and nothing helps fix them.

So, the question about tooth extraction, poor oral hygiene and possible associated medications are totally legitimate. I may have a

unique subset of patients who have not had dental extractions in the majority of the cases. Poor oral hygiene, possibly, but again many of my patients are edentulous, so poor oral hygiene or tooth extraction has nothing to do with it.

Associated therapies, you know, possibly. We don't know. All I can say is that I have never seen this until recently.

What is the prevalence? Who do we prevent it, and what do I do to treat these patients? I think we have databases that are available to us to look at. We are just in the process of looking into this at Kaiser Permanente.

I don't know the prevention, and I certainly don't know the treatment, but I would love to know what the treatment could be. We have had our patients discontinue the bisphosphonates. I have not had a single lesion heal. I have not seen a single lesion regress. I have only seen

them become worse.

So, I don't know if I have a unique subset of patients or what.

Thank you.

MS. CLIFFORD: The next speaker is Scott Santarella and Bruce Holmberg.

MR. SANTARELLA: Good afternoon. My name is Scott Santarella. I am the Executive Director of the Multiple Myeloma Research Foundation located in New Canaan, Connecticut. Personally, I receive no financial support from Novartis, however, our organization has received unrestricted educational grants for educational programs relative to multiple myeloma disease.

The MMRF is a nationally recognized 501(c)(3) nonprofit. We are the world's largest nonprofit funder of myeloma research, and I thank you for providing me a few moments to speak today.

On behalf of the nearly 200,000 patients, family members, and caregivers associated with our organization and the issue of osteonecrosis of the jaw and bisphosphonate use, I would like to just

say a few words.

As an organization that devotes 80 percent of the funds we raise to support research efforts, we have access to and committed partnerships with the world's leading myeloma experts.

In addition, our secondary focus of providing the myeloma community with educational and informational programs relative to the latest treatment options and therapies, we have become a well-respected resource with more than 500,000 visitors to our website annually.

In addition, our focus for the last eight years has been providing patients, clinicians, caregivers, and nurses with the most current information on treatment options and clinical trials available, as well as educating patients on supportive care therapy like the use of bisphosphonates in treating multiple myeloma.

With this information as a backdrop, it has been our experience in working with the hundreds of the world's leading myeloma researchers and local hematologists, as well as the tens of

thousands of patients who rely on bisphosphonates in the treatment of bone disease suffered by those patients, that bisphosphonates are considered an essential part of supportive care for this disease community.

As an organization, we feel the relatively small number of cases of osteonecrosis of the jaw, although worthy of note and attention, are minimal in comparison to the benefits bisphosphonates provide the majority of the patients.

In addition, it has been our experience that the information available on bisphosphonates use provided by companies like Novartis have always been presented in a very detailed format with explanation of dosing levels, as well as preventative measures one would undertake to avoid possible risk factors associated with the use of these compounds.

It is our hope that ODAC will undertake a complete review of not just the incidence of osteonecrosis of the jaw, but the overall research, both historically and currently, that shows the

treatment value and benefit of bisphosphonates in the care of multiple myeloma patients, as well as other cancer patients relying on these compounds to help them in the treatment of their disease, and recognize it as an essential to their care and quality of life.

MR. HOLMBERG: Good afternoon. My name is Bruce Holmberg. I have absolutely no financial connection with Novartis.

I live nearby in Rockville and I am multiple myeloma patient, diagnosed with Stage I IgA multiple myeloma in May of 2000 when I was 61 years old. I am treated here at the National Naval Medical Center in Bethesda.

I am here today to give you a brief experience or a brief view of my experiences with bisphosphonates as it relates to my multiple myeloma.

When I was diagnosed, like so many, I had never heard of this blood cancer. My only signs were anemia, and at the results of my first skeletal survey, which occurred a month after I was

diagnosed, showed only some slight lesions in my skull.

When I heard my diagnosis, I asked the hematologist two questions, what was my prognosis and what is my treatment. To the first, he said, "Well, statistically, three to five years, but you may be one of these patients who goes on for many, many years."

To the second, he said, "There is none, your disease is not bad enough yet to treat, and we just watch your disease as it progresses until the treatment is less harmful to you than the cancer, then, we do something."

That answer thoroughly baffled me until I went home and researched multiple myeloma on the website. What I saw were terms like immune system failure, kidney failure, incurable, fatal, and bone destruction.

The treatments were chemo and stem cell transplants primarily, and neither did more than buy much time, or buy time, and not much at that.

I changed doctors to one who was more

proactive. At my second appointment, he related a conversation he had with a prominent myeloma researcher at the association, at a recent Ash meeting, where he had asked if Aredia could be given as a prophylactic before the onset of bone destruction to suppress the effects of the myeloma.

The answer was yes, that there was a good possibility that Aredia had a suppressive effect on the development of the myeloma cells themselves.

I began a monthly Aredia treatment immediately. My disease progressed very slowly, so that Aredia, and then Zometa, when it became available, and I did make that switch, was my only treatment for three years.

In 2003, it got bad enough to warrant the addition of low-dose thalidomide and later the steroid dexamethasone. Thalidomide and Zometa alone helped, but I had an immediately and near complete response to these combined treatments of Zometa, thalidomide, and dex.

While I know this treatment is likely temporary, that sooner or later the cancer will

mutate around the treatment, I am incredibly grateful for this respite.

My quality of life is really important to me. I am very physically active. I hike, bike, work out daily, ski. I am still an active patrolling member of the National Ski Patrol. So, bone health is at the very top of my list.

Despite the progress of my disease, my bone structure remains as it was when I was diagnosed, only slight skull lesions that have never gotten any worse, probably damage that was done before I was diagnosed and started on bisphosphonates.

My hematologist, my dentist, and I understand the potential issues with jaw osteonecrosis. If I need a dental procedure that might pose a risk, we plan to suspend the use of Zometa for a period in advance of the procedure.

I acknowledge that as more information becomes available, more precautions may be necessary, but the benefits of bisphosphonates to us multiple myeloma patients significantly outweigh

any known down sides.

Let me add one more point. None of the treatment options we myeloma patients have available are without side effects, some of them serious, but we take them and we tolerate the side effects and mitigate them when we can because the alternative is so unsatisfactory.

I have no side effects or have had no side effects in the five years of taking Aredia and now Zometa, no bone pain, no kidney issues, and no jaw problems.

I urge you to weigh all of the benefits, as well as the potential risks as you make your deliberations.

Thank you.

MS. CLIFFORD: Thank you, Mr. Holmberg.

Our next speaker is Michael Katz.

MR. KATZ: My name is Michael Katz and I am a Vice President of the International Myeloma Foundation. This is an uncompensated volunteer position. The organization receives unrestricted educational grants from Novartis, I receive none,

no compensation from either the IMF or Novartis, and I have paid my own way to come to this meeting.

As an advocate, I am in constant contact with patients and caregivers with multiple myeloma. With the IMF, I have helped conduct over two dozen patient and family seminars across the country, I lead two in-person myeloma support groups, and moderate an on-line myeloma-specific listserv with over 1,300 members, hosted by the Association of Cancer On-Line Resources.

I also do phone counseling as part of the IMF hot line. I am here today to speak to you as a patient. I was diagnosed with multiple myeloma in 1990. Over the past 15 years, the disease has relentlessly attacked my bones, causing serious damage to my pelvis, both hips, multiple ribs, two vertebrae, my skull, and my shoulders.

I have had various systemic therapies including steroids, Melphalen, thalidomide, 8 courses of radiation including radiation therapy to the jaw. I began taking Aredia in January of 1995, over 10 years ago, and I have since had over 120

infusions.

As such, I am very concerned about the rapid rise in reports of osteonecrosis of the jaw in patients with myeloma and other cancers. I applaud the FDA and ODAC for taking the initiative to have a public dialogue on this very serious safety issue.

Even with the potential risk of ONJ, bisphosphonates are an important part of therapy in minimizing bone damage to patients with myeloma and other cancers that threaten the bone.

ONJ is preferable to a collapsed vertebrae or broken femurs. It is important that bisphosphonates are made available to patients who can benefit from them, but we also need to make sure that we can protect our bones from destruction by cancer, and at the same time, minimize the risk that we will develop serious problems like ONJ.

Dr. Durie and I had met with representatives of Novartis at last spring's ASCO meeting to understand what could be done to better understand this issue and provide more practical

information to both patients and physicians.

The idea for the web-based survey that was discussed earlier initially came up at this meeting.

As Dr. Durie said, we were able to recruit over 1,200 respondents within 30 days. Participants completed an extensive survey detailing diagnosis, treatment history, dental care habits, and any dental issues including both explicit diagnosis of ONJ, as well as symptoms that would be indicative of undiagnosed ONJ.

The results of this survey, which Dr. Durie presented earlier, were dramatic, showing increased time dependent risk associated with Aredia and Zometa, and no statistical association with any of the other treatments reported including steroids, thalidomide, or Valcade, radiation or alkylating agents.

As Dr. Durie stated, the time dependent risk associated with Zometa was dramatically higher than that associated with Aredia. People this morning and outside this forum have characterized

osteonecrosis of the jaw as a long-standing issue in oncology patients. They call it rare. They raise issues about the condition being imprecisely defined and standardized criteria for diagnosis not being established.

They cite the many other risk factors that could contribute to or cause the problem. The fact remains, though, that almost all of these risk factors have been facts of life for decades in myeloma and other cancers. Why, one must ask, has this problem become so much more pronounced in these few short years.

They also point out the limitations of anonymous surveys and of patients and caregivers self-reporting medical information. Are there limitations with this type of survey? Certainly, there are. Indisputably, prospective clinical trials are the gold standard for efficacy and safety data.

Having said all of this, though, I must ask if these same people had cancer and had to make the decision to put the IV in their arm every month

and hang that bag of bisphosphonates, I wonder if they would be so dismissive of data provided by 1,200 concerned fellow patients.

Would they ignore this data and wait two, three, four, or more years until these studies could be completed and better data is available? I doubt it.

It is clear that osteonecrosis of the jaw is a problem that has mushroomed in the past few years. To quote Dr. Robert Kyle of the Mayo Clinic, who chairs the IMF Scientific Advisory Board, I quote, "In my 40-plus years of caring for patients with multiple myeloma, I had not seen or heard of osteonecrosis of the jaw in this disease until one to two years ago."

Prospective trials take years to design and execute. When dealing with serious safety issues like ONJ, we cannot afford to wait years. These trials should be done, but we need to use the data that we can acquire more quickly via retrospective studies and surveys to help patients and their doctors make better decisions today.

I applaud you for allowing us to share this data with the scientific community and the public, and I applaud you for daring to ask the

question how can we use this data to help patients and physicians make better decisions today while we work to learn more tomorrow.

ONJ is not a stroke, it is not a heart attack, it is seldom life-threatening although I must say I did meet a woman last month at our patient seminar in Dallas whose husband died of complications resulting from his ONJ.

More commonly, though, ONJ is a painful condition that can destroy a cancer patient's quality of life. It is painful, the patient's teeth fall out. It can interfere with speech, make eating difficult. It can also prevent patients from receiving life-saving treatments like transplants.

Yet, bisphosphonates are proven to prevent or lessen the severity of cancer-induced bone damage and must remain available to the patients who need them. Having said all of this, what would

and my fellow patients ask of the FDA and Novartis?

First, please be more proactive in getting the word out to patients, caregivers, hematologists, oral surgeons, and, for God sakes, the regular dentist, because those are the people that are pulling teeth out and triggering this condition.

The labeling changes, the white papers, the Dear Doctor letters, they are all steps in the right direction, but they don't go far enough in terms of audience or message.

Second, please provide answers as soon as possible, and I know these are tough questions, to the following four questions:

1. If patients have been on Aredia or Zometa for a long period of time, is there a point at which they should consider decreasing the treatment frequency or dosage?

2. If there is a dental problem that requires invasive surgery, to what extent can the risk of ONJ be reduced by stopping or tapering Aredia or Zometa therapy?

3. Given the risks, under what circumstances is prophylactic use of Aredia justified?

4. Lastly, given the evidence of increased risk of ONJ and kidney damage, and the lack of evidence of any incremental benefit of one drug over the other, why should any myeloma patient be given Zometa as opposed to Aredia?

One last thought. In the preapproval setting, the possibility of harm must be excluded by proving that a drug is safe. Drugs are guilty until proven innocent. In the post-marketing setting, where we now find ourselves with these drugs, we change our tune, requiring proof of harm rather than proof of safety. Drugs are innocent until proven guilty.

As a patient taking these drugs, I find this difficult to understand.

I than you for the opportunity to speak, and I thank you for your diligence in investigating this matter.

MS. CLIFFORD: Thank you, Mr. Katz.

Ron Rogers?

MR. ROGERS: I, too, have multiple myeloma. It was discovered in 1999. Approximately two months later, I went on Zometa. I have continued on Zometa to this day, and live an extremely active lifestyle, skiing, writing,

hiking, hunting, fishing.

In January of 04, I was diagnosed with osteonecrosis. With antibiotics, it had cleared up within approximately six months, and I still am on Zometa, and I am thankful to be able to have the kind of lifestyle I have.

Thank you.

DR. MARTINO: The Committee is grateful to all of you who have spoken, and as always, you have a way of putting all of this in the right context for those of us that sit here. I am personally grateful to each of you for this morning's contribution.

Committee Discussion

DR. MARTINO: The next portion and the final portion of this meeting is actually the

discussion amongst the panel. There really are three sets of questions that I want to focus you on, and the time is short, so again, please be succinct, I want your thoughts and not your ramblings.

The first question really relates to given that we recognize that there is a potential problem here, have we appropriately informed the necessary people.

The second question relates to do we know what to do, either in terms of preventing this problem or in terms of treating it once it occurs.

Thirdly, are there additional studies that need to be done.

I would like to address the first question first, however. Have we informed the right people and in the proper manner? To that, can I ask the company to basically, briefly, summarize what they have done in terms of informing and who have they informed.

DR. YOUNG: I am going to invite my colleague, Peter Tarassoff, to the stand to talk

about the communication efforts of Novartis.

DR. TARASSOFF: Good afternoon. My name is Peter Tarassoff. I am with Novartis Oncology, Medical Information and Communication. I would just like to briefly summarize the steps that we have taken to bring this matter to the attention of the patient groups.

We maintain an ongoing dialogue, as Dr. Young had indicated, with a number of patient advocacy groups. In May of 2004, we hosted a meeting hear our offices in New Jersey to which we invited a number of representative patient groups to come and listen to the discussion that we had in terms of what we knew about the topic of osteonecrosis of the jaw.

Again, we had further meetings with representatives of additional groups at the Ash Meeting in San Diego in December 2004, and provided further updates on this information.

At the time that the Dear Doctor letter was published by Novartis in September 2004, we did publish this patient brochure that had several

topics of pertinent information that would be useful to patients.

We have distributed, as Dr. Young had indicated, approximately 55,000 copies of this brochure to our sales representatives to give to the health care professionals that they see during the course of their daily activities, and we have been very vigorous in instructing them to be proactive, to be sure that offices where Zometa is given, that this particular information was given out.

It contains information for patients to be able to recognize the signs and symptoms of osteonecrosis. It calls to their attention the fact that there are certain items of dental hygiene that they need to be aware of, and thirdly, it provides them information that they should share with their dental professionals in terms of their cancer treatment and things that a dental professional should be aware of.

We have this information also available on the Novartis U.S. Zometa website. This information

is here. A number of the patient advocacy groups, we understand also have this information on their website, so we try to use as much of the new IT technology that we have available to us to make this information available to greater numbers of patients.

This is the white paper that represents the two advisory board meetings that we held in December 2003 and again in March of 2004, to try to put together in a succinct format information that could be made available to health care professionals, to bring to their attention this topic of osteonecrosis, what might be able to be done to prevent it, what should be done in terms of treatment.

We have distributed this initially at the ASCO meeting in New Orleans in June 2004. Through our offices, we have distributed an additional 3,000 copies that have gone out to health care professionals who have questions about the topic of ONJ. We provided them this information, as well as a copy of the Dear Doctor letter.

So, we have tried to look at a number of different avenues by which we can share this information with both patient communities and also

with the oncology and dental communities.

We do have a manuscript that stems from this white paper that is now undergoing final review, and our plan for that is to submit it to journals that will be read by oncologists, as well as health care providers in the dental fields.

Thank you.

DR. MARTINO: A question on the Dear Doctor letter. I am assuming those are sent to oncologists, or are they sent more broadly? I am particularly concerned with the dental professionals.

DR. TARASSOFF: The 17,000 copies, slightly more than 17,000 copies of the Dear Doctor letter were sent out to hematologists, oncologists, urologists, and oral surgeons in the ADA database. We have considered also the idea of sending it to dentists, and that is something that is under consideration.

DR. MARTINO: That would strike me as a key group to whom this should be disseminated since they are more likely to be the ones who see patients for these problems.

Dr. Brawley.

DR. BRAWLEY: I am interested in what is

being done in terms of promotion of Aredia and Zometa for usage right now. For a while after Zometa's approval, it was sort of like a freight train moving toward it being malpractice for those of us who take care of patients who have metastatic disease or the threat of metastatic disease, to not put them on Zometa.

I am wondering what now is the company doing in terms of promoting the usage of both Aredia and Zometa.

DR. YOUNG: I am going to invite our colleague, Dr. Deborah Dunsire, to speak about the promotion of Zometa and Aredia.

DR. DUNSIRE: Good afternoon. My name is Dr. Deborah Dunsire from Novartis.

Zometa is actively promoted by the

Novartis Oncology Sales Forces at this time. Aredia is no longer promoted. It has been generically available since 2001, and at the present time, there is practically zero Aredia utilization. Any pamidronate use has moved over to generic pamidronate, and the promotion is always within the FDA label and within the OIG guidelines.

If there is anything further I can clarify, please ask.

DR. BRAWLEY: I am not satisfied with the answer, but I don't know exactly how to ask for a better answer. You are still promoting Zometa. I mean literally in Atlanta, virtually everyone with metastatic disease was donating $6,000 to Novartis for Zometa treatment, and that may be an overusage of the drug.

So, I will just leave it at that. I don't know if you want to respond to that or just leave it as a comment.

DR. DUNSIRE: I think that the drug is promoted for patients with bone metastasis because of the benefits that it provides.

DR. MARTINO: Dr. Perry.

DR. PERRY: I have a comment and a suggestion, Dr. Pazdur. Richard, this seems to me

to be a great topic for dissemination through the CCOP [ph] mechanism, and perhaps a great research project for them to get cancer control credits perhaps by first making people, their patient populations aware of the potential problem, and then when we get a little bit--hopefully, a whole lot smarter, knowing how to identify and treat it better, then a treatment program.

I take it you still talk to those people and can convey that suggestion.

DR. PAZDUR: I think that is an excellent idea and we will bring it back and discuss it with the CCOP people, but I think that is even an area to look at, even a registry potentially incorporating their practices in, because it does represent perhaps even a more real world type of usage of these drugs outside of a cancer center, which may have its own peculiarities about it, as the M.D. Anderson data is doing.

DR. MARTINO: Dr. Levine.

DR. LEVINE: Several comments. First of all, one of my problems is that the patients who are being educated are those who are perhaps more involved, i.e., they are members of support groups, they are on the Internet, and so forth, and I am

worried about the regular patients out there who may not be involved in that sense.

I am not sure, so I will defer and ask you, but I believe the company markets this on television directly to the patients, and if that is true, then, I would absolutely ask that you market something else about this. If you don't market, I would still do that. It needs to go to the general population.

The reason I feel strongly is that I am worried that simply by stopping the product for a month or two, that is not really going to help as far as what to do, and what you have to do is prior, I guess, some of the sense I am getting, is that you may want to advise patients to take care of dental work prior to ever starting these

products.

So, you have to do it in a proactive way. I also agree with what has been said as far as educating very carefully the dentists, and when I go into the dentist, the technician says to me, you know, any change in your medical health, but I would want the technician to be saying to me, have you taken these drugs, and list them right there.

The second thing, and I have to go, so I am not going to answer this properly in order, but one of the questions that really needs to be answered here is what is the appropriate duration of use of these drugs, is there, in fact, a moment where the risk outweighs the benefit, and I don't think there are data to address the question. That would be an extremely important one.

There was a New England Journal article, not about this at all, but several years ago, using one of these products for osteoporosis, and I think the finding was that one dose a year was as good as once a month or whatever it is. So, those kinds of questions really have to be addressed.

DR. YOUNG: I would first like Dr. Deborah Dunsire to address the question about promotion, and then I will address your question about longer

term duration of therapy.

DR. DUNSIRE: Deborah Dunsire from Novartis clarifying that Zometa is not promoted on television at all, and that the direct-to-patient and outreach to the regular patient, who isn't engaged in the Internet, is really through their physician.

It is the only way we can get to them, and that was the purpose of the patient brochure around osteonecrosis of the jaw, and in our regular patient education materials, which can be given to a patient when they start Zometa, we have also added information on osteonecrosis of the jaw, hoping and encouraging all the professionals, physicians and nurses, who are in contact with patients, to give this to the patient, so that they can become aware. Thank you.

DR. YOUNG: I just wanted to add that I was kind of rushed at the end of my presentation,

but one of the studies that we are undertaking, which we have actually been in discussions about the FDA, is a study that takes patients who have been on treatment for a year with multiple myeloma and metastatic breast cancer, and then randomizes them to either Zometa in the label dose very 3 months or placebo, and that is really a large study that is designed to get at this question about demonstrating continued benefit and safety of therapy, and also it is a good setting to be able to monitor for osteonecrosis of the jaw.

DR. MARTINO: Dr. D'Agostino.

DR. D'AGOSTINO: I have a couple of comments and I am going to jump from the first and the third question. I think in the first question, in terms of the information being sent out, I think there is a lot of information. The program seems to be moving along well.

My concern is, is there an evaluation component, how do you know you are actually reaching anybody, and especially the patient and the oral surgeon, are they thinking this way, and

they get a lot of information, they may just chuck it in the pail, I don't know.

So, I think there should be, and there may be, but I think there should be an evaluation component that the FDA may want to insist on.

In terms of the clinical trials, I think the registry idea is good, and I think the clinical trial, they have got ongoing clinical trials, which sound very nice. My concern there is are they long enough and are they big enough to pick up the safety issue if they are designed for other things.

So, I think if they embed this question within a clinical trial, it has to have some hope of getting at an answer to this particular problem.

DR. MARTINO: Dr. Hussain.

DR. HUSSAIN: I think some of the issues I wanted to raise was raised by Dr. Levine, but I want to reiterate the issue that Dr. Brawley had brought up, and I think maybe I can rephrase what he said. There is aggressive marketing in areas where it shouldn't be marketed, and I will give you an example.

I can't give you proof, but I can give you examples. Patients with metastatic hormone-sensitive prostate cancer, if you look at

the absolute indication, there is no indication in that setting. Yet, under the umbrella of bone disease, the drug is being marketed to the prostate cancer patients.

If I saw correctly what is up there, it seems to me there is almost a relationship to how long you live, and then osteonecrosis and side effects, if you don't live long enough, you are not going to get that side effect, because you just died.

So, in those patients, their average longevity is three years, some of them live longer. I think there is a risk in there. There is multiple trials from Europe that showed no benefit to the addition of bisphosphonates albeit second generation in that setting, so I would be very careful about marketing it indirectly.

Otis, is that about something similar?

The second issue I think is the issue of

frequency and the need to start these medications, and I think it is important--I can't speak about myeloma, but in looking at the data for prostate cancer, correct me if I am wrong, but the patients that the drug was tested in were really far advanced prostate cancer patients.

This is not the patient whose PSA went from 0.1 to 0.3, and the unfortunate approval is a blanket approval, you know, anytime you develop androgen-dependent disease, you are going to go get the drug, and yet, if I am not mistaken, again, correct me if I am wrong, the median PSA for these patients that went on it is in the several hundreds.

So, not only I think education needs to be given about the setting, but actually the timing of its use, and not the minute the patient becomes androgen independent.

DR. MARTINO: Dr. Perry.

DR. PERRY: I would like to ask Dr. Young or someone from the company how many patients get this product a year?

DR. YOUNG: I am going to have to call on Dr. Deborah Dunsire again. How many? Do you want in the U.S.?

DR. PERRY: It doesn't have to be to three decimal points. I mean are we talking about 5,000, 50,000, 500,000?

DR. DUNSIRE: It's variable by indication. To be clear, lung cancer patients generally get it for a shorter period of time. So, overall, we know that since 2001, about a million patients have been treated. There are probably several hundred thousand treated at some point during a year.

DR. PERRY: In the United States?

DR. DUNSIRE: No, that would be global.

DR. PERRY: How many patients in the United States get this drug per year?

DR. DUNSIRE: I would have to look to get you exact figures, but it's in the tens of thousands.

DR. PERRY: Tens of thousands, and we have given out 55,000 booklets. It doesn't seem to me to be enough.

DR. DUNSIRE: Right, there would be less than 55,000 patients, however, in a year.

DR. PERRY: My assumption is that you have reached 25 percent or less of the patients.

DR. DUNSIRE: We are actively continuing.

DR. PERRY: I understand that, but I am

trying to get a handle on the magnitude of the problem.

DR. DUNSIRE: Absolutely.

DR. PERRY: It seems to me that there a lot more patients who get the drug than get the booklet.

DR. MARTINO: Dr. Proschan.

DR. PROSCHAN: I think that the reaction of Novartis is somewhat defensive, and I think that hurts. I am looking at this, the adverse reactions, and the first sentence is, Osteonecrosis of the jaw has been reported in patients with cancer receiving treatment regimens including bisphosphonates. Now, if you read that just a little bit differently, I realize there is no comma in there, but you could read that as Osteonecrosis

of the jaw has been reported in patients with cancer receiving treatment regimens including bisphosphonates.

In other words, it has been reported with a number of regimens, and this is one of the things. That may very well have been accidental, but I think it comes off as being defensive. Many of these patients were also receiving chemotherapy, you know, and I think it would be a lot better to take those defensive things out.

DR. MARTINO: Is that wording from the company or is that wording from the FDA?

DR. PAZDUR: This was negotiated, labeling changes, that we were in discussion and agreed with, with the sponsor, but we will be more than willing to renegotiate these if the committee feels that this is too weak.

DR. MARTINO: I just wanted to make that clear. I mean it is not really entirely their choice of wording. I mean it's an interaction.

DR. PROSCHAN: Like I said, that first one may very well have been accidental. I mean even if

you changed it to, instead of including bisphosphonates, if you change it to "that include bisphosphonates," that is a minor change that doesn't have that potential misinterpretation.

DR. MARTINO: I think for me the issue is, you know, as time is going on, there are more and more of these cases, recognizing that we don't know the denominator. So, perhaps what might have been an appropriate stance to take, you know, a year ago or 18 months ago, may be not quite appropriate today, that we know more right now in terms of the fact that, yes, this does occur.

The other thing I have to say I don't have a real sense of is the severity of this. I mean I have seen one speaker this morning imply that these tend to be fairly minor issues, and then I have seen another speaker with a very different experience.

So, as a clinician, I am just kind of here struggling trying to figure out, not only is the frequency of this problem, but I don't feel I really have an understanding of that.

DR. REAMAN: I would echo the same thing and again I would also criticize we are being asked to comment on the materials that have been provided

to patients and the public without having had the opportunity to review them.

But I am totally baffled about this whole entity, which has been attributed to bisphosphonates. We have heard people claim that they have never seen it before in their lives or rarely saw it, but yet it is associated with a number of well-established risk factors is what it says in this.

So, if we know so much about it, that it is associated with well-established risk factors, it seems to me a great deal of double talk. As a physician, I don't understand what this statement says. As I patient, I am certain that I wouldn't have been able to understand.

DR. MARTINO: Rick, did you have something you wanted to say?

DR. PAZDUR: Well, by no means I don't think it is anyone saying that this is a trivial

situation, and with any clinical expression of a toxicity, there are various manifestations of it that could be progressive in many patients, but I want to make sure.

The reason why we are having this meeting is to bring attention to it. We, at the FDA, are somewhat limited in what we could do to notify the public. We change labels, we send out e-mails, we had advisory committees, and I think is kind of the apex of what we could do with the toxicity, to spend time in an open public forum to bring this to people's attention here.

I don't think it is well characterized, and I think the surrounding areas that are associated with it are areas that are characteristics of patients that have it, whether they are causal effects, whether they are casual associations, I think that is to be further delineated and to be further examined with more time.

DR. BERENSON: May I comment briefly on this? Every patient who is seen in our practice is

informed of the renal risks, the osteonecrosis of the jaw risk, as well as the flu-like symptoms in detail, and every patient is evaluated by a dentist now before they actually begin therapy.

In addition, those patients with possible jaw problems are referred to an expert at UCLA for further evaluation. The spectrum of patients that I am seeing are amongst everybody who gets treated with bisphosphonate for myeloma, so I am not seeing necessarily the extreme cases, I have seen just six, but I can only comment on my own experience, but we are very aggressive about making sure these patients are informed about this complication.

DR. PAZDUR: Unfortunately, perhaps many aren't, as was pointed out by the oral surgeon from Kaiser, medical oncologists don't get into people's mouth many times. That isn't a focus of some of their examinations, and especially in an unrecognized problem, they may not be paying attention to this.

Many patients are started on aggressive chemotherapy regimens without a visit to the

dentist or without a really thorough examination. Here again, I think this points out not only to a problem with a drug, but also a problem with our practice of medicine in oncology, that we need to pay more attention to, so there is various factors that go into this.

DR. MARTINO: As a clinician, I am not sure that I have even a clear understanding of how I would recognize this. In other words, what would the patient say to me other than it hurts here, Doctor, and they would be pointing to their jaw.

I mean I don't have an understanding that if I sent them to a dentist, the dentist will do anything more than I would do, which is to look in the mouth and decide if they need a tooth pulled or some gross basic thing like that.

What I am most at loss of is an understanding of what is the actual behavior of this disease, and if the company has the ability to sort of characterize it, that would be great.

DR. PAZDUR: You have Dr. Ruggiero here, I believe, and perhaps he would like to address this.

DR. YOUNG: I will invite Dr. Ruggiero. I just want to say I think this is a critical condition, and based on the kinds of information

that we have now, which is spontaneous reports, it is very hard to sort out these things.

I mean we have a variety of symptoms and signs that are reported. You know, we may have a mixed group of cases at this point, so I think this is why we really critically want to put together a definition, a severity system, a grading system, so that we can prospectively look at this going forward and get a better idea of the natural history.

DR. PERRY: Yes, I think that is where the FDA could really do something instructive is to get together a group of experts and come up with a scoring system, so that if what we have seen are Grade 4's on the usual CTC system, we would have a better idea of what kind of elephant we are dealing with.

DR. MARTINO: Dr. Brawley, you are next.

DR. BRAWLEY: Dr. Hussain was much more

eloquent in describing the question I have. I remember when Novartis brought this before the ODAC before, and we suggested that it might be approved, and I don't regret voting for it being approved, because I think there is some benefit to the drug, but I recall that of the skeletal-related events that they talked about, and the decrease in the skeletal-related events, they increased the number of events found and increased the number of events, reduced in the Zometa arm by doing screening of the spine with x-rays.

So, many of the skeletal-related events that were prevented with Zometa were asymptomatic fractures that were here nor there to the patient, but they were prevented nonetheless.

So, when I see that and I heard about the advantages of Zometa, I worry about is the promotion of the drug as accurate as I would like.

DR. MARTINO: Dr. Reaman.

DR. REAMAN: Just a question. Are there any kind of screening studies that could be done? I mean when I go to the dentist and say something

hurts, the first thing that is done is x-rays. I mean is there a recommendation for doing some sort of radiographic studies based on duration of exposure?

DR. YOUNG: I am going to ask Dr. Landesberg. I want an oral surgeon to speak about this.

DR. LANDESBERG: Regina Landesberg from Columbia University. I believe that as far as a screening exam, we have documented what we would recommend for that, and it really just includes something that should be done by every dental oral surgical professional, a complete oral exam, examining the head and neck structure, but it really requires that you are diligent.

We believe that there will be some predictive indices and we may be able to see changes on radiographs, but that has not been established at this point. I do believe that we can find some predictive indices that will indicate who is going to be at risk for this disease.

DR. REAMAN: I think it's great that

dentists are made aware of this, but are oncologists who are prescribing this made aware of this, and are they being told that this is something that they have to do for patients for whom they are prescribing this drug.

DR. MARTINO: Actually, that may really be a very worthwhile thing to do. I mean I will tell you I have never had the habit of sending my patients to a dentist prior to this, and I don't know that that would solve the problem, to be honest with you. I am not sure right now that I have that feeling, but it is not an unreasonable thing to do.

DR. PERRY: I was wondering, you know, I was a little troubled when I first looked at this by the fact that the same doctor had reported so many of these cases, I am just wondering whether this is something that is very easy to see and confirm, and whether anyone else did confirm those.

DR. MARTINO: I think we have got that doctor here, and I must admit I had that same reaction as to was this somehow a selected are we

looking for.

DR. RUGGIERO: Well, there are a bunch of questions that I have to address here.

First, it was, when we first started seeing these problems, very interesting to me that we were the only center that was seeing such a number of cases, we were really were. At the beginning, we were seeing 10, 20 cases where people weren't seeing this at all.

As of yesterday, I logged the 105th patient in our local database in my practice alone, and I don't know why we are seeing so much. Clearly now, because of all the publicity, I am seeing more and more patients, but a lot of them are local people.

The spectrum of disease, as you have mentioned before, there is truly a spectrum from small, little tiny areas of exposed bone that are very easy to diagnose. This is not something that is rocket science to diagnose. It's simple, it's easy. You look in the mouth, you see exposed bone, you have a diagnosis.

So, yes, I don't expect the oncologist to be looking in the mouth, but if an awareness is sort of made to the patient that this is a possible

problem, then, the diagnosis can be easily made. There is a spectrum, and we have seen that here today. Dr. Levine showed cases of massive exposure of bone. I have many cases like that. Likewise, I have many cases with small, little areas of exposed bone that remain quiescent over a very long period of time and respond very well to treatment.

I have a lot of patients who have not responded to treatment, and have done very poorly and lost their job over this complication, and it is very frustrating because we don't have any clinical indices right now to predict who is going to be the person who loses their job, who is going to be the person that is going to continue to do well on rinses alone.

I think one of the things that has to come out of this meeting and meetings like this, is to educate the patients, educate the oncologists, and more importantly, educate the general dentists,

because I think the dentists are probably the ones that are kind of caught in the middle here. They are looking at things, and they don't really know what they are looking at.

Oftentimes, it winds up in the oral surgeon's office and they are now one of the professional groups that is probably more aware of this than any other group, probably oral pathologists, as well, since they are reading all these specimens.

The oncologists are a distant third, and I think that is getting better, but I think the main focus at this point is to educate the oncologists, and that is going to be as well as myself, and a few of my colleagues, to educate the ADA, and we are doing that in the process of getting some of this data off to them.

But, if you have any more questions?

DR. MARTINO: Doctor, when you see these patients, what do you do as a way of managing the problem, how do you, quote, unquote "treat"?

DR. RUGGIERO: It depends upon the

symptoms that they have when they present. If they present with exposed bone, but they are asymptomatic, they have no pain, they have no evidence of infection, I do relatively nothing.

The main goal here, in my mind, is to maintain the highest quality of life possible, because this problem, if left unchecked, or if it progresses, can be in many patients' own testimony to me, is worse than any other chemotherapy they have ever gotten, because it can be very painful.

So, if they present and they have exposed bone, but they are asymptomatic, we leave it alone. The worst thing to do in my mind, and I have been through this loop because when we first started seeing these patients, we thought this was just exposed necrotic bone, we went after it surgically. I took jaws off, I took sections of jaws off. They don't heal, and we have made it worse.

So, we have to learn, as a profession, to put the scalpel in the holster most of the time, and just follow these patients, and when they are symptomatic with pain infection, hit them hard with

antibiotics.

Now, these are recommendations that have developed over the course of time based on my experience and a few other oral surgeons across the country, and we have come to somewhat of a consensus.

Is it based on a lot of good data? The answer is no, it's my own personal preference, and we have had some success with it. It has to be looked at in a more structured way.

There have to be some prospective studies looking at why this happens, how to prevent it, how to identify patients who are at risk of developing this, and we just don't know that right now.

DR. MARTINO: Yes.

DR. AVIGAN: I was just going to emphasize the importance to distinguish between case identification criteria where the clinician would be prepared to identify the case and then appropriately manage it, and prevention and risk mitigation, which is really a different arena, where we clearly from what we have heard today,

need more information to determine the relationship between duration of treatment, cycled therapies, susceptibility factors, is there a threshold effect of what the total dose is, and that would then inform benefit-risk for those patients who might have a longer course disease.

So, you have to think about the natural course of the disease that they have, on one side of the scale, and then the other side is the natural course of the treatment and its effect on the hazard and risk over time, which needs to be studied.

DR. MARTINO: Thank you.

Dr. Pazdur, do you have any other needs from this committee today? Are there questions you have that we have not answered for you?

DR. PAZDUR: I think some of the questions that we have laid out here perhaps don't have answers at this time. I think we have evolve that data. In my own mind, listening to what has been said, I think there are several major areas that Novartis, FDA, the investigator community have to

work on, number one, duration, and I think that is an important issue and how optimally to use this drug.

The half-life of this drug in bone is very, very, very long. Do people need the same dosing schedule over a long period of time? Greater awareness by the community that treats this, not only oncologists, oncology nursing personnel, oral surgeons and dentists.

Is there a preferential bisphosphonate, Aredia versus Zometa? There some very interesting data that was presented by the group here. We have to remember that the basis for approval in multiple myeloma was on the basis of a non-inferiority for Zometa.

So, is there a big advantage is we have a toxicity issue? Here again, we don't know this. This is data that is hypothesis generating that we heard, but these are I think major questions that need to be answered and hopefully they can be answered.

Here again, our reason for bringing this

to the committee, we really wanted to highlight the safety issue. It's an important issue. This is one of the few opportunities that we get to have a public face to the FDA, and I think that this is important to illustrate, not only efficacy, but important safety issue.

So, I thank you and I don't have any questions at this time.

DR. MARTINO: Thank you, and this meeting is adjourned.

[Whereupon, at 1:27 p.m., the meeting adjourned.]

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