ATDEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE

72nd Meeting

Tuesday, September 24, 2002

8:30 a.m.

Kennedy Ballroom
Holiday Inn
8777 Georgia Avenue
Silver Spring, Maryland

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Karen M. Templeton-Somers, Ph.D., Executive Secretary

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Otis W. Brawley, M.D.
John T. Carpenter, Jr., M.D.
Bruce D. Cheson, M.D.
Stephen L. George, Ph.D.
David P. Kelsen, M.D.
Silvana Martino, D.O.
Jody L. Pelusi, F.M.P., Ph.D.,
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Gregory H. Reaman, M.D.
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P R O C E E D I N G S

Call to Order and Opening Remarks

DR. PRZEPIORKA: I would call the meeting to order. Dr. Pazdur has some opening remarks.

DR. PAZDUR: We would like to bid fond farewell to people that have been on the committee for several years and we really appreciate their service over these years. They have provided insights into drug development both on the committee and also individually in consultation on various applications throughout the years.

These members that are leaving the committee include Kathy Albain from Loyola University, Stacy Nerenstone, our former Chairman of this ODAC Committee, and George Sledge from the University of Indiana.

On behalf of the division and office and also on behalf of the FDA, we really appreciate their efforts in providing us this consultation.

With these members leaving, we have three new members. I would like to introduce them. They include Gregory Reaman who is Executive Director for the Center of Cancer and Blood Disorders at the Children's National Medical Center here in Washington, D.C. We really thank Dr. Reaman for his efforts not only on this committee but as a liaison to our Pediatric Oncology Advisory Committee which

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is a subcommittee of this committee which will be holding its next meeting in October. So we really appreciate his efforts to provide a pediatric insight into these diseases.

The next new member is Bruce Cheson who is Professor of Hematology Oncology and Chairman of Hematology at Georgetown University here in Washington, D.C. Bruce was formerly head, for many years, of the Medicine Section at the NCI, Division of Cancer Diagnosis and Treatment, Cancer Therapy Evaluation.

We, as government employees here in the Division, really thank Bruce for his many years of government service. On a personal note, I would like to also thank him for the guidance that he has given us throughout the years on specific consultations regarding hematological applications.

Our next new member is Silvana Martino who is at the John Wayne Cancer Center and is the Chairman of the SWOD Breast Committee. Likewise, Silvana has helped us in many applications and we appreciate her help.

With Stacy Nerenstone's departure, we have a new Chairman. This is Donna Przepiorka, Head of Malignant Hematology and Transplant at the University of Tennessee in Memphis Tennessee. Donna, we look forward to your leadership and we really thank you for taking this opportunity to work with us.

Thank you.

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DR. PRZEPIORKA: Thank you, Dr. Pazdur. Again, welcome to the new members of the committee. We will start the meeting this morning. We have a rather long agenda that we are going to try to get through in a reasonable period of time. I will turn the microphone over to Dr. Somers to read the conflict-of-interest statement.

Conflict-of-Interest Statement

DR. TEMPLETON-SOMERS: I have a couple of announcements first. Welcome to everyone. We are glad to see that there is so much interest in ODAC and apologize up front for the crowded conditions. We do have a large overflow room available down the hall with a t.v. feed so you can watch from there if you get tired of standing in the back.

We also do have to honor the fire code so, if the hotel management tells you that you must leave because you are blocking the fire aisle, please honor that request.

We are also asking for a little more air conditioning because, with this many people, it will get warm. So I apologize up front. The temperature usually is a little variable.

The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda and

information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the following exceptions.

I accordance with 18 U.S.C, Section 208(b)(3) and Section 505(n)(4) of the FD&C Act, Dr. David Kelsen has been granted waivers for his ownership of stock in a competitor valued between $5,001 to $25,000.

Dr. Silvana Martino has been granted a waiver under 18 U.S.C. 208(b)(3) for her membership on two data-monitoring boards for a competitor and her review of a manuscript for a competitor. These activities are unrelated to the competing products. Dr. Martino receives less than $10,000 for serving on the data-monitoring boards and from $5,001 to $10,000 for the manuscript review.

Dr. Sarah Taylor has been granted a waiver under 18 U.S.C. 208(b)(3) because her employer is participating in National-Cancer-Institute-sponsored studies and an expanded access program involving the sponsor's product. The sponsor provides the drug only for the expanded-access program.

Dr. Thomas Fleming has been granted a waiver under 18 U.S.C. 208(b)(3) because he serves on three data-safety monitoring boards for a competitor on products unrelated to

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the competing products. He receives from $10,001 to $50,000 a year.

Dr. Douglas Blayney has been granted waivers under 18 U.S.C. 208(b)(3) and Section 505(n)(4) of the FD&C Act for his ownership of stock in two competitors. The first stock is valued from $5,001 to $25,000 and the second from $25,001 to $50,000.

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

In addition, we would like to note that Dr. Stephen George is permitted to participate in today's discussions but he is excluded from voting.

Lastly, we would also like to note for the record that George Ohye is participating in this meeting as an industry representative acting on behalf of regulated industry. As such, he has not been screened for any conflicts of interest.

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

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

Thank you.

DR. PRZEPIORKA: Thank you.

Introduction of the Committee

I would like to turn next to the introduction of each member of the committee. What we will do is we will ask each member to introduce themselves starting with Mr. Ohye.

MR. OHYE: Good morning, everyone. I am George Ohye, the Industry Representative nominee.

DR. GEORGE: Stephen George, Duke University, Biostatistics, Member of the Committee.

DR. MARTINO: Silvana Martino from the John Wayne Cancer Institute. I am a medical oncologist.

DR. BLAYNEY: Doug Blayney, a medical oncologist, Wilshire Oncology Medical Group, Pasadena, California.

DR. VARRICCHIO: Claudette Varricchio from the National Institute of Nursing Research.

DR. BRAWLEY: Otis Brawley, medical oncologist, Emory University.

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DR. PELUSI: Jody Pelusi, oncology nurse practitioner, Northern Arizona Hematology Oncology Associates. I sit as the consumer rep.

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

DR. PRZEPIORKA: Donna Przepiorka, malignant hematology and transplantation, University of Tennessee, Chairman of the Committee.

DR. TEMPLETON-SOMERS: Karen Templeton-Somers, Executive Secretary to the Committee, FDA.

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

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

DR. KELSEN: David Kelsen, medical oncology, Sloan Kettering, New York.

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

DR. CHESON: Bruce Cheson, hematology-oncology, Georgetown University, Lombardi Cancer Center, Washington, D.C.

DR. TAYLOR: Sarah Taylor, University of Kansas Medical Center, medical oncology.

DR. SIMON: Tom Simon, Atlanta Georgia, patient representative.

DR. COHEN: Martin Cohen, Food and Drug Administration, medical reviewer.

DR. WILLIAMS: Grant Williams, Deputy Director, Division of Oncology Drug Products.

DR. PAZDUR: Richard Pazdur, Director, Oncology Drug Products.

DR. TEMPLE: Bob Temple, Director of Office of Drug Evaluation I in which Oncology lives.

DR. PRZEPIORKA: Thank you all.

We will move next to our open public hearing. I want to start with a statement from Dr. Somers.

Open Public Hearing

DR. TEMPLETON-SOMERS: We have had a lot of interest in this open public hearing and we may be differing a little bit from the list that has been put out as a handout. So please be patient with us and we will try and follow it as much as possible. But open public hearing speakers, if you come up and it is not your name, make sure that you state it loudly for the record if you are a little bit out of order because there are a few rearrangements in there.

In addition, there have been many people submitting letters and e-mails to the committee. Everything

that was received by last Wednesday was sent to the committee last Wednesday. In addition, the committee has copies of materials that were received through Sunday.

Copies of these have been provided to the committee in those ways and are also available for public viewing. There are two large binders out at the information desk. They will also be posted on the FDA website after the meeting and are considered part of the permanent meeting record.

Thank you.

DR. PRZEPIORKA: Thank you.

If we could have the first speaker to the podium, Mr. Carl Dixon from the Kidney Cancer Association.

MR. DIXON: Good morning. The May, 2002 Oncology Times carried an article entitled, What is it Like to Be ODAC Chairman. It reported some very troubling comments in my mind from former ODAC Chairs and members about the open public hearing and the contribution of patient advocates.

The article stated that, "Most of the Chairmen said that patient presentations were a federally mandated nuisance to be endured before real business got under way." An additional quote from an ODAC Chair summarized the sentiment as, "It is not as though we have no idea cancer is a terrible disease."

The FDA's advisory committee process is the only forum in which the people of this country have an opportunity to listen and participate in drug review. The scientific and regulatory details of oncology drug review are very daunting. Occasionally, even committee members can be confounded by the dizzying array of data and the convolution of comments on it.

Except for the information the drug companies are willing to disclose about their drugs, which is often favorably biased, the information on new drugs is simply not available to the average American. So what can the taxpayers, the public, fit into this complex drug-review process.

As someone who has attended and spoken at these meetings, I know that most often all the data the ODAC members receive is not available to the public before the advisory committee meeting. This leaves the citizen interested in speaking about a new drug in an untenable position. We are able to comment only from anecdotal experience, not from the scientific relevant information.

Well, perhaps what we have to say is not, indeed, scientifically relevant. The committee does have a choice about how they handle advocacy comments. The ODAC members can choose to understand that the deck is stacked against the public and pay close attention to the speakers and,

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perhaps, ask them questions which would inform the committee about an insight or experience of a "non-physician," otherwise known as "of the public" or a patient advocate.

It is dangerous when Americans' comments on the activities of their government are viewed as a "federally mandated nuisance." It might make the average American wonder if the rulers aren't just a little bit too far removed from the ruled.

Thank you.

DR. PRZEPIORKA: Thank you, Mr. Dixon. I just want to say, speaking for the committee, that we recognize that the recommendations that we make as a committee to the FDA affect not only the FDA, the industry and the medical community, but also all of the patients and their families. So we welcome all the input from the patients as well as their families and other individuals at this meeting so that we can have as much information as possible in order to make informed recommendations for the FDA.

Having said that, it is with pleasure that I will announce the next speaker to go on and get additional input from Rick and Jane Lesser from Redondo Beach, California.

DR. PAZDUR: Donna, if I could just mention, to follow up on Carl's comments, some of the things that we have done in the Division to really bring the Patient Advocacy Program into drug regulation. We have an ongoing

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Patient Advocacy Program where the advocates are actually consultants to the FDA and sit in in our Phase II, end of Phase II, meetings, our Phase III meetings with the sponsors.

We have an organized monthly telecom session where we go over regulatory matters with the advocacy community that are members of this group. That has been arranged by OSHI, both of these programs, Office of Special Health Issues.

In addition to this, we have been very active at sending not only myself but other members of the Division to various advocate meetings throughout the year. So I believe that these were very unfortunate comments. Obviously, they do not reflect those that are in the division where we are taking, really, efforts to basically be more inclusive of the advisory community and patients in general.

Thank you.

DR. PRZEPIORKA: Thank you. We apologize to the Lessers for the brief delay, but we appreciate Dr. Pazdur's comments.

MR. LESSER: No problem. We will try not to be a nuisance. My name is Rick Lesser. This is my wife, Jan. We are kind of unique because we are a happy lung-cancer story. In February, 2000, Jan presented at UCLA with Stage 4 non-small-cell lung cancer. She had a brain tumor

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the size of a golf ball. She had two lung tumors. She had two liver tumors.

She went through the usual protocol of the carbon-based, or the platinum-based. That didn't work. I learned about oncology words when they say the results are mixed. It means it didn't work. She had a second one. She had Gemzar. That didn't work. She had radiation then after they had taken out the brain tumor.

She then has laser surgery to get rid of the lung tumor. She went to a third cancer drug. At Thanksgiving, she spent the day in bed and I was trying to figure out how to raise three small kids.

The next day, she started with the IRESSA program with Dr. Natale at Cedars. We had been at UCLA where they didn't have it. The gal there sent us to him. Within a week, she felt better. Within a month, her tumors were half. Within two months, they were and now are gone.

This is the outside of Jan. You are going to see the inside of Jan later. But she is healthy. She is happy. We swim. We dive. We are spending our retirement rather dramatically. We have been diving all over the world, scuba dive. She runs. She works out three times a week. And she takes care of the kids.

We live our family like we did before this ever came along. If IRESSA works for other people like it did for us, it is the best thing that has ever happened.

Jan, say something. She is not big on public speaking, but just being here is enough. Tell them how you felt and what you are doing.

MRS. LESSER: Exactly what Rick said. I just--thank you very much, IRESSA.

MR. LESSER: Does the committee have any questions for her? We have got to kind of squeeze it out of her because, like I said, what do you say when you feel great and you feel normal? That's essentially how you are.

MRS. LESSER: Again, and my hair is coming back.

MR. LESSER: Thank you very much. Again, thanks to the IRESSA people.

DR. PRZEPIORKA: Thank you very much. Next is Abbie Myers from NORD.

MS. MYERS: NORD is the National Organization for Rare Disorders. Lung cancer is not rare. We are the consumer organization that worked for the Orphan Drug Act and we monitor its implementation. The reason that we are involved with this drug is that we operate mediation-assistance programs for people who have no health insurance, mostly for orphan drugs and we somehow became expert in early access programs because most of the time,

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manufacturers don't make enough of an experimental drug to give to large numbers of people.

Very often, with hopeless diseases, like lung cancer, there is a tremendous public demand. So AstraZeneca asked us to run or administer the early-access program for this drug. It became a very, very large program. There are more than 12,000 people in this program which is so unusual because AstraZeneca has been very generous with the drug.

Most manufacturers will give us a small amount of drug and we have an infinite number of people who want access to it. With this, we were enrolling 300 to 500 people per week through a randomized computerized program so that there is no chance of bias and that all people stood an equal chance of their name being drawn.

The most unusual thing is that companies don't like to start an early-access program while they are enrolling people for clinical trials. AstraZeneca wanted to enroll people for clinical trials and, at the same time, allow people who didn't qualify for the clinical trials to get this drug.

So it has been an extraordinary program. We have heard some extraordinary things and we have brought with us today a number of patients who just felt that the advisory committee concept gives them a very unique opportunity to

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speak to their government. These people truly want to speak to their government.

In reference to what Mr. Dixon said before, the advisory committee process is extremely important to the American public. I have served on the Biological Response Modifiers Committee and I understand some of the feeling behind it. But, as people come up to speak to you, it is their once-in-a-lifetime opportunity, other than voting every year, to talk to you and tell about their personal experiences.

So I hope that you will listen to these people today because their stories are really quite miraculous. I can't make any judgment about the scientific viability of IRESSA but we have heard stories about some people doing very, very well and some people who didn't do so well. You are the ones who are going to measure all the scientific facts.

But to people who were on their death bed and are now alive, a lot of them with no tumor at all, it has been an extraordinary experience for us as well as for them.

Thank you.

DR. PRZEPIORKA: Thank you, Ms. Myers.

DR. TEMPLE: Can I ask a question?

DR. PRZEPIORKA: Yes.

DR. TEMPLE: I want to break tradition here. Abby, did you say that in the early stages of the access program, people were randomized to treatment or not because there wasn't enough drug?

MS. MYERS: They called one centralized telephone number and they were screened at that number to see if they were appropriate for the clinical trial. If they were not appropriate for the clinical trial, they were sent to the early-access, the expanded-access, program.

DR. TEMPLE: But there was enough drug for everybody who met those criteria to be in the program?

MS. MYERS: Yes. Not only in the United States but even outside of the United States. It is extraordinary how AstraZeneca has supplied enough drug to meet the public demand. Yes.

DR. TEMPLE: I was tempted to ask because you mentioned the attempt to reduce potential bias. And I thought maybe--

MS. MYERS: No. The bias in the expanded-access is everybody's name goes into the computer. If we have enough drug to give to 100 people that week, the computer picks the 100 names and everybody else's name stays in the computer. The next week, when there is another selection, their name is in there so they have another chance of their name being pulled out.

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But human beings don't pull the names. If the CEO of AstraZeneca got lung cancer, he would not be able to get access to the drug unless the computer pulled his name.

DR. PRZEPIORKA: Carolyn Aldige from the Cancer Research Foundation of America.

MS. ALDIGE: Good morning. My name is Carolyn Aldige and I am President and Founder of the Cancer Research Foundation of America which is a National Organization based here in Washington dedicated to the prevention of cancer.

Since 1985, CRFA has supported cancer research, education and public-awareness programs in excess of $57 million. The organization has funded more than 600 peer-reviewed research projects in more than 200 different institutions. Some of this research has resulted in the identification of new molecular targets and the development of promising agents for preventing cancer, among other types of research.

We are proud of our record of achievement, yet always mindful of the great unmet medical needs of people living with cancer throughout America. We at CRFA are also mindful that we, or any other nonprofit organization, cannot tackle the challenges of cancer research and drug development alone. That is an understatement.

We applaud the creativity of government agencies and the pharmaceutical industry and encourage their still

stronger commitment to partnering with one another and with advocacy organizations for the benefit of cancer patients and their families and we are proud to work with them.

In that regard, I would like to disclose that CRFA has received unrestricted educational grants from AstraZeneca as we have from other leading pharmaceutical companies and companies that are part of other industries. No part of this company's support has funded IRESSA-specific activities, however, and I appear here today because I think it is important. AstraZeneca is not paying any expenses incurred in connection with this meeting.

Every day, our work in lung cancer makes it all too clear that patients living with the disease have too few effective therapeutic options. Too often, they are blamed for their disease and told to go home, get their affairs in order and await the end of their lives. I am familiar, personally, with more than one patient who has been given this type of advice but entered a clinical trial for IRESSA and is doing well months and even years after being given a limited life expectancy.

IRESSA is, therefore, an especially welcome development representing an important new treatment option that provides hope for those who have seldom known it. As you know, lung cancer kills more than 150,000 people each year in the United States. With statistics of this

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magnitude, even an 11 percent response rate will be helpful. We, therefore, urge that your committee give careful consideration to the needs of advanced lung-cancer patients.

It is especially gratifying to see that the first in a new class of cancer compounds has been submitted for your review. New ways of attacking cancer will mean new ways of looking at clinical benefit, new ways of reviewing drugs and new ways of balancing risk-benefit when looking at treatment options.

With the advantage of selectivity, we have the ability to free cancer patients from so many of the devastating side effects of traditional chemotherapy. Studies have consistently shown that patients fear the nausea and vomiting and alopecia associated with chemotherapy, in addition to the more life-threatening side effects such as neutropenia or tachycardia.

For patients with advanced non-small-cell lung cancer, preserving an optimal quality of life has been found to be a very high priority. IRESSA and related compounds address patients' needs and should be made available to them.

I was with a woman on Friday who, two and a half years after she starting taking IRESSA, alluded to the fact that she has had three more years to celebrate anniversaries with her husband. She was able to see her first grandchild

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graduate from high school and her last grandchild in her first grade. She said those milestones--"This drug has given me the ability to live life and achieve those milestones in my life," with very few side effects which, I think, is really extremely important.

I wish to comment AstraZeneca for conducting innovative research on quality of life with the cooperation of one of the foremost experts in this field, Dr. David Cella using validated instruments such as the FACT-L Questionnaire. The company has made an important contribution to the design and execution of clinical trials.

We urge the committee and its staff to consider quality-of-life data and symptom improvement as integral parts of new drug applications representing, as they do, an important priority for patients living with advanced non-small-cell lung cancer and other diseases.

These are exciting times in clinical oncology marked by the development of so many new and promising treatment options. We at CRFA believe that they required a new perspective in their regulatory review and that quality of life and other data should be an important part of any decision-making process.

As cancer treatment changes, so must the approval process. Like all other responsible cancer patient groups, we look forward to working with you to insure the system

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remains agile and responsive to patients who desperately need new drugs.

Thank you.

DR. PRZEPIORKA: Thank you very much.

Next, we will hear from Susan Nelson from Paris, California.

MS. NELSON: Good morning. I would like to begin by thanking the Food and Drug Administration Advisory Committee for simply allowing me to speak. As well, I would like to give a special thank you to the National Organization of Rare Disorders, NORD, for helping me with my travel expenses in order to make this experience possible.

My name is Susan Nelson. I am a non-smoker and I have lived thirteen years with a lung cancer titled bronchoalveolar carcinoma. At the age of thirty-six, I was an athlete and a health-conscious person and it was absolutely devastating to receive the news that I had this type of disease. At that point, in '89, I went through surgery and upper right lobectomy. However, in five years, in 1994, the cancer returned metasticizing to both lungs.

Travelling throughout the United States and visiting world-renowned medical facilities for possible treatment then became my new life as the cancer continued to grow. Due to the nature, though, of my disease, commonly prescribed cancer treatments were not options for me. The

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only hope actually offered to me was in Los Angeles where I was recommended to be a recipient for a donor heart and set of lungs with the understanding, though, that the surgery was very invasive and that the life expectancy was minimal.

By the Year 2000, it was clearly apparent that I was losing my battle with the onset of physical disabilities and increased lung-cancer symptoms. Although I never gave up hope, each doctor's appointment ended with the disappointing news until one year ago, August 2001, when I became eligible for the IRESSA expanded-access program.

Certainly, at that time, even today, I knew that we were on the cutting edge of some absolutely remarkable medical discoveries but I never ever imagined that a pill such as this would be available within my lifetime nor would I have the opportunity to experience this first-hand.

In my case, IRESSA began eliminating cancer symptoms in precisely seven days. In just five weeks, my CAT scans showed a significant decrease in my tumors. It has continued to improve my health to this day. Tumor shrinkage is now up to 90 percent in some of the masses and I am completely symptom free with a normal breathing capacity.

Here I stand, before all of you, forty-nine years old and stronger and more active than I have been in years. My story is no more compelling than any other cancer

patient's story. Today you are going to all be hearing heart-felt testimonials when it comes to those who have actually been in the trenches.

However, our stories are a little bit different than many of those who have experienced cancer because we have had an astonishing turn of events, thanks to IRESSA. As a committee, all of you have the difficult task of trying to see things from the perspective of the most important clients, those fellow human beings who have been fighting for their lives as well as those who may be in the future.

I speak for many by asking that you approve IRESSA as simply another choice, another choice, for the cancer patient. Please join us as pioneers in moving forward. Give others the gift that we have received, which is the gift of comfort and time.

Thank you.

DR. PRZEPIORKA: Thank you, Ms. Nelson.

Next is Anita Johnston from Each Norwich, New York.

MS. JOHNSTON: Good morning to all of you. I appreciate the opportunity of coming here to speak before you and I hope that what I say can make a difference.

My name is Anita Johnston and I have lung cancer. I have had it for about twelve years. When I was first diagnosed, I had surgery. I had a bilateral lung resection

through a sternotomy. I chose this mode of surgery because I had lesions in both lungs and didn't wish to go through two different surgeries within two months.

My right upper lobe was removed and a wedge section taken from my left lung. I was told that I had two synchronous primary tumors, that the one in the left lung was not a metastasis from the right lung. My cancer seemed to disappear for a while, and several years later I was diagnosed with yet another primary. It was, like, pretty unbelievable. This time, it was in my left lung and in the lymph nodes in my mediastinum.

I was treated with what was then, and what may still be, the first-line of chemotherapy. It is carbo and Taxol. It made me very sick. I was nauseated and vomiting. I had a lot of lower-bowel problems. I had reflux. Of course, I lost all my hair. I was just overwhelmed with fatigue and I experienced terrible neuropathy in my hands and feet which I still have, and, most unkind, the loss of some of my cognitive powers.

I figured, you know, I was getting old and nothing good was getting left anymore but my mind. My God; I was so proud of my mind. This was also leaving.

I live alone and I had to get to and from my six-hour infusions all by myself. I had to change my own sheets when I soiled them. Happily, my cancer receded and I was

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cancer-free for another two years. When the same lesion in my left lung returned, along with metastases in my adrenals and in my liver, this time I treated with gemcibine and vinoralbine. The side effects of these were equally unpleasant; the same fatigue that I had experienced from the Taxol carbo returned and the residual neuropathy just was exacerbated.

I didn't lose my hair although it became very sparse. Actually, the first time, if you have never experienced it, it just came out in one sad little puddle in the shower. The second time, it was kind of molting. I looked like my cat in the spring. It was just a little hair and a little there and it was just not beautiful.

By this time, I became very sophisticated about lung cancer and I am now the regional representative of ALCASE which is the Alliance for Lung Cancer Advocacy Support and Education. I have been associated with them for six years and I speak with hundreds of people all over the United States and in Europe. I use the phone and e-mail. I belong to several support groups. My experience with traditional chemo can be multiplied by the suffering of almost all the people that I serve.

Since I have exhausted the traditional methods of chemo, the next time it came around I asked my doctor for IRESSA. It was that or go home and get in touch with your

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lawyer and make out your will. That was two years ago. IRESSA is a piece of cake. You pop a pill every morning with your vitamins. The side effects are minimal. I have not had diarrhea that I was told to expect. I do experience pox-like eruptions occasionally.

My nails are soft and my hair is straw-like but it is still on my head. My cancer is not discernable on a CAT or PET scan but, best of all, my life is not on hold while I take this extra pill in the morning. I am not concerned that I am alone while my children, who live in other states, are not frantic that I will crash the car coming home from an infusion high on steroids.

I almost forgot, speaking of steroids. I don't look like a blown-up balloon anymore either.

IRESSA is easy on your body. It appears to work as a single agent for people who had previous chemotherapy. I hope that IRESSA will become just another drug in the panoply of drugs that are used in the treatment of lung cancer.

Thank you.

DR. PRZEPIORKA: Thank you.

Next, Gloria Caruso from Tampa, Florida.

MS. CARUSO: Good morning. My name is Gloria Caruso. I am a sixty-three-year-old female, life-long non-smoker, who was diagnosed with non-small-cell lung cancer

when a 1.5 centimeter nodule was removed in an upper right-lung lobectomy in December of '98. This was found during a routine chest X-ray that was taken along with my annual physical mammogram.

It was a small spot that was detected and the follow-up tests led to the surgery. Two lymph nodes were also removed during the surgery and one of them had microscopic traces resulting in my chemotherapy treatment of Taxol and carboplatin.

My chemotherapy consisted of four infusions, twenty-one days apart, from February through April of '99. It is almost impossible to describe your life under this type of chemo to someone who has not experienced it. You get extreme fatigue, nausea, pain in your joints, loss of appetite. The hair loss is to be expected, but the overwhelming malaise that drains you of any energy was just unbelievable. I could not work and I was in bed most of the time.

I looked and felt very sick. The only thing that kept me going was my normal high optimism, my family and friends and my faith in God. Follow up CAT scans were scheduled after my chemotherapy every six months and, by the end of '99, the cancer was back in the lymph nodes and the superior and anterior mediastinum.

Due to my lack of other symptoms and otherwise general good health, I decided to take a watchful "wait and see" course of action. In July of 2000, I had a PET scan which showed the nodule involvement had progressed to the supraclavicular areas on either side of my neck as well as the mediastinum. This news led to my search for clinical trials that might offer something better than the surgery and chemotherapy I had already endured.

My research on-line into clinical trials was frustrating at first because I discovered that my previous conventional treatments, in fact, disqualified me from most clinical trials. I was so fortunate to come across the new expanded-access program for IRESSA which was then starting in that Fall of 2000 and did not exclude me due to my previous treatment.

When I consulted with Dr. John Ruckdeschel at Moffit Cancer in Tampa concerning this program, he agreed to try to get their facility approved as one of the trial sites. After a few months of paperwork to set up the program, I was selected and began the once-daily dosage of 250 milligrams of IRESSA monotherapy.

My results at the first three-month CAT scan were better than my doctor or I had ever dreamed was possible. The tumors, in just those 90 days, were 90 percent gone and subsequent checkups over the last nineteen months have

continued to show dramatic shrinkage of my tumors. They cannot locate them in my body anymore.

I know this is not a cure but my quality of life for these last nineteen months with IRESSA has been light-years away from my previous treatment. The fact that my tumors were gone as well is unbelievable but my quality of life--I work. I enjoy my family. In my case, the side effects were minimal, consisted primarily of skin acne and skin dryness and itching which are relieved with topical medications.

I can now describe myself as I truly am, a wife, a mother, grandmother, world traveler, a friend and co-worker--I am still working full-time--and grateful participant in the expanded-access program for IRESSA. I enthusiastically endorse the approval of this new drug and hope many more patients suffering with non-small-cell lung cancer can benefit in this same manner.

I want to thank this committee for the opportunity to participate in this hearing.

Thank you.

DR. PRZEPIORKA: Thank you.

Next we will hear from Robin Prachel from the National Patient Advocate Foundation.

MS. PRACHEL: Please bear with me. I am a little bit nervous and I am not feeling well. Actually, I am going through chemotherapy right now.

I am standing before you today to state some statistical facts you may already been familiar with. This year, 154,900 Americans will die from lung cancer. That is more than breast, prostate and colorectal cancers combined. While I may not be one of the statistical numbers this year, I may be one of the numbers next year or the year after.

Lung cancer accounts for 28 percent of all cancer deaths. I'm in the process of buying my burial plot because there is a 90 percent chance statistically speaking that I will die within the next three to four years.

It is estimated that there are 169,400 new cases of lung cancer this year. That is hard for me say, so I apologize if I get a little emotional, but when I sat down to write my speech, when you see all these numbers in black and white and you see the statistical numbers, and you see your own number, and you see your mother sitting in the audience, it is very hard. But, as I was saying, it is estimated that there are 169,400 new cases of lung cancer this year. That is a lot. I just never thought I would be one of them.

Smoking is directly responsible for 80 percent of all lung-cancer cases. I have never smoked.

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Smoking is, by far, the most important risk factor in the development of lung cancer, as I just stated. Not all people get lung cancer from smoking. My cancer is a byproduct from my work in construction. I supervised construction on the outer banks of North Carolina. I built a new hospital, an aquarium and a couple other commercial buildings. Unfortunately, while working in construction, I was exposed to asbestos and dust-related particles and they have now settled in the bottom of my lungs and are now mass-producing tumors.

Only 15 percent of people are diagnosed in an early localized stage. Cancer treatment has come so far. In November, 2000, when I was first diagnosed, I was one of the lucky ones. I was Stage 1. Mine was confined to the lower left lobe of my left lung. With the type of cancer I have, BAC, two years ago, the aggressive protocol for treatment was to remove the malignant tumor and/or section the lung with no chemotherapy to follow.

Now, the preferred choice of treatment has changed. Lung cancer is having significant results with chemotherapy first then followed up with surgery as was reported in May's American Society of Clinical Oncology (ASCO) conference in Orlando, Florida.

This past summer, while most people were taking family vacations, I had another lung resection. I had brain

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surgery and started chemotherapy, and a lot more. Would my outcome have been different if the drug IRESSA had been available when originally diagnosed two years ago? Now I am at Stage 4 with only a 10 percent survival rate projected for the next three to four years.

Two years ago, even six months ago, I was a healthy, active single mom who never smoked. I coached soccer. I taught Sunday school. I have volunteered with the Civil Air Patrol and much more. Now I am sick. I feel sick. I am scared to say, I feel like I am dying, and it is not from the cancer at the present moment. It is from the chemotherapy that kills your good cells and your bad cells.

You go through many emotional stages when you find out you have cancer. They are hard to understand unless you have been there. To be honest, the last three weeks, I have been battling this feeling over and over again; is this really helping me? Would I have eventually gotten sick if I didn't decide to fight this disease head-on.

Cancer is not all scientific facts. Yes; you need to fight to disease, but you hear, again and again, it is the patient's overall emotional state that helps win the battle. In my case, as I stated before, chemotherapy was not given with the original diagnosis due to the detrimental side effects it would pose to my lungs.

IRESSA, without the side effects, may have been more readily given and certainly would have helped my physical and emotional well-being by keeping the healthy cells doing what they are supposed to be doing. Chemotherapy, with all its side effects is tough, both physically and emotionally. It is tough to stay positive when you look in the mirror, or when you look at your child scared face, it is a constant reminder that your cells are being killed, hopefully, for the greater good.

Common sense tells you you have to fight this. But sometimes it is hard. When I first started dealing with the cancer recurrence, I kept telling myself I wanted to live to see my grandchildren. Now, I just want to see my sons graduate from high school. It is a scary feeling. It is probably normal to feel this way, but it is very real to me and to my family.

I may not be telling you anything you may not have already heard before, but I hope you take this into consideration, you think of the person, a person like me, or you, with your families, when you make your decision today.

Thank you.

DR. PRZEPIORKA: Thank you, Ms. Prachel.

Next is Melissa Mahoney from Virginia Beach, Virginia. I would like to remind the speakers, or ask the speakers, to disclose any financial assistance including

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travel that they have received from any pharmaceutical companies or advocacy groups.

MS. MAHONEY: Good morning. Thank you for the opportunity to speak to you today about my experience with the experimental drug IRESSA. When I registered with this meeting, I was asked if I would be using a visual aid. It didn't take me very long to realize that the very best visual aid I could use is me.

The very fact that I am standing up here today is nothing short of a miracle. In February of this year, I was at the end of the line. I had received the best standard care available; surgery, radiation, various and numerous chemotherapy regimens, two separate phase I clinical trials at a large teaching hospital.

My condition continued to worsen. Disease progression compounded by the physical toll of the treatments was very hard. My performance status was poor. I was on daily pain medication and I was so short of breath I could barely walk up a flight of stairs. The simple act of taking a shower wiped me out for hours.

On February 16, I began taking IRESSA. Within days, and I mean days, I felt significantly better. By the end of March, I was power-walking on the beach in Fort Lauderdale as I was vacationing with my family.

Let me read you my oncologist's report from my June CT. "The patient is recovering and responding very well to IRESSA. She actually is having a dramatic response to the drug with an improvement in performance status. Her CT scan is quite amazing. There has been a 90 percent-plus reduction in hundreds of pulmonary nodules. There is no new disease present. She feels very well and continues on treatment."

The actual radiologist's notes say, "There has been almost complete resolution of numerous small pulmonary nodules in both lungs seen in the previous study with very few tiny faint nodules remaining in the left lower lobe either representing a remarkable response to chemotherapy," the radiologist did not know that I was on IRESSA, "or complete resolution of opportunistic infection."

The doctors' reports put in clinical terms the evidence you see before you. I urge you to approve this drug. Also, I hope you recommend additional trials with IRESSA as a single first-line agent. On chemotherapy, I was sick and fatigued. It was painful and time-consuming. I experienced numerous unpleasant side effects and the emotional toll of losing one's hair is very hard to explain to someone who has not experienced it.

With chemotherapy, it was months before it could be determined if this treatment was working or, in my case,

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not working. IRESSA is a blessing. When this drug works, it works fast and it works well. One little pill a day. I had had the side effects of skin rash and diarrhea but they are manageable and well worth the benefit. With IRESSA, I am not merely living. I am thriving.

It has not just given me more time. It has given me my life back. In August, my physician apologized to me. He said that if he had had any idea IRESSA would work so well, I could have been spared much suffering. But that decision was not in his hands. He could not have prescribed it to me and I had to fail several chemotherapy regimens before I could receive through the expanded-access program.

Members of the advisory committee, the decision is in your hands. I am alive today thanks to the grace and mercy of the Lord in providing me with this wonderful drug. I would ask that you would remember this visual aid and approve IRESSA.

Thank you.

DR. PRZEPIORKA: Thank you, Ms. Mahoney.

Next is Janine Hutchison from Las Cruces, New Mexico.

MS. HUTCHISON: Good morning. My name is Janine Hutchison and I am from Las Cruces, New Mexico. I am 59 years old and non-smoker. Sounds familiar. I was diagnosed on November 3, 2000 with non-small-cell carcinoma in the

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fourth stage at Memorial Medical Center in Las Cruces, New Mexico. I had pleural effusion of the right lung and a thoracentesis was done at that time. Fluid was sent to Mayo Clinic and confirmed the presence of adenocarcinoma.

A CT of my chest showed a lobulated soft-tissue mass in the anterosuperior mediastinum and right peritracheal region. A bone scan was also done and showed osteoblastic activity in the prenemial right femur. An MRI of the femur showed metastatic disease.

I went to MD Anderson in Houston, Texas for a second opinion. I was only offered chemotherapy and given a year to live. I was also told my passing would not be too hard. This was hard to take. I decided to go home and fight as I felt there must be some other newer treatment somewhere available.

I was hospitalized again in December, 2000 at Memorial Medical Center in Las Cruces. This time it was to have a pleurodesis which was to drain my right lung on a machine for a week and then try to seal it with talc. We hoped it would work. It did. A portacath was also inserted at that time.

Chemo was started at the end of December, 2000. I had six cycles of cisplatin and Gemzar ending in April of 2001. I improved somewhat. My CEA had been normalized from 5.9 to 0.6. A CT scan at that time showed stable disease

with pleural thickening along the right lateral chest wall with blunting of the right costaphrenic angle. There was also persistent right peritracheal density that was still persistent disease.

After chemo, my doctor said that there was nothing more that he could do. I remember telling him that there must be something out there. On my next visit, he asked me how I would feel if I was given an experimental drug. I said, "I'm there. Make an appointment."

My oncologist then referred me to Dr. Jesus Gomez in El Paso, Texas who was at the El Paso Cancer Treatment Center as a possible candidate for IRESSA in the IRESSA expanded-access program. I was examined by Dr. Gomez and he thought I would make a good candidate.

The paperwork was submitted and I was accepted by the program and started on IRESSA June 25, 2001. Each month, I showed an improvement and, by December of 2001, the only signs I had were a small pleural effusion with calcified pleural density. My last CT scan, taken on June 28, 2002 was fantastic. There was even further resolution of air-space opacities in the right lower lobe and in the right hemithorax with calcified pleural density unchanged which was from the pleurodesis.

No lung mass, no nodule, no lymphadenopathy, no effusion. I have also had a bone scan done September 28,

2001 and it also showed that my problem in my pronemial right femur had shrunk.

I can remember back when I was first diagnosed that I found it even hard to walk down the hall in the house and had to have someone to help me dress. I would be out of breath and coughing. It was the darkest time of my life.

I can now walk briskly, run, drive, drive my car and work in my garden and play with the grandchildren that I love. Life once again has meaning. I thank God every day that he gave such wonderful brains to the people that are responsible for this drug. I am very fortunate, especially when I think of the people that have passed on in a lot of agony with not a glimmer of hope.

At this time, I would like to ask you to take this drug under serious consideration as I feel that it could help so many people. These are people in the advanced stages of cancer of the lung, non-small-cell carcinoma, as, up to this point, there has only been chemotherapy, radiation and surgery.

These options may bring a person a couple more months of life or a somewhat longer life, but the majority of these people feel that, in the long run, there is no option but to die. The side effects of chemo and radiation are numerous--example, myself. With chemotherapy, I have a loss of hearing, arthritis in my joints, and the nerves in

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my feet are dead. I have no feeling. And, of course, I lost my hair while on the treatment.

On the other hand, with IRESSA, all I have are pimples. It makes me feel like a teenager again. IRESSA is commercially available in Japan. Japan has had the foresight to be on the cutting edge of the new technology while we here, in the United States, seem to be dragging our feet which means that every day someone is dying that we could have helped.

Please give patients with non-small-cell lung cancer back hope and a renewed quality of life. They have nothing to lose.

Thank you.

DR. PRZEPIORKA: We appreciate your comments, Ms. Hutchison.

Next is Adrienne Riddle from San Bernardino, California.

MS. RIDDLE: Good morning and thank you today for this opportunity to speak with you. When I first learned of this meeting a week ago, my mother and I, we felt it was essential that I come and tell you about my story.

We have come here independently of any sponsorships. Even my doctor, Dr. Natale, didn't even know I was coming and was surprised to find out I was here. My

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name is Adrienne Riddle. I am from San Bernardino, California and I was born in 1982.

I graduated from San Bernardino High School in 2000 and went to San Jose State on a water polo scholarship. I finished out my Freshman year, having played the whole season to come home and become very, very sick. When I came home, I was diagnosed with a tangerine-sized tumor in my right lung and had a complete pneumonectomy on 6-7-2001.

After an MRI and a CAT scan, it showed nine to ten tumors in my brain. It was throughout my lymph nodes and there were nodules in my left lung. I was classified as a Stage 4 non-small-cell adenocarcinoma.

I have never been around second-hand smoke. I have never picked up a cigarette. I was just this healthy incredible athlete. After six months of exhausting chemotherapy, I finally had to stop. I couldn't take it any more. At this time, my tumors appeared to be regressing. I then found about IRESSA from Dr. Natale. He suggested that we try to IRESSA expanded-access program. I felt that this trial study showed hope in the midst of very, very few options.

In January, 2000, I started IRESSA. Since that time, all the remaining brain lesions and nodules in my left lung have ceased to appear. Approval of this drug is very important to me. It has given me a chance to turn 20. I am

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no longer a teen-ager anymore. It has given me a chance to return to college, to just live life, grow.

I urge you to approve this drug because, if someone like me can get lung cancer at age 18, then the future will bring more. IRESSA has helped me fight through this an I feel it was truly the missing links along with chemotherapy and my surgery. It was a group effort among the options that I decided to take. It has given me a second chance.

Thank you very much for this time. I know you will make the right decision.

DR. PRZEPIORKA: Thank you, Ms. Riddle.

Next, we will hear from Blanche Taylor from Sparta, New Jersey. Following her, we will be going out of order just a bit and we will hear from Laura Turpak.

MS. TAYLOR: My name is Blanche Taylor. This is so hard because this drug has given me back my life. I was diagnosed in December and given a very short life expectancy. I have cancer in both lungs, no metastases outside of the lungs. I had a second opinion from Sloan Kettering and they agreed.

I was directed eventually by Dr. Fazal Bari, my oncologist, to try IRESSA. I was grateful because the chemotherapy regimen I was on did not affect my cancer. My cat scan showed continued growth every time.

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The very first day I took IRESSA, stopped coughing. I would cough every day, every fifteen, twenty minutes to clear my lungs and my chest, my bronchi. At night, I never slept through the night. I would wake up every hour to clear my chest and my bronchi. I would become very fragile, weak.

With the IRESSA, the very first day it changed. I am strong and healthy. I am back to work. I do everything myself. I do all my housework. I have twelve grandchildren that I would like to see grow up. Their ages are two to twenty-one. I have a husband who loves me and needs me and two daughters. I am just very, very grateful to IRESSA for providing this pill for me.

Please consider it for others. They need a chance to live. I would also like to thank NORD for providing me the means to get here. This is my helper, my daughter. NORD notified me the opportunity to speak, I knew I had--when I got that letter a week ago, I knew I had to come. As you see, I am not a speaker--and AstraZeneca for their incredible for and for their dedication to helping cancer patients.

Thank you very much.

MS. TURPAK: My name is Laura Turpak and I am the daughter of my mother. I didn't even know I was going to have the opportunity to speak so I will make it very short.

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My father died of lung cancer that metasticized to the brain. After many chances of getting diagnosed, it took them over a year and a half to figure out what he had. And we had one week. I found out and a week later he had passed away.

Had I had the opportunity of IRESSA, I would have certainly done everything in my power to get the medication to him. Now I am faced with my mother's illness and I cannot thank AstraZeneca for being so incredibly supportive, cooperative--Sloan-Kettering as well--for giving me the direction to help my mother. And, of course, my mom's oncologist, Dr. Bari.

But I have to say, if I may, this is a science, obviously. You can get caught up in the figures. You can get caught up in the financial end of things. But the bottom line is that it is extending the quality and quantity of many people and I am really hoping--I am not a good public speaker either, but I am really hoping that, since this was our last resort, since my mother was diagnosed Stage 4 lung cancer that you will, as a no-brainer, approve this drug.

I am begging you, please, to approve this drug because, if it was you, any of you doctors, nurses, professionals--if you only had one last resort, and you knew

it was helping others, I am sure you would want it available to yourself.

Thank you for letting me speak.

MS. TAYLOR: I just want to say one more thing. I didn't plan to say this but I want to realize the jolt you can have when your doctor tells you the results of all your tests and he tells you to get your affairs in order. Think about it.

DR. PRZEPIORKA: Thank you.

I would like to call to the podium Pat Meredith from San Diego, California, please.

If Ms. Meredith does come later, we will hear from her. But right now, we are going to move to Mr. Charles Reilly from Tarrytown, New York.

MR. REILLY: I, for some reason, received the notice of this meeting really late. It was Wednesday and I haven't had much time to really put this together. I thought I would have a lot less time and I boiled it down quite a bit.

I will give you what I have got. Good morning, ladies and gentlemen. My name is Charles H. Reilly. I own a home at 36 Hamilton Place in Tarrytown, New York. I am forty-six years old, been married for eleven years and have a four-year-old son. I am speaking to you today because IRESSA saved my life.

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I have come here on my own, at my own expense. I am not being compensated in any way by AstraZeneca, nor have I ever met or spoken to anyone from AstraZeneca. If they wish to compensate me for this trip, I would be delighted.

But I really think the most important thing is that I have the opportunity and the privilege to speak here where the most can be made from what I have to say. Some of you today will have the chance to make a decision that could accomplish incredible good. IRESSA has made me one of the luckiest people alive.

In January of 2000, I was diagnosed with inoperable lung cancer. A pancose tumor in my right lung had spread to the base of my neck. I had a group of the best doctors at Sloan Kettering in New York City. I insisted that they tell me what they really thought would happen to me.

Without treatment, I had about seven months. Even with radiation and chemotherapy, I would live for about two-and-a-half years. I received the treatments but the cancer came back in the same places. Now the only option was chemotherapy by itself and two other types were tried to no avail. By now, I was in tremendously bad condition.

As with many patients receiving these treatments, I developed blood clot in my right arm which limits its use and a weakening of my heart resulted in me having a heart

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attack. This is now permanent, physical damage which is potentially life-threatening.

Looking at me now, it is hard to believe the devastation the treatments, themselves, caused. I had nothing left to lose so a friend convinced me to look into IRESSA. I was immediately accepted into the program and began taking IRESSA July 30, 2001. The next test I did showed all my cancer getting smaller. I have had two other MRIs after that showing the cancer smaller each time.

Without chemotherapy, I started feeling better within a few weeks. To the best of my knowledge, I have had no bad side effects whatsoever. I just keep getting better and better and there is no question that IRESSA is the only reason I am alive today.

The chances given to me of success with IRESSA were much better than they were with radiation and chemotherapy, both of which have done serious permanent damage to me. It is inconceivable to me to think IRESSA should not be given the same chance as any other treatment. Had I started with IRESSA, I could have avoided going through so much mental anguish and physical pain and avoided the possibility of another heart attack.

I am proof that IRESSA will save lives. The only next logical step is to approve IRESSA and to allow it to be used as a first-line of defense. Not only will IRESSA save

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lives, it may greatly increase the quality of the life saved.

DR. PRZEPIORKA: Thank you, Mr. Reilly.

Next is Erica Hertz from The Wellness Community.

MS. HERTZ: Hello. Thank you for the opportunity to speak today. I'm the last on the roster, so I appreciate that. My name is Erica Hertz. I am the Director of Patient Education and Outreach for The Wellness Community. We are a national nonprofit organization with twenty-five facilities serving cancer patients worldwide.

For the record, The Wellness Community receives unrestricted educational grants from AstraZeneca. However, no funding was received today for my compensation to be here.

By way of background, The Wellness Community provides emotional support, education and hope to people with cancer and their loved ones at no cost and our facilities provide support groups, educational seminars on treatment decisions, nutritional workshops, exercise, mind-body programs and more.

Our aim is to help people with cancer and their loved ones regain a sense of control over their lives and their disease and to help them feel less isolated, restore their hope, regardless of the stage of their disease. We

have grown to serve an estimated 25,000 people just this year alone.

Since we do see a wide range of diagnoses and provide services directly to thousands of people at every stage of lung cancer, we have learned a great deal from the patients we serve. People with lung cancer often feel alone, afraid and without hope after they receive their diagnosis. They often don't know what their options are and they need to know that they have access to innovative approaches to treating their cancer.

As you know, we are in great need of improved treatment options, especially those that have limited toxic side effects, and provide alternatives for patients when prior therapies fail. It is critical that new treatments not only fight the cancer but also allow patients to experience a meaningful quality of life, whether that means continuing to work, travel or enjoy time with family and friends, as you have heard today, with an estimate of nearly 170,000 new lung-cancer diagnoses each year, this year alone, the availability for more treatment options is critical.

So I would ask today that you carefully consider the plight of the patients with lung cancer and endeavor to understand the range of both the medical and emotional issues that these patients face on a daily basis. I would

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ask that you seriously consider the need that patients with lung cancer have for new and broader range of treatment options with better outcomes for reduced side effects in the hope that there is more that can be done to fight the disease.

You have heard several important personal stories today and you have the power to bring hope to thousands of people who just need to know that they have more choices for the possibility of longer, better lives even after receiving a diagnosis of cancer.

Thank you.

MS. TEMPLETON-SOMERS: Again, I would like to remind everyone that the letters and e-mails received are available for your viewing at the information desk. The majority do speak positively of IRESSA but there are also some stories of negative and neutral experiences, and they will be part of the meeting record also.

Thank you, speakers.

DR. PRZEPIORKA: This actually ends the open public hearing. If there are no more speakers, we appreciate the comments that were provided to us and we will now move on to the sponsor presentation.

I would like to call to the podium Dr. Blackledge from AstraZeneca and ask that he introduce the topic as well as the speakers. The format will be presentation over one

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hour by AstraZeneca. I would ask that the committee members hold their questions to completion of the presentation and after the FDA presentation.

Thank you.

IRESSA (ZD1839) Monotherapy for NSCLC

Introduction and Rationale for Clinical Development

DR. BLACKLEDGE: Good morning, Dr. Przepiorka, ladies and gentlemen.

[Slide.]

I am representing the sponsor, AstraZeneca, for today's presentation to the FDA Oncology Drugs Advisory Committee. My name is George Blackledge. I am clinical vice president of oncology for AstraZeneca and I have worked with IRESSA from when it was first administered to humans.

[Slide]

The agenda for our presentation is shown here. I will begin by providing an introduction and review the scientific rationale and clinical development program for IRESSA. Dr. Frances Shepherd will discuss the impact of refractory non-small cell lung cancer and the clinical unmet need. Dr. Ronald Natale will review the clinical efficacy from our pivotal trial program and supportive study. Dr. Alan Sandler will review the safety profile of IRESSA and, finally, I will summarize our presentation.

[Slide]

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We also have a number of other experts available for questions and answers. Dr. Jose Baselga, who has participated in clinical trials with IRESSA, has also conducted some of the preclinical studies. Dr. David Cella developed the quality of life tool that we have used in assessing the patients' clinical symptoms in these trials. Dr. Gary Donaldson is a statistical expert on quality of life and psychometric analyses and he is also with us today. In addition, Drs. Mark Kris and Thomas Lynch, who are internationally acknowledged lung cancer experts and who have participated in IRESSA clinical trials, are also with us.

[Slide]

We also have a number of experts from AstraZeneca who are available to answer questions if required.

[Slide]

We need to acknowledge that third-line non-small cell lung cancer has a high unmet clinical need. There are literally tens of thousands of patients who develop this disease each year, and when the disease returns it is a disease of symptoms. These patients feel ill. As you have heard today, they are ill. It is an enormous unmet medical need. IRESSA has demonstrated unprecedented activity in this target population. In addition, we have demonstrated

that symptom control correlates with response and IRESSA has an excellent safety profile.

[Slide]

That is why we are applying to the FDA for accelerated approval. Our data will demonstrate that IRESSA 250 mg once daily orally can be used in the third-line treatment of patients with locally advanced or metastatic non-small cell lung cancer.

[Slide]

Now let me share with you a little bit about the development of IRESSA. In 1990 our research colleagues began to look at molecular targeted agents, particularly in common solid tumors. We wanted to look at agents which had a new mechanism of action and, hopefully, would be active in new settings with better tolerability. We particularly focused on the epidermal growth factor receptor pathway which is known to be activated and over-expressed in many common solid tumors.

In 1994 ZD1839, known by the trade name IRESSA, was discovered. Following preclinical safety studies which showed excellent tolerability, we were able to start our initial studies in human volunteers.

[Slide]

Let's look at a little bit of the science behind IRESSA. This is the beginnings of the EGFR signal

transduction pathway. We can see from this diagram of a cell that the epidermal growth factor receptor is a transmembrane receptor. Now, when a ligand binds, such as EGF or TGF-alpha, there is homodymerization and heterodymerization and this leads to autophosphorylation at the tyrosine kinase site on the internal domain of the receptor. This results in a downstream cascade of the MEK kinase pathway which leads to cellular proliferation and, through the AKT pathway, to the inhibition of apoptosis or programmed cell death.

[Slide]

We also know that stimulating these pathways is responsible for other factors such as the stimulation of angiogenesis and the potential for metastasis. If you can inhibit this pathway in some way, you may have an effect on proliferation, and by inhibiting tyrosine kinase on the internal domain of the receptor you get down-regulation of the entire pathways, inhibition of proliferation and other factors which influence the malignant process. IRESSA down-regulates these key pathways.

[Slide]

We know that IRESSA is selective for the epidermal growth factor receptor tyrosine kinase enzyme. There is 100-fold selectivity for this enzyme over other cellular kinases. We also know that IRESSA works in EGF-stimulated

cells, and you can see that it inhibits EGF-stimulated cells, at the bottom of this slide, at nanomolar concentrations compared with serum-stimulated cells where there is only micromolar inhibition.

[Slide]

We have also seen activity for IRESSA in lung cancer cell lines. This is xenograft data, and here we have a lung cancer xenograft growing in an uncontrolled way. When you co-administer IRESSA to this xenograft for about 20 days you see inhibition of growth. When you stop IRESSA, the tumor starts to grow again. If you administer IRESSA for prolonged periods of time you can continue to see inhibition of cell growth.

[Slide]

With our clinical pharmacokinetic studies we demonstrated approximately 60 percent bioavailability and a half-life of 41 hours. This meant that we had an agent which could be given orally on a daily basis.

[Slide]

Let me now spend a little time taking you through the clinical development program for IRESSA. Our program has four key components. First is our Phase I clinical trials. Second, which is the subject of this submission, is the third-line monotherapy trials, trials 39 and 16. We also investigated IRESSA in first-line in combination

chemotherapy, which I will be discussing today. Both of these two programs were separate fast track designations by the FDA and were developed in full consultation with the agency. In addition, as you have heard, in response to both patient and physician demand, we opened an expanded access program 2 years ago, which I will present to you as well.

[Slide]

Let's now review our Phase I clinical trials. We evaluated doses of IRESSA ranging from 50 mg to 1000 mg daily. From this large clinical trial program we demonstrated a safety profile which suggested that the most common toxicities were Grade 1-2 gastrointestinal and skin toxicity. The dose-limiting toxicity was reversible Grade 3 diarrhea at around 800 to 1000 mg daily.

What was really exciting about this Phase I program is that we saw striking symptom improvement and anti-tumor activity in non-small cell lung cancer. We had 10 objective responses in 100 patients with non-small cell lung cancer. That is a 10 percent response rate. Now we have 17 patients that have been on study for more than 6 months.

[Slide]

Here is a radiograph of one of the patients with non-small cell lung cancer demonstrating the extent of the disease. You can see disease in both lungs and the very

significant clearing observed after only 14 days of treatment with IRESSA. These kinds of radiographs are things that we found exciting.

[Slide]

Now let me introduce you to the third-line monotherapy program which is the subject of this submission.

[Slide]

The reason we carried out this program was that we had seen activity in the Phase I trial and that there was no approved therapy for third-line non-small cell lung cancer patients. There was, therefore, a clear clinical need for a therapy that provides objective responses and symptom improvement in this highly symptomatic disease and, if at all possible bearing in mind the clinical condition of these patients, was also well tolerated.

[Slide]

The Phase II trials have demonstrated clinically meaningful responses. The response rate was 10 percent in trial 39, with an additional 30 percent stable disease. This was also associated with highly significant symptom improvement. We also have similar supportive data which you will hear in trial 16. In all of these trials we have a highly acceptable safety profile.

[Slide]

Let me now touch briefly on the first-line combination therapy program, which is not included in this submission but since we recently obtained the results we reported these to the FDA.

[Slide]

Our rationale for initiating the combination therapy trials was that we had an agent with a novel mechanism of action and we had seen objective responses in Phase I trials. Therefore, we felt that this was the next logical step after the third-line therapy trials with the goal of improving outcomes in non-small cell lung cancer.

The trial design included previously untreated patients with advanced, unresectable non-small cell lung cancer. The patients were all treated with standard combination chemotherapy and randomized to one of two doses of IRESSA or placebo. The primary objective of these 2000-patient trials was to determine if IRESSA could increase survival in this setting.

[Slide]

The results from both well-controlled trials were representative of typical first-line populations. Each trial had well-balanced baseline patient characteristics. The results, in short, were that there were no differences in overall survival rates across treatment arms in both trials, and we did not achieve our primary endpoint. In

addition, if we look at the secondary endpoints, response rate and time to disease progression, again we showed no additional benefit for IRESSA when added to 2-drug chemotherapy. A positive outcome of these trials were the safety results. We did not identify any additional safety issues in this randomized, placebo-controlled setting.

[Slide]

We believe that these first-line results, although disappointing, are not germane to the results demonstrated in third-line non-small cell lung cancer. First-line therapy represents a different treatment setting, combination with chemotherapy rather than monotherapy. The lack of a survival benefit in first-line therapy does not negate the anti-tumor responses and symptom improvement that we will report in the third-line trials.

[Slide]

We have tried to think about why we should have got this result when there was so clearly activity in our Phase I studies and Phase II third-line studies. Numerous colleagues have examined these results in an attempt to understand the data.

We have had discussions with Dr. Larry Norton, who is the immediate past president of the American Society of Clinical Oncology, and here are some of his comments: With Genentech's anti-VEFG announcement recently, SWOGs evidence

of interference by tamoxifen in the efficacy of breast cancer adjuvant therapy and the IRESSA results, I think we're seeing a pattern emerge that is really, paradoxically, quite hopeful. We've said that these new therapies are dramatically unlike chemotherapy but we've tried to develop them as if they were. Now we know they're not, and IRESSA has to be used following different paradigms.

[Slide]

That is exactly what we want to do. You will see the third-line monotherapy data today. We have taken note of the first-line data and here you can see some of the trials that are either ongoing or planned. We will have trials across the whole continuum of non-small cell lung cancer, but initially they will focus on monotherapy.

[Slide]

Finally, let me summarize the expanded access program. The rationale behind establishing the expanded access program was based on the evidence of unprecedented clinical effects we saw in the Phase I trial. These preliminary results were presented at various scientific meetings, such as ASCO, which resulted in significant patient and physician demand for access to the compound. Therefore, we developed this program in close collaboration with the FDA, the National Organization for Rare Disorders, patient advocates and medical ethicists. The population for

the expanded access program was patients with advanced non-small cell lung cancer and no other treatment options.

[Slide]

The program has confirmed a very high unmet need in refractory non-small cell lung cancer. More than 18,000 patients worldwide have enrolled into this program. We administer the drug as a 3-month supply and, therefore, we can measure the rate of resupply. We know that currently there are more than 40 percent of patients continuing IRESSA beyond 6 months in this program. These data suggest a sustained clinical benefit.

As you take into consideration all the evidence from all the patients treated, it is important to consider the patients that we have heard from today and the many thousands of other patients treated in expanded access. We must look at the whole body of data.

[Slide]

Our clinical development program for IRESSA that we will present today will focus on third-line monotherapy which has been designated fast track by the FDA.

[Slide]

As we go through our presentation, you will need to bear in mind the four questions that you have been asked to address by the FDA.

[Slide]

We will demonstrate to you the relevance of our symptom improvement data. We do not agree that symptom improvement cannot be adequately evaluated in this Phase II setting, and we will show you the data to support this.

[Slide]

We will demonstrate to you that the response rate of 10 percent in trial 39 is a robust endpoint predicting clinical benefit. The disappointing results from the first-line program do not impinge upon the validity of this endpoint.

[Slide]

We will discuss with you the expanded access program and implications of different decisions.

[Slide]

And, we will welcome potential study designs to provide a confirmatory trial following accelerated approval for IRESSA in third-line non-small cell lung cancer.

[Slide]

IRESSA addresses a high unmet medical need in a large patient population. We will demonstrate a consistent response rate that correlates with symptom benefit with a drug that is well tolerated and easily administered.

Now I would like to introduce Dr. Frances Shepherd who will describe the unmet clinical need in refractory non-small cell lung cancer. Dr. Shepherd?

The Need for Third-Line Therapy

in Non-Small Cell Lung Cancer

DR. SHEPHERD: Thank you, Madam Chairman, members of the ODAC committee and guests for the opportunity to present to you today. I am Frances Shepherd, a medical oncologist from the Princess Margaret Hospital, in Toronto.

[Slide]

In 2002, the American Cancer Society estimates that 170,000 Americans will be diagnosed with lung cancer. This represents 13 percent of all cancers diagnosed in the U.S. Non-small cell lung cancer accounts for 80 percent of these malignancies. Regardless of the stage at diagnosis, the majority of patients with lung cancer are candidates at some time for systemic therapy. Approximately 50,000 persons undergo surgery, however, nearly half of these relapse with distant metastatic disease. Another 70,000 have locally advanced disease. Sadly, among this group 80 percent or more will suffer disease recurrence and may require chemotherapy. However, the majority of initial cases present with advanced metastatic disease and are primarily treated with systemic therapy. In total, therefore, more than 110,000 new patients are eligible for systemic therapy each year in the United States.

[Slide]

The only proven systemic treatment for non-small cell lung cancer is chemotherapy. Decades of research have demonstrated that in the first-line setting chemotherapy modestly improves survival and lessens the symptoms of non-small cell lung cancer. Platinum-based regimens remain the standard of care for first-line treatment, although recommendation to date has demonstrated an uncertain benefit in patients with performance status 2. Unfortunately, as you have heard so eloquently from our patients this morning, the benefits of chemotherapy are often offset by its toxicities such as febrile neutropenia, anemia, neuropathy and hair loss and, in particular, overwhelming fatigue.

[Slide]

Docetaxel is the only therapeutic agent that is approved for second-line treatment of non-small cell lung cancer. The response rate to docetaxel is low, at only 6 to 7 percent. But despite this low level of activity, clinical benefit has been demonstrated in trials. However, as docetaxel is a chemotherapeutic agent, all the issues of toxicity that apply in the first-line setting are also applicable here.

[Slide]

Despite the growing number of patients in need of third-line therapy, little research has been focused on this group, and no studies have identified patient populations

who have the potential to benefit most from further therapy. Specifically for non-small cell lung cancer, there is no standard definition for disease refractoriness in either the second-line or the third-line setting. In fact, the issue has not yet been considered relevant in this disease where response rates are often measured only in single digits.

In general, most physicians feel that patients treated previously with cisplatin or carboplatin combinations, as well as second-line docetaxel are unlikely to benefit from further additional courses of these same agents. Thus, most oncologists currently turn to other commercially available chemotherapy agents, either alone or in combination in a third-line setting, despite the lack of proof that they are either effective or safe.

[Slide]

Massarelli et al. presented data for the use of chemotherapy in the third-line and fourth-line setting at the 2002 meeting of the American Society of Clinical Oncology. Only 1 of 143 patients in their series experienced a radiographic response to treatment. Furthermore, the median survival of their cohort was only 4.5 months and the 1-year survival from the start of third-line therapy was only 5 percent.

[Slide]

Surveys have shown that the vast majority of patients with advanced non-small cell lung cancer receiving any line of therapy, and particularly third-line therapy, suffer from disease-related symptoms. Pulmonary symptoms are the most common, including shortness of breath, cough and chest tightness. Poor appetite, fatigue and weight loss also occur.

[Slide]

Thus, it is absolutely critical that studies of new treatment strategies in the third-line setting address not only the classical endpoint of tumor response but also the important endpoints of clinical benefit and tolerability. In fact, these latter factors may be more important to patients than response and survival.

[Slide]

In a survey recently done in patients with advanced non-small cell lung cancer who had received platinum therapy, the majority of patients clearly voiced the desire for symptomatic relief. In fact, despite the known side effects and modest benefit of chemotherapy, they would choose to have further chemotherapy if symptoms could be substantially reduced even in the absence of a survival benefit of 3 months.

[Slide]

As we develop agents for use in the third-line therapy of non-small cell lung cancer, we must select treatment goals specific for this patient group. To be useful, an intervention must improve disease-related symptoms and symptom improvements also must be shown to allow the patient to maintain or resume their normal life style. Moreover, the treatment itself must not add any burden to the patient.

An oral treatment might be expected to best meet the needs of this patient population. Oral drugs can provide a holiday from more difficult and potentially more toxic intravenous medications. Because these drugs can be administered anywhere, oral treatments help the patients spend more time at home or even at work. In addition, some patients feel that an oral treatment provides them with an enhanced feeling of control over their disease.

[Slide]

In conclusion, in the United States today there is an increasing number of patients with non-small cell lung cancer who are in need of third-line therapy. Most of the persons seeking third-line therapy suffer from life style limiting disease-related symptoms. There are no approved agents for us in the third-line setting. Therefore, third-line therapy for non-small cell lung cancer represents an unmet medical need of major medical importance.

Thank you. I will now invite Dr. Ronald Natale to present the clinical efficacy for the two second and third-line trials of IRESSA in non-small cell lung cancer.

Clinical Efficacy

DR. NATALE: Good morning. Madam Chairman, committee members, thank you for giving me the opportunity to help you make a recommendation to the FDA that will be in the best interests of a large number of patients who suffer a terrible and usually fatal disease.

[Slide]

I am Dr. Ron Natale. I am a medical oncologist and a clinical investigator from the Cedar Sinai Comprehensive Cancer Center in Los Angeles. I have had a primary interest in clinical investigations of lung cancer for 25 years and I have been heavily involved in the IRESSA development program for over 2 years. I was the major accruer in trial 39 and I have enrolled over 125 patients in the expanded access program. Therefore, I have had extensive clinical trial and bedside experience with IRESSA as monotherapy.

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My presentation will consist of four parts. The first part, which is the major focus of our presentation today, is the pivotal trial data for trial 39. This trial was conducted entirely in the United States. The second

part will consist of key efficacy findings from the supportive trial 16, a trial conducted entirely outside the United States in patients with less advanced and less heavily pretreated disease. The third part will drill down on the important inter-relationships between objective response, patient assessment of symptom improvement and physician assessment of performance status. This analysis provides physicians and patients with the information necessary to arrive at the optimal and appropriate therapeutic decisions. Finally, I will give our conclusions.

[Slide]

The primary goal of all physicians caring for non-small cell lung cancer patients in the third-line setting, with limited survival, is to provide palliation of the debilitating symptoms. Cytotoxic chemotherapy can sometimes be offered but only to the few better performance status patients who are willing to accept more chemotherapy. Unfortunately, objective response and true palliation are rare; toxicity is certain.

As presented by Dr. Shepherd, there is no effective treatment for patients following second-line therapy. In these patients disease progression is inevitable. The best these patients can hope for is that disease-related symptoms will stabilize for a brief time

with optimal supportive care. Sustained improvement is rare; more likely, symptoms will worsen. The need for a novel biologically based oral agent with intrinsic anti-tumor activity and minimal toxicity would satisfy this large unmet need. IRESSA would satisfy this unmet clinical need if the Phase I findings--objective responses and physician observation of an apparently rapid and durable palliation--could be confirmed in a subsequent trial.

[Slide]

Therefore, in discussions with the FDA trial 39 was developed with the following aims: To determine for each dose the objective response rate and symptom improvement rate using prospectively defined criteria. Patients served as their own controls. For both endpoints we had hypothesized that a response rate greater than 5 percent would be clinically significant in the setting where no effective therapy exists. Lastly, as will be discussed by Dr. Alan Sandler, we sought to determine the safety profile of IRESSA. Patients were randomized in a double-blind manner to either 250 mg or 500 mg daily oral doses.

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The rationale for dose selection was as follows: Although a response was observed at the 150 mg dose level in Phase I trials, 250 mg was chosen because it was considered to be the minimally effective dose that would ensure

adequate drug exposure in a patient population. And, 500 mg was chosen because it was considered the highest dose that is well tolerated on a chronic daily basis by most patients. Remember that dose-limiting toxicity occurred at doses of 800 mg to 1000 mg in the Phase I trial, thus, a 500 mg dose level ensured a wide safety margin. The randomized trial design allowed for an assessment of the optimal dose based on efficacy and safety.

[Slide]

This slide details inclusion criteria as worded in the protocol with respect to prior therapy. These criteria were both specific and relevant to a third-line patient population and defined the unmet clinical need.

First, patients must have received prior therapy with at least 2 chemotherapy regimens that had to have included platinum and docetaxel given concurrently or in separate regimens. Secondly, prior regimens must have failed the patient because of disease progression on third-line or unacceptable toxicity.

Patients who entered the trial due to disease progression on therapy had to have documentation that their most recent dose of chemotherapy had been within 90 days prior to progression. Again, this is defining a very heavily pretreated patient population who have exhausted all therapy options using standard available chemotherapies.

[Slide]

Patient eligibility issues have been raised by the FDA. Ninety-six percent of patients recruited to this trial satisfied the inclusion criteria as worded and defined. The investigators in this study interpreted the eligibility criteria in a way that did not require patients to have disease progression on treatment with platinum and docetaxel given separately or concurrently.

Furthermore, we believe the distinction between refractory, resistant and sensitive is not relevant to third-line non-small cell lung cancer and is without precedence. The limited data available, as presented by Dr. Shepherd and the universal bedside or clinical experience indicates that patients rarely respond to any third-line therapy, regardless of the interval or response to the second-line treatment. Thus, there was no available therapy for all of the patients entered into this clinical trial.

[Slide]

Objective responses by the treating investigators used the SWOG modification of the UICCC/WHO criteria. These criteria are standard and well-established, and allow response assessment in patients with both measurable and non-measurable disease. Response categories, including CR, PR and stable disease, required confirmation by a second assessment at 28 days or later. Tumor responses were

assessed on days 28, 56 and every 2 months afterwards. All tumor responses were independently verified by the FDA.

[Slide]

In this trial symptom improvement was a coprimary endpoint and response criteria were prospectively defined. For this assessment we used the Lung Cancer Subscale, or LCS of the FACT-L. This is a validated, sensitive and reliable instrument and it has been validated in multiple languages. This simple tool asks patients to score 7 symptoms, 4 pulmonary and 3 related to advanced cancer on a scale of 0 to 4, with 0 representing the worst possible symptoms and 4 representing no symptoms. The scores of each of the 7 items is totaled so that a score of 28 represents a patient who is completely asymptomatic. Total scores decreasing towards zero represent worsening symptoms. As in the case of radiographic assessments of response, patients completed pretreatment baseline LCS questionnaires and served as their own controls.

[Slide]

A minimum improvement of 2 points or more in total LCS score for a minimum of 4 weeks was the response criteria established and stringently applied in this study. It was based on a large validation study of the LCS in a 573-patient Eastern Cooperative Oncology Group trial in which changes in LCS scores were anchored to and found to have

statistically significant association with clinically important outcomes such as objective response, time to tumor progression, survival and changes in performance status and body weight.

[Slide]

Symptom improvement criteria were applied stringently. LCS assessments failing to confirm a 2-point or greater improvement for a minimum of 4 weeks without a worsening of 2 points or more from baseline were considered symptom improvement failures. This stringency was based on the belief that symptom improvement of greater than 4 weeks in a patient with an expected median survival of 6 months would be clinically meaningful, and would serve to reduce the influence of a placebo effect in which improvements are usually very short-lived.

In trials 39 and 16 LCS was assessed weekly following the start of treatment. Therefore, patient assessment in changes of their lung cancer-related symptoms preceded radiographic assessment and eliminated the potential bias of knowledge of objective disease response or progression. If high compliance could be achieved the weekly assessments would provide a very large database that would minimize the impact of an occasional missing data point.

[Slide]

Now for the results of trial 39, again focusing on the key primary endpoints.

[Slide]

The patient population in this trial had a median age of approximately 61. There were slightly more males than females. Notably, approximately 20 percent of patients had a performance status of 2. These patients are known to tolerate chemotherapy poorly and to rarely respond even in the first-line setting. As is typical of non-small cell lung cancer trials in the United States and other developed countries, about two-thirds of patients had adenocarcinoma histology. Approximately 90 percent had metastatic disease, with two-thirds of patients having 2 or more metastatic sites. The median time from diagnosis to entry was approximately 20 months, 24 in the 250 mg group and 17 in the 500 mg group. This is to be expected in third-line clinical trials, reflecting the interval between the initial diagnosis and first-line platinum treatment, the 10-month median survival to first-line therapy, the interval needed for the second-, third- and fourth-line treatments given to the patients entered in this trial.

[Slide]

This slide summarizes prior treatment history and 214/216 patients had received 2 or more prior regimens, including platinum and docetaxel. As specified by the

protocol, 80 percent of patients had progressive disease during or within 90 days of their most recent therapy. About 17 percent of patients entered the trial because of unacceptable toxicity with their most recent therapy.

[Slide]

As you will see, this is a highly symptomatic patient population. This bar graph shows the range of baseline scores for the 7-item LCS, with 28 representing patients who are asymptomatic for all 7 items and progressively lower scores representing progressively more severe symptoms. Baseline scores were obtained from all patients entered into this trial. All but one patient satisfied the eligibility criteria of a baseline score of 24 or lower. The median score in this group was 16. Compare this to the baseline median score of 19 in the ECOG LCS validation study in chemotherapy naive patients with newly diagnosed advanced or metastatic non-small cell lung cancer. This confirms the natural history of non-small cell lung cancer in which symptoms progressively worsen over time through successive failed chemotherapies and reflects the highly symptomatic patient population entered into this trial.

[Slide]

This slide graphically presents the radiographic response data. Ten percent of patients achieved a confirmed

and FDA-verified objective response. There were no statistically significant differences in the 250 mg and 500 mg dose levels, with patients in the combined groups and in the 250 mg level meeting the prespecified statistical criteria of greater than a 5 percent response rate. Although the 95 percent confidence interval around the response at the 500 mg dose level does not quite clear the 5 percent mark, there is considerable overlap in the two error bars.

It is important to note that the response rates are identical for intent-to-treat populations, as well as for the 139 selected patients by the FDA. The lack of a difference in response rate speaks to the activity of IRESSA regardless of prior chemotherapy history.

[Slide]

Twenty-two patients achieved a partial response. Thirteen of these had bulky disease with a sum surface area 10-60 cm^2. Five responding patients had less than 10 cm^2 of measurable tumor at baseline. Four patients had non-measurable disease. Almost all of these patients had multiple metastatic sites. In the third-line setting a distinction between high versus low tumor burden is neither an accepted standard nor is it useful. Objective responses occurred rapidly, with 16 partial responses occurring by week 4 and later confirmed.

Objective responses had a median duration of 7.4 months at the 250 mg dose level and 5.8 months at the 500 mg dose level. Responses occurred regardless of the number of prior regimens, performance status and age and were documented in both men and women. The lack of relationship to the number of prior regimens and performance status is a remarkable observation that distinguishes this biologic agent from cytotoxics which rarely produce objective responses in patients with more than 2 prior regimens or with performance status 2.

[Slide]

This slide graphically presents the symptom improvement rate. Forty percent of patients reported a 2 point or greater improvement in disease-related symptoms sustained for a minimum of 28 days. There was no statistically significant difference in the symptom improvement rate between the two randomized dose level arms of the trial.

Please note that the lower 95 percent confidence interval was greater than 5 percent in both dose levels. It should be emphasized that the average weekly compliance rate of LCS data collection was 84 percent. This remarkably high compliance rate is unprecedented in quality of life and symptom assessment endpoints in cancer clinical trials, and speaks to the rigor with which this study was conducted.

[Slide]

This slide graphically presents the average or mean change in LCS score from baseline by week in all patients. A 2.6 overall change in mean LCS score was rapid, sustained and durable. There were no differences in the 2 dose levels in the study and for simplicity the data are combined in this graph. As I will show you shortly, the mean change among the 40 percent of patients meeting or surpassing the minimum criteria for symptom improvement was 4.6.

[Slide]

Overall, 84 patients, 40 percent, can be classified as symptom improvers. In this group the mean change was 4.5, with the greatest score improvement occurring in the 4 pulmonary items of the LCS, shortness of breath, cough, ease of breathing and chest tightness.

The improvement occurred rapidly, meeting or surpassing the 2 point or greater criterion within the first 4 weeks, in other words, prior to the first radiographic assessment.

Symptom improvement was durable, lasting at least 3 months in 75 percent of patients; at least 6 months in 65 percent; and with the median duration not reached by the time of data cut-off in this analysis.

The quality of symptom improvement produced by IRESSA is reflected in its lack of relation to the number of prior regimens or patient performance status, age or gender. Forty percent of the symptom improvers reported a 1 point or greater improvement in 6 or 7 of the individual items in the LCS. As many of you know, advanced lung cancer patients present a number of management problems in that they frequently require changes in supportive medications such as bronchodilators, cough suppressants, antibiotics, pain medications, etc., raising the possibility that this symptom improvement was due to concomitant medications rather than IRESSA, however, please note that the percentage of patients requiring any new supportive medications was significantly lower, 32 percent in the symptom improvement group compared to the group without symptom improvement in which new medications were prescribed in 46 percent.

[Slide]

In summary, IRESSA produced a confirmed and verified objective response rate of 10 percent in heavily pretreated patients with non-small cell lung cancer. Forty percent of patients achieved a significant improvement in specific disease-related symptoms. The radiographic responses in symptom improvement occurred rapidly, were durable and similar for both dose levels.

[Slide]

Trial 16 was conducted entirely outside the United States--Europe, Australia and Japan, and offers a unique and valuable opportunity to examine IRESSA's objective response and symptom improvement rates in lung cancer patients with a different cultural and ethnic background.

[Slide]

Trial 16 used the same basic design and methods, prospective, randomized, double-blind, timing of assessments, etc., as used in trial 39. Patients served as their own controls. However, there were significant differences in patient eligibility criteria. They were less heavily pretreated, requiring a maximum rather than a minimum of 2 prior regimens which had to have included platinum. Although many patients had received prior treatment with docetaxel, it was not required. Disease progression during or within 90 days of study entry was not required. There was no minimum severity of symptoms required for patient entry.

[Slide]

The results are as follows.

[Slide]

This slide summarizes patient characteristics. Similar to trial 39, the median age in this trial was 61 and about two-thirds of patients had adenocarcinoma. Compared to trial 39, there was a slightly greater preponderance of

males; a slightly lower proportion of patients with performance status 2 and metastatic disease; approximately 13 percent of patients had PS 2. The median time from diagnosis to trial entry was 14-19 months, shorter than in trial 39, as expected in a predominantly second-line study. About two-thirds of patients had symptom scores of 24 or lower at baseline and were, therefore, eligible for assessment of changes in disease-related symptoms. All patients received prior platinum therapy. Slightly less than half had received a second-line treatment.

[Slide]

The overall objective response rate was 19 percent, with no significant difference between the 2 randomized dose levels.

[Slide]

There were a total of 39 responders in trial 16. One patient achieved a CR, 38 patients achieved a partial response. Disease was bulky in 26 patients, with baseline tumor area totaling 100-85 cm^2. One patient had a non-measurable disease response.

Responses occurred rapidly, with first evidence of partial response subsequently confirmed occurring with the first radiographic assessment at week 4. Responses were durable, with the median duration not reached at the time of data block, with 90 percent ongoing with 4 to 8 months of

follow-up. Responses were independent of the number of prior regimens, performance status and age and were observed in both men and women.

[Slide]

One hundred and forty, a subset of the 210 patients in trial 16, were evaluable for symptom improvement. The compliance rate was 64 percent, good but slightly lower than in trial 39. The results, however, are nearly identical, with 39 percent of patients achieving the minimum criteria for symptom improvement overall. There was no significant difference between the 2 randomized treatment arms.

[Slide]

In summary, trial 16 achieved an overall objective response rate of 19 percent and an overall symptom improvement rate of 39 percent. These results are highly corroborative in support of trial 39 results.

In a clinical trial lacking a comparison control group it is important to examine whether there is an association between the 2 validated and independently assessed primary endpoints--tumor response and symptom improvement.

[Slide]

This slide demonstrates the strong association of tumor response with symptom improvement. Twenty-one of 22,

96 percent of the patients achieving radiographic partial responses enjoyed significant symptom improvement. Some patients in the radiographic stabilization category achieved tumor regressions, slightly less than the stringent criteria required for partial response, or stabilization of prior progress of disease. This probably accounts for the lower but important symptom improvement enjoyed by some of these patients. A few patients with disease progression satisfied the minimum criteria for symptom improvement.

[Slide]

Let me remind you of the 2.6 mean change in LCS score from baseline by week in all patients. This curve is a composite of the 3 radiographic categories of partial response, stable disease and disease progression, and is broken down in the following slide.

[Slide]

You should note that there is a logical rank order in the magnitude of change of these 3 categories with the partial responders in yellow, stable disease in red, progressive disease patients in green.

[Slide]

Let us focus especially on the partial responders. Please again note the rapidity of improvement, the magnitude of improvement with the mean change of 4.8 and with the lower 95 percent confidence limit of 3.1 being well above

the minimum criteria of a 2-point improvement. Please also note the consistency or stability of improvement week to week to week and the duration. The strength of this result virtually eliminates the possibility of a placebo effect.

[Slide]

Several patient examples served to illustrate some of these important points. Patient 37, at the time of trial entry, was a 46-year old woman with Stage 4 non-small cell lung cancer, brain metastasis, progression of disease on platinum and docetaxel, failure to respond to gemcitabine and vinorelbine. At baseline she has a 6 by 5 cm right lower lobe lung mass and 1 or 2 large hepatic metastases are depicted. Within 1 month there was a substantial regression in cancer. The cancer was minimally visible 12 months later.

[Slide]

This represents her symptom improvement. Symptom improvement occurred rapidly, prior to the radiographic assessment, and correlated throughout with continued response of treatment. There was a temporary decrease in performance score, symptom improvement at a time when this patient developed symptoms of radiation necrosis, she underwent a craniotomy for removal of that tissue and, after recovering from surgery, resumed IRESSA and promptly resumed a near normal symptom improvement state. Most of her

improved symptoms were in cough, appetite and chest tightness. Her score went from 11 to near normal. She regained her life. As she and her husband said so eloquently, now, 2 years later, she is normal.

[Slide]

Patient 166 was 1 of the 5 responding patients identified by the FDA reviewers as having non-bulky and, therefore, implying more easily responsive disease. This patient was almost bedridden at the start of treatment. This patient achieved an objective response in 6.1 cm^2 of liver metastatic disease, as well as a significant regression of non-measurable disease in other sites such as lymph nodes. Although this patient suffered pneumonia that blunted her initial symptom improvement in LCS score, an 11-12 point improvement was achieved and maintained for over 6 months of therapy. Most of the improvement occurred in breathing, cough and appetite. This patient was able to resume a 2-mile daily walk after being nearly bedridden.

[Slide]

We found that improvement in physician assessment of performance status was also strongly associated with tumor response. The importance of this association is based on the fact that performance status is 1 of the strongest independent predictors of a favorable outcome in patients with non-small cell lung cancer. Eleven of 22 responders

had an improvement in performance status. Nine of the remaining 11 maintained their initial performance status of 0 or 1; there was little room for improvement. Sixteen percent of patients with stable disease had an improvement in performance status. Improvement in performance status was rare among patients with progressive disease.

[Slide]

In summary, data show that IRESSA produces a significant rate of objective response and symptom improvement from which we believe patients derived significant clinical benefit. Significant symptom improvement was rapid and durable.

[Slide]

The overall efficacy conclusions are as follows: IRESSA produces a 10 percent objective response rate as third-line therapy in non-small cell lung cancer. Although modest, unlike other Phase II trials, this radiographic response rate was confirmed, verified by FDA reviewers, and durable. In fact, it is the highest response rate ever observed in this far advanced disease setting. A few of these responses have been dramatic with imminently terminal patients surviving, and surviving well for a year or more.

IRESSA produces a 40 percent symptom improvement rate in highly symptomatic patients with advanced non-small cell lung cancer. The strong association of this outcome

with radiographic response and its rapidity, magnitude, week to week stability and durability indicates a placebo effect to be very unlikely. The decreased use of other supportive medications in the symptom improvers compared to the symptom non-improvers rules out an effect of concomitant medications.

These efficacy findings have been corroborated by a second large clinical trial conducted entirely outside the United States. It is clear that the effects of IRESSA cut across geographic and cultural boundaries. We believe that the totality of the data satisfy a rigorous definition of clinical benefit in the radiographic responding patients. The efficacy of IRESSA was comparable at both the 250 mg and the 500 mg dose levels.

The only remaining question relates to the safety of this agent. The data and discussion will be presented by Dr. Alan Sandler, a major co-investigator in this trial. Thank you.

Safety Profile

DR. SANDLER: Thank you, Dr. Natale.

[Slide]

I am Alan Sandler. I am an associate professor of medicine at Vanderbilt University, and it is my privilege today to provide you a summary of the safety profile of IRESSA.

As you will see, IRESSA with its selective, targeted mechanism of action has a safety profile that is exceptionally favorable and distinct from that of traditional chemotherapy.

[Slide]

The safety data for IRESSA is based predominantly on the database submitted to the NDA, comprised of data from trials 39 and 16, as well as from 6 additional Phase I trials. The favorable profile is further reinforced by the extensive patient experience in over 18,000 patients in the expanded access program, as well as from investigator initiated trials in other tumor types. I will be presenting the safety data from trial 39. The safety is further corroborated by the data in trial 16 and the additional supportive safety information.

[Slide]

This slide summarizes the most frequent adverse events, occurring in 15 percent or more of the 216 patients exposed to IRESSA in trial 39, regardless of causality. The most frequently occurring adverse events were diarrhea and skin rash. Skin rash was also commonly reported as acne, dry skin or pruritus.

Other commonly reported events were related to the gastrointestinal track or were reported as asthenia, dyspnea or cough, symptoms commonly associated with advanced non-

small cell lung cancer. Notably absent from this list are hematologic toxicity, neurologic toxicity and alopecia, commonly observed with chemotherapy.

[Slide]

This slide shows the drug-related skin adverse events by both dose and grade. All of these events were Grade 1 and 2 for the 250 mg dose. The majority of events for the 500 mg dose were also Grade 1 and 2. However, the overall frequency and number of Grade 3 events were clearly higher in the 500 mg dose. Note, however, there were no Grade 4 skin events in either group and, again, no Grade 3 events in the 250 mg group.

[Slide]

A similar pattern of frequency and severity was also seen with respect to the gastrointestinal toxicities. Reversible diarrhea was the most commonly reported event. Nausea, anorexia and vomiting were much less frequently reported and, again, there were few Grade 3 toxicities and no Grade 4 toxicities in either group.

[Slide]

This slide shows the other Grade 3 and Grade 4 drug-related adverse events that were reported in trial 39. Any of these events might be seen in this advanced cancer population and there are no patterns to suggest an association with IRESSA therapy.

[Slide]

Further evidence of IRESSA's safety is shown by the low frequency of drug-related withdrawals and deaths. Only 1 percent or 1 patient in the 250 mg group had a drug-related withdrawal compared to 4 percent or 4 patients in the 500 mg group. Most deaths on study were due to disease progression. The several deaths resulting from adverse events were largely due to pulmonary events such as pneumonia or other co-morbid conditions. The only drug-related adverse experience leading to death was observed in a patient receiving the 500 mg dose. This was a 70-year old gentleman who had received prior chest radiotherapy, pulmonary fibrosis and had hemoptysis prior to entering on study. Additionally, he had a large left upper lobe cavitating mass with mediastinal adenopathy. He continued to suffer with hemoptysis and expired 2 weeks into therapy.

[Slide]

In addition, few patients required dose interruptions or dose reductions. Only 15 percent of the patients taking the 250 mg dose had dose interruptions. Only 1 percent had a dose reduction. These were uniformly mostly associated with rash or diarrhea and the dose interruptions generally lasted two to three days, after which patients were then able to resume IRESSA at the same dose.

[Slide]

With respect to subgroup analyses, demographic subgroup analyses demonstrated no specific safety concerns in special populations characterized by gender, ethnic origin, age, body mass index, performance status or renal impairment. These findings were also confirmed by a similar analysis in trial 16, as was the overall safety profile.

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In summary, IRESSA was found to be well tolerated. The safety profile was characterized by predictable, low grade and manageable skin and gastrointestinal events. The adverse experiences were reversible, noncumulative, and IRESSA was especially well tolerated when compared to cytotoxic chemotherapy. There are no special population safety concerns. The data consistently demonstrates that the 250 mg dose provides a more favorable safety profile than the 500 mg dose.

I would now like to reintroduce Dr. George Blackledge who will provide a summary of today's presentation.

Summary

DR. BLACKLEDGE: Thank you, Dr. Sandler.

[Slide]

I will now summarize the data that we presented today which has established the safety, anti-tumor activity

and clinical symptom benefit in third-line non-small cell lung cancer patients. In addition, I will place the data in context with the questions raised by the FDA.

[Slide]

The first point I want to stress as a clinician is that the goal for third-line for patients with non-small cell lung cancer is treating a disease of symptoms. There is an incredibly high unmet medical need, with thousands of patients each year falling into this clinical situation. These patients are usually highly symptomatic and there is no available or proven therapy.

[Slide]

I think what we have done with IRESSA is to suggest that it fulfills this unmet medical need in this setting. We demonstrated to you that we have achieved a 10 percent response rate which is predictive of clinical benefit in third-line non-small cell lung cancer.

[Slide]

It is worthwhile reminding you how we define clinical benefit. The FDA guidance indicates that clinical benefit can be demonstrated either by prolongation of life, or better life, or an established surrogate for either or these.

In our submission for IRESSA, we have demonstrated that the clinical benefit endpoint is a better life.

Responding patients exhibit meaningful radiographic response, which occurs rapidly in bulky disease and in numerous metastatic sites and is durable. These objective responses are linked to improvement in lung cancer symptoms and, as such, confer a better life.

[Slide]

It is worth saying a little bit more about the lung cancer symptoms. We conducted a thorough and informative investigation assessing symptom data in an advanced cancer patient population. The trials had a rigorous design and implementation with high compliance and minimal missing data. This is especially significant considering that the patients completed the forms on a weekly basis.

[Slide]

What we demonstrated in trial 39 was a highly significant correlation between the objective response and symptom improvement. We demonstrated measurable improvement across the whole population, something that is really quite unprecedented in this clinical setting.

In addition, we saw clinically important and personally important improvements to individual patients, observations that are unlikely to be a placebo effect.

[Slide]

In fact, let's look again at this slide showing the three plots for response, stable disease and disease progression in terms of the Lung Cancer Subscale. At 4 weeks, prior to their being any radiographic assessment, patients who showed eventual radiographic response had already distinguished themselves from the other groups in terms of symptomatic benefits. It is hard to explain this as a placebo effect. Furthermore, the symptomatic benefits persist and we do not agree.

[Slide]

Secondly, there is the question of the response rate. We do not believe that the combination of first-line results are applicable to the application of IRESSA in the treatment of third-line non-small cell lung cancer. We have reproducible data from our Phase I trials where we saw a response rate of 10 percent.

The rest of the world trial 16 demonstrated a response rate greater than 10 percent. In our pivotal trial 39 there was an unequivocal 10 percent response rate. The FDA has confirmed the objective responses. These objective responses are associated with and highly correlated with symptomatic improvement and, therefore, the 10 percent response rate is reasonably likely to predict clinical benefit.

[Slide]

The FDA has raised issues about the expanded access program. We have given this careful consideration and whatever happens, AstraZeneca will continue to supply IRESSA to patients already enrolled in the program. We believe the best solution for patients appropriate for the expanded access program would be accelerated approval for IRESSA. However, we need to bear in mind that if the FDA considers that IRESSA cannot be approved based on the current data, then the ethical premise of continuing to accept patients into the program will need to be reevaluated with the FDA, and we will have to seriously consider our position.

[Slide]

Finally, AstraZeneca would welcome suggestions concerning potential study designs. We already have many trials ongoing, both in non-small cell lung cancer and other diseases, and ideas which have been preliminarily presented to the FDA for a confirmatory trial following subpart H approval.

As Dr. Norton has said, we need new paradigms for the development of novel agents, and proposals for a confirmatory trial following the granting of accelerated approval of IRESSA would be appreciated.

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Those are the questions that the FDA has raised. But there is a fifth question and that relates to the approvability of this application. We would like to ask you, on the basis of the data presented today and under subpart H, whether IRESSA is approvable for the treatment of patients third-line for non-small cell lung cancer. For patients and their families, their physicians and us, that is the critical question. Thank you.

DR. PRZEPIORKA: Thank you very much, and we are going to hold the questions until after both presentations are completed. It is time now for a break. I would like to return at 11:20 on the dot to begin. So, please, return at 11:18 to get settled. Thank you.

[Brief recess]

DR. PRZEPIORKA: I would like to add to the record that Mr. Rick Lesser has informed us that he has no conflict of interest and AstraZeneca or any advocacy group did not pay for his trip here. That is just to add that to the record. Thank you.

The next part of this meeting will be the FDA presentation of their review of IRESSA, and I would like to start with Dr. Grant Williams who will introduce the FDA review and the other reviewers involved.

FDA Review

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Introduction and Regulatory Background

DR. WILLIAMS: Good morning. Dr. Przepiorka, members of ODAC, ladies and gentlemen, I would like to introduce now the FDA presentation.

[Slide]

First I want to recognize the FDA review team headed by Amy Baird, our project manager. This slide lists the various primary and secondary FDA reviewers who evaluated this drug application. This includes pharmacists, chemists, medical oncologists, clinical pharmacologists, toxicologists and clinical site inspectors.

Under the fast track regulations, FDA is conducting a rolling review of this ZD1839 application. Some parts of the application were submitted earlier than other parts. The last component of this application was received in August.

[Slide]

This slide presents the outline of our presentation. I will start with the regulatory background and an introduction of critical issues. Then Dr. Cohen will present the medical review, followed by Dr. Sridhara's statistical comments. Finally, I will briefly summarize the FDA findings and introduce questions for the committee, though they actually have been introduced and answered.

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[Laughter]

[Slide]

This slide summarizes the key FDA findings from review of this application. I will return to it briefly at the end of our presentation. In brief, AstraZeneca claims that ZD1839 provides symptom benefit in study 39, but FDA finds this claim unconvincing without a control arm.

FDA and AstraZeneca agree there is a 10 percent response rate in 139 patients with refractory non-small cell lung cancer, and there is no benefit of ZD1839 when added to chemotherapy in the first-line treatment of non-small cell lung cancer.

The key question for ODAC is, in light of these data, is the 10 percent response rate in refractory non-small cell lung cancer reasonably likely to predict clinical benefit? An affirmative answer to this question would be basically a recommendation to FDA to grant accelerated approval.

[Slide]

FDA must assure that marketed drugs are safe and effective for their proposed use. The efficacy requirement is from a 1962 law that requires substantial evidence of efficacy from adequate and well-controlled investigations.

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Efficacy endpoints must have clinical meaning. That is, they must measure clinical benefit.

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As we begin the discussion of this drug and of the endpoints proposed to support its effectiveness, it is useful to reflect upon endpoints used by FDA to support cancer drug approval. It is often misstated in the media or in the oncology literature that FDA only approves cancer drugs based on survival. However, this is clearly not the case. Recently, the Division of Oncology Drug Products evaluated the basis of approval for drugs in our division since 1990. As shown on this slide, survival was the approval endpoint in the minority of applications. Excluding accelerated approval applications, 67 percent of approvals were not based on survival, and for all applications 73 percent of all approvals were not based on survival.

[Slide]

This slide discusses tumor-related symptoms, one class of non-survival endpoints that FDA has used for approval of cancer drugs and also one relevant to the ZD1839 application. The FDA considers improvement in tumor-related symptoms to be clinical benefit, not just a surrogate. Therefore, studies adequately demonstrating improvement in

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tumor symptoms can support regular approval, not just accelerated approval.

Tumor-related symptom observations were important in the approval of several oncology drug NDAs, including symptom improvement in patients with obstruction from lung or esophageal cancer; patients with cutaneous or subcutaneous tumors; and patients with painful bone metastases.

[Slide]

This application also included a description of symptom changes in patients with cancer. However, there are fundamental problems, in our view, with AstraZeneca's symptom benefit claims. Without a concurrent control arm we cannot know whether these symptom results might not be entirely from placebo effect; from a patient's hope that a company is getting a promising investigational cancer drug. As Dr. Cohen will discuss, some symptom improvements could be attributed to concomitant medications given to palliate these symptoms.

Finally, AstraZeneca notes a correlation between symptom benefit and tumor response. However, a correlation between symptom improvement and tumor response might be expected regardless of whether the tumor response caused the symptom benefit. For instance, there could be patient bias.

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One might expect responders would feel better after being informed of their tumor status. Certainly, assessment bias would be expected. For instance, patients going off study early because of tumor progression might go off too early to be documented as a 28-day symptom responder. This would force an association between early tumor progression and lack of symptomatic response.

Lastly, an association between tumor response and symptom change could be caused by shared baseline prognostic factors between tumor responders and symptom responders. This would be an association rather than a cause and effect relationship.

In the final analysis it is unclear that the changes observed on the LCS symptom scale represent significant clinical benefit and that the changes observed can be confidently attributed to ZD1839 treatment. In order to substantiate these claims we believe a randomized study comparing ZD1839 to a non-ZD1839 treatment would be required.

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Let's return to regulatory issues. We are considering this application under the 1992 accelerated approval regulations. This slide lists the major issues.

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These regulations are for diseases that are serious or life-threatening where the new drug appears to provide benefit over available therapy.

The key point for our consideration is that accelerated approval can be granted on the basis of a surrogate endpoint that is reasonably likely to predict clinical benefit. After accelerated approval, the applicant is required to perform a post marketing study to demonstrate that treatment with a drug is, indeed, associated with clinical benefit. If the post marketing study fails to demonstrate clinical benefit, or if the applicant does not show due diligence in conducting the required study, the regulations describe a process for rapidly removing this drug from the market.

[Slide]

This is a list of ten drugs approved by our oncology division using tumor response under the accelerated approval regulations. The last addition to this group, oxaliplatin, was approved for refractory colon cancer just last month with data from a randomized study showing increase in the surrogate endpoints of response rate and time to progression compared to a control arm.

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I want to emphasize an important point about accelerated approval, one you may have heard from our office director, Dr. Temple. The quality and amount of evidence required is no different for accelerated approval than for regular approval. We still expect substantial evidence from well-controlled clinical trials. We cannot accept borderline evidence. The difference is that the evidence may focus on a surrogate endpoint rather than a clinical benefit endpoint.

[Slide]

Here are the important points from accelerated approval regulations. In the following slides I want to discuss two of these in depth.

[Slide]

Because accelerated approval must show a benefit over available therapy, use of a single arm design for a clinical trial limits the treatment indications where accelerated approval may be used. It would be difficult to show superiority to other therapy in a single arm trial. So, practically speaking, accelerated approval can be used in a single arm trial only when there is no available therapy.

Returning to the ZD1839 studies, because approved therapies exist for both first-line and second-line

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treatment of non-small cell lung cancer, our accelerated approval considerations are limited to third-line treatment of non-small cell lung cancer. Hence, only the 139 patients in study 39 are directly relevant to our accelerated approval deliberations.

[Slide]

The next accelerated approval point I want to emphasize is that the surrogate endpoint must be reasonably likely to predict clinical benefit. Obviously, this is a judgment based on scientific knowledge and on experience, and we must consider all available evidence.

Whether a 10 percent response rate in lung cancer is reasonably likely to predict clinical benefit is a good point for discussion. Clearly, similar response rates in some tumors have correctly predicted subsequent clinical benefit, for instance, the 12 percent response rate of irinotecan in refractory colon cancer. However, we also have an unprecedented additional consideration.

[Slide]

We have results from 2 large randomized studies of excellent design that show no benefit of ZD1839 added to chemotherapy and first-line treatment of non-small cell lung cancer. Ironically, had ZD1839 already received accelerated approval, these studies would have served as the Phase IV

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post marketing commitment to verify its clinical benefit. Now that these results have become available prior to a regulatory decision we must weigh the significance of these negative findings on the accelerated approval process.

That concludes my opening comments and Dr. Cohen will now present details of the medical review.

Medical Review

DR. COHEN: Thank you, Dr. Williams.

[Slide]

Madam Chairman, members of ODAC, ladies and gentlemen, I will present the FDA medical review.

[Slide]

As you have heard this morning, at the present time the FDA has approved three cisplatin containing doublets, as well as single agent vinorelbine for the initial first-line treatment of newly diagnosed non-small cell lung cancer patients with Stage 3B or 4 disease.

In addition, docetaxel has been approved as a second-line treatment that is to be used after failure of first-line treatment. As you have further heard, there is no treatment that has been approved to date for patients who have progressed or who have been intolerant of their first-line and second-line treatments. This is an unmet medical

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need. Third-line treatment is what is targeted in the current application.

One fact that must be kept in mind when evaluating third-line non-small cell lung cancer studies is that the study group is highly selected. Unfortunately, most advanced stage non-small cell lung cancer patients do not live long enough or do not have a good enough performance status to participate in these studies.

[Slide]

The sponsor has submitted data from several clinical trials. Trial 39 is a third-line treatment trial for advanced non-small cell lung cancer patients. It was submitted for the purposes of obtaining accelerated approval for the treatment of advanced non-small cell lung cancer patients for whom there is no available therapy. As was indicated by Dr. Williams, accelerated approval is generally based on a surrogate endpoint that is reasonably likely to predict clinical benefit. The most commonly used surrogate endpoint is objective responder rate. The second submitted trial, trial 16 is primarily a second-line trial and, thus, serves to provide additional ZD1839 efficacy and safety information.

Summary data for 2 first-line trials, which are called INTACT 1 and 2, was also submitted and, as was

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mentioned previously, these trials were to be the basis for full approval of ZD1839. In my presentation this morning I will present the FDA analysis of trials 39 and 16. Dr. Sridhara, who follows me, will discuss the results and implications of the INTACT trials.

[Slide]

The 2 submitted trials, trial 39 and trial 16, had identical design and randomized patients to ZD1839 administered in a dose of 250 mg per day versus ZD1839 500 mg per day. The deficiency of the above design is that all patients received ZD1839. There was no non-ZD1839 comparator treatment regimen. Because the efficacy results were comparable for the 2 ZD1839 doses, we are essentially left with what turns out to be a noon-randomized, non-blinded, single-arm ZD1839 study.

[Slide]

Trial 39 coprimary efficacy endpoints were objective response rate and disease-related symptom improvement. As you have heard earlier, the instrument used for the latter evaluation was the Lung Cancer Subscale of the FACT-L questionnaire. It was recognized during sponsor-FDA discussions that the absence of a comparator treatment regimen would make symptom improvement data difficult to

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evaluate. The sponsor's task was to demonstrate that symptom findings are credible in a single-arm study.

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Trial 39 patient characteristics are summarized on this slide. As indicated, the intent-to-treat population included 216 patients. Eighty percent of patients were ambulatory with mild or no symptoms as judged by the healthcare professional doing the performance status assessment. The predominant histology was adenocarcinoma, and 66 percent of patients had this histology and an additional 7 percent of patients had mixed squamous cell and adenocarcinoma. It should be noted that adenocarcinomas generally have the slowest doubling time of all lung cancer histologies, and this is reflected in the long interval between date of initial diagnosis of lung cancer and date of trial 39 randomization. The median time was 20 months.

At the time of diagnosis 50 percent of study patients had Stage 4 or metastatic disease, and at the time of study entry 89 percent of patients had metastatic disease. Since the median survival of newly diagnosed lung cancer patients with metastatic disease is in the range of 6 to 9 months this, again, suggests that the study population was enriched with slow growing, less aggressive tumors.

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As stated previously, trial 39 was designed for patients with no available therapy, that is, a third-line treatment group. Study eligibility criteria, therefore, required that the patients be refractory or intolerant to 2 prior chemotherapy regimens. These regimens must have included a platinum drug and docetaxel administered either concurrently or sequentially.

As indicated on this slide, only 139 of the 216 total study patients met the eligibility criteria. This is the patient group for whom there is no available therapy and for whom the accelerated approval regulations apply. The 58 patients who were refractory or intolerant to docetaxel but not cisplatin, the 11 who were refractory or intolerant to a platinum drug but not docetaxel and the 8 who were refractory or intolerant to neither drug provide supporting safety and efficacy information.

[Slide]

Turning now to trial 39 efficacy results, there were a total of 22 study patients with an objective tumor response, 12 who received ZD1839 250 mg per day and 10 who received 500 mg per day. The characteristics of these patients are summarized on this slide.

As indicated, responders were enriched for females and patients with adenocarcinoma. The study population

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included 43 percent females while 82 of responders were female. Sixty-six percent of the population had adenocarcinoma, whereas 80 percent of responders had that histology. While 59 percent of responding patients had metastatic disease at the time of diagnosis, their duration of illness was often prolonged. Thus, while 3 responders were less than 12 months from diagnosis to randomization, 12 were 13-24 months and 7 were more than 25 months from diagnosis. Approximately two-thirds of responding patients had received 3 to 5 prior chemotherapy regimens.

[Slide]

As described on a previous slide, only 139 of 216 trial 39 patients were refractory to both a platinum drug and to docetaxel and, thus, had an unmet medical need. The objective response rate for this population was 10.1 percent. The response rate among the 77 patients who were not doubly refractory or intolerant was 10.4 percent. This observation is somewhat surprising since one generally expects higher response rates in less refractory patients. We will come back to this point again when trial 16 results are discussed.

[Slide]

The coprimary endpoint of study 39 was disease-related symptom improvement. FDA had numerous problems in

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assessing symptom improvement. First, since all patients received ZD1839 and since ZD1839 250 mg per day and 500 mg per day had comparable efficacy, all patients were essentially receiving the same treatment. Since there was no comparator regimen, both patients and caregivers were unblinded as to the treatment.

Second, patients who had an objective tumor response were informed that their cancer had significantly decreased in size. Providing that information introduces a potential bias that can help explain the correlation between response and symptom improvement.

Finally, there was no prospective plan for managing concomitant medication. I will go into that in more detail on the next slide.

[Slide]

Classes of concomitant medication that were received by study patients during their time on study are listed on this slide. Most study patients were on multiple concomitant medications. It is clear that each of the drug classes listed on this slide can have a profound effect on lung cancer symptoms that were evaluated, including shortness of breath, cough, chest tightness and ease of breathing. Information on the doses and schedules of administration of concomitant medication was not collected,

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making it impossible to determine whether ZD1839 or concomitant medications were responsible for the observed symptom improvement.

[Slide]

Turning now to trial 16, as you remember, trial 16 is only a supporting trial. Eligibility for this study required that patients be refractory to 1 or a maximum of 2 chemotherapy regimens, and that they had to receive prior platinum treatment. This study population does not have an unmet medical need. Trial 16 simply provides additional ZD1839 safety and efficacy information.

Two hundred and nine patients comprised the intent-to-treat study population. As shown, 87 percent of the patients were asymptomatic or mildly symptomatic, that is, performance status 0 to 1. About two-thirds of patients had adenocarcinoma. The median and mean interval from diagnosis to trial 16 randomization was 12 and 16 months respectively, and 79 percent of patients had Stage 4 disease. Approximately half of all study patients were Caucasian, primarily from Europe but also from other centers worldwide, and half were Japanese.

[Slide]

This slide summarizes prior chemotherapy treatment of trial 16 patients. As indicated on the slide, all

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patients had received a platinum drug. However, only 35 percent of patients had progressed on prior chemotherapy; 65 percent of patients had not progressed on prior chemotherapy.

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The objective response rate, which was the primary efficacy endpoint of trial 16, is shown here. As indicated, there was 1 complete response and 38 partial responses among the 209 study patients, for an overall response rate of 19 percent.

[Slide]

Characteristics of responding patients are summarized on this slide. Twelve percent of male and 34 percent of female study patients had an objective response. Caucasian patients had an 11 percent response rate, while Japanese patients had a 27 percent response rate. The reason for this difference is not known. The 11 percent response rate in Caucasians is disturbing because, as stated previously, less refractory patients are expected to have higher response rates than more refractory patients. As we will see in the next slide, most Caucasian patients had not progressed on prior chemotherapy. Consequently, a higher response rate than was seen in trial 39 was expected.

[Slide]

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This slide reviews the relationship between response rate and prior chemotherapy progression. Looking at Caucasian patients, there were 9 responders from 62 patients who had never progressed on chemotherapy. This is an analogous population to what might have been treated in a first-line setting, and is a patient group most likely to respond to chemotherapy. The response rate of 15 percent is somewhat disappointing for Caucasian patients who had progressed on either first- or second-line treatment the response rate was 5 percent. For Japanese patients the response rates were 28 percent and 27 percent for patients who had not progressed or who had progressed on first-line treatment and, obviously, they are comparable.

[Slide]

I had planned to devote one slide to safety information but that has been adequately summarized by Dr. Sandler earlier today and I will only say that the FDA safety analysis confirms that ZD1839 is well tolerated, especially in the 250 mg per day dose.

[Slide]

To summarize efficacy data, the response rate was the primary efficacy endpoint for both trials. In trial 39 the response rate for doubly refractory or intolerant patients to a platinum drug and to docetaxel, the

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accelerated approval population was 10.1 percent. The 95 percent confidence interval was 5.6 percent and 16.3 percent. Trial 39 patients less than doubly refractory had a 10.4 percent response rate. In trial 16 Caucasian patients who were refractory to most single chemotherapy regimens had a 10.8 percent response rate. Japanese patients had a 27.5 percent response rate.

This response rate data from the pivotal clinical trial and from Caucasian patients in the supporting clinical trial does not fit the classic oncology model of less refractory patients having higher response rates than more refractory patients. There is no clear explanation for this finding. As previously mentioned, there is also no clear explanation for response rate differences for Caucasian and for Japanese patients.

[Slide]

Similar to concerns about response rates in relationship to refractoriness to prior chemotherapy, there are also concerns about the responding patient population in trial 39. As is evident on this slide, the responding patient population does not reflect a typical non-small cell lung cancer patient with metastatic disease, rather, the responding patient population is enriched for slowly growing cancers of low biologic aggressiveness.

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Evidence of the slowly growing nature of these cancers is the fact that the median time from cancer diagnosis to randomization in trial 39 was almost 20 months. Further, the large majority of responders had adenocarcinoma, the slowest growing of all lung cancer histologies. The low biologic aggressiveness of these cancers is evidenced from the fact that despite the long interval from diagnosis to randomization and the prior therapy with several chemotherapy regimens, 16 of the 22 responding patients still had a baseline performance status of 0 or 1, indicating no symptoms or only mild symptoms by this measure.

[Slide]

Similar to problems in interpreting response rate data, there are problems in interpreting symptom improvement data. Foremost, the study was not blinded since there was no comparator regimen. It is probably impossible to assess symptom relief in such a setting. Further, patients were receiving concomitant medications while on study that might have contributed to symptom relief. Unfortunately, drug dose and schedule information was not collected so that it was impossible to judge the relative benefit of ZD1839 to symptom improvement.

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Finally, the relationship between treatment response and symptom improvement is also difficult to evaluate. Telling a patient that his or her cancer is shrinking is likely to make the patient feel better. Also, this type of analysis has the same flaws as does any other comparison between responders and non-responders.

This concludes my presentation and I would like to call on Dr. Sridhara.

Statistical Review

DR. SRIDHARA: Thank you, Dr. Cohen, and thank you to the committee and everybody here.

[Slide]

I am here to present some of the major statistical concerns with this application. The registration trial 39 conducted in a third-line setting of non-small cell lung cancer patients was designed as a single-arm trial to eliminate a response of less than 5 percent. That is, even though the trial was randomized between 250 mg of ZD1839 and 500 mg of ZD1839, the trial was not sized to compare between the 2 arms and, in fact, was sized to independently evaluate efficacy in the 2 ZD1839 treatment arms.

Secondly, the patient population was heterogenous, as previously presented by Dr. Cohen, in that both second-line and third-line patients were included in the trial.

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Also, the sponsor specified 2 primary efficacy endpoints, namely, objective tumor response and symptom improvement rate. The agency had clearly communicated to the sponsor, in June and August of 2001, that the Lung Cancer Subscale, or LCS, data will only be considered as supportive to the validity of the response rate for accelerated approval. When the sponsor proposed once again to retain symptom improvement rate as a coprimary endpoint, the agency left to the sponsor the burden of demonstrating that the symptom findings are credible in a single-arm study. The most critical issue is that there was no comparative control arm in this study.

[Slide]

The results of the study with respect to tumor response have been extensively discussed by Dr. Cohen. Just to recap, there were 139 patients in the 250 mg and 500 mg ZD1839 arms who were refractory to 2 chemotherapy regimens, and 14 of the 139 had partial responses. The 95 percent confidence interval for the response rate of 10.1 percent was between 5.6 and 16.3.

[Slide]

The total of LCS score was the specified score to be evaluated for efficacy regarding symptom improvement. The 7 items included in this subscale were shortness of

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breath, losing weight, clarity in thinking, cough, good appetite, tightness in chest and breathing is easy. These were measured on a scale of 0-4, as given here, with 0 being not at all and 4 being very much. Note that the highlighted 4 items, namely, shortness of breath, losing weight, cough and tightness in chest are in reverse order. However, in the computation of total LCS score these 4 scores were inverted so that 0 meant worst symptom and a score of 4 meant no symptom on all items. Thus, a total LCS score of 28 would be asymptomatic and a score of 0 would be symptomatic.

[Slide]

The sponsor defined a patient as symptomatic at baseline if the total LCS score was less than or equal to 24. For example, at baseline if 4 of the 7 items were scored as 4 and the others as 0, as highlighted in yellow here, then the total baseline score would be 24. All patients who had less than or equal to a total LCS score of 24 at baseline were considered by the sponsor as symptomatic patients.

[Slide]

Improvement was defined by the sponsor as an increase in the score by at least 2 from baseline score for a duration of 28 days. For example, if the score increased

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by a score of 1 in 2 items, as in this illustration, then the patient is recorded to have improved in symptoms. That is, in this illustration an increase from a baseline score of 24 to 26 is considered as improvement. Please note that there is a ceiling effect on the maximum score of 28 that a patient can have.

I would like to add another comment here regarding the reference that was brought up by the sponsor regarding the publication where a 2-point change was considered to be meaningful. This was based on a retrospective analysis and this was a hypothesis generating publication, and this was based on looking at the difference in scores from baseline to 12 weeks, and not the way it is done here , and also in a combined group of patients receiving 3 different treatment regimens. Thus, it was not compared to any control arm.

[Slide]

As per the sponsor definition of symptom improvement explained in the previous slides, in the combined 250 mg and 500 mg ZD1839 treated arms, there were 45 patients who were scored as having improvement in the LCS symptoms among the 139 third-line or double refractory patients.

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This is an example of the LCS profile of a patient from the start of the treatment to 24 weeks. This example illustrates the difficulty in interpreting the total LCS score without a comparative control arm. This patient had a baseline score of 24. As seen in this graph, this particular patient did not have scores recorded between the weeks 1 and 4. At 4 weeks an increase of 4 points was recorded to 28, which is the ceiling effect. Then, between 5 and 9 weeks, an increase of 2 points from baseline was recorded, that is, a score of 26 for a period of 4 weeks, qualifying this patient to have symptom improvement although in later weeks there were some variations in these scores and, in fact, in this case a worsening of symptoms.

[Slide]

This is the same example as presented in the previous slide, except that the profile of each of the LCS scale over the same period of time is presented here. The 7 horizontal lines in this graph represent each of the 7 items in the LCS scale. The first line corresponds to shortness of breath; second, losing weight; third, thinking is clear; fourth, coughing; fifth, appetite; sixth, tightness in chest; and seventh, breathing is easy.

In the previous slide we saw that improvement was recorded between 5 and 9 weeks, which is the time period

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between the green and the red vertical lines in this slide. The improvement observed is basically in 1 or 2 items by a point. This illustrates that a 2-point change on a scale of 28 is difficult to interpret without a comparative non-ZD1839 arm because of minor changes of a point in 1 or 2 items.

[Slide]

This slide illustrates the percentage of patients who were evaluated for symptom improvement at each of the time points starting from baseline. As seen here, 25 percent were lost by week 1, and about 25 percent remained at 16 weeks. The attrition may be due to progression of disease. However, again, without a comparative arm it is not possible to comment on this attrition rate.

[Slide]

To summarize the critical issues in the registration trial 39, they are that the efficacy with respect to objective tumor response with ZD1839 could be as low as 5.6 percent. Symptom improvement is uninterpretable without control data. Symptom improvement is possibly confounded by concomitant medication effect and patient characteristics.

[Slide]

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Approximately 4 weeks back the sponsor shared with the agency results of 2 well-conducted, double-blinded, placebo-controlled randomized Phase III studies in first-line non-small cell lung cancer patients. These trials are also referred to as INTACT trials 1 and 2. The agency expected these studies to be the confirmatory studies of the Phase II study 39 under review here.

Study 14 had 3 treatment arms, gemcitabine, cisplatin plus 250 mg of ZD1839, gemcitabine plus cisplatin plus 500 mg of ZD1839 and gemcitabine plus cisplatin plus placebo. A total of 1093 patients were treated in the study and overall survival was the primary endpoint of the study.

[Slide]

The results of the overall survival analysis of this study are as presented in this graph. The green line represents the chemo plus placebo arm. The blue line represents the chemo plus 250 mg ZD1839 arm, and the red line represents the chemo plus 500 mg ZD1839 arm. Although the difference between the ZD1839 arms and placebo were not statistically significant, the observed difference favored the chemotherapy plus placebo treated arm. That is, the green line is above the blue and red lines. The comparisons presented here were the protocol specified comparisons. At

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the time of these analyses, 70 percent of the events had occurred and the survival data was mature for analysis.

[Slide]

Progression-free survival and response rates were 2 of many secondary endpoints studied in this trial. This graph represents the analysis of comparing progression-free survival of the 2 ZD1839 arms versus placebo. Again, the green line represents the placebo arm. The blue line represents the 250 mg arm and the red line represents the 500 mg arm. There is no apparent difference between the ZD1839 and placebo treated arms in this study.

[Slide]

This table gives the response rates in each of the 3 treatment arms and an estimate of the 1-year survival rate. The response rates ranged from 45 percent in the placebo arm to 50 percent in the 250 mg arm. Estimates of the 1-year survival rate range from 42 percent in the 500 mg arm and 45 percent in the placebo arm.

[Slide]

The second randomized study in first-line non-small cell lung cancer patients was study 17 which had 3 treatment arms, Taxol plus carboplatin plus 250 mg of ZD1839; Taxol plus carboplatin plus 500 mg of ZD1839; and Taxol plus carboplatin plus placebo. A total of 1037

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patients were treated in this study and overall survival was again the primary endpoint of this study.

[Slide]

The results of the overall survival analyses of study 17 are as presented in this graph. Again, the green line represents the chemo plus placebo arm. The blue line represents the chemo plus 250 mg arm and the red line represents the chemo plus 500 mg arm. No differences were observed between the ZD1839 arms and placebo treated arms. Again, these were the protocol specified comparisons.

[Slide]

This graph represents the analysis of comparing progression-free survival of the ZD1839 treated arms versus placebo in study 17. The green line, again, is the placebo line; blue is 250 and red is the 500 mg arm. There is no observed difference between the ZD1839 treated arm and placebo treated arm.

[Slide]

This table gives the response rates in each of the 3 treatment arms and an estimate of 1-year survival rate in study 17. The response rates range from 34 percent in the placebo arm to 35 percent in the 250 mg arm. Estimates of 1-year survival rate range from 38 percent in the 250 mg ZD1839 arm and 42 percent in the placebo treated arm.

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[Slide]

In conclusion, the results of the 2 well-conducted, double-blinded, placebo-controlled randomized studies in over 2000 patients are as follows. In both the studies there was no statistically significant difference between ZD1839 treated arms and placebo treated arm with respect to overall survival. There appears to be no difference between the ZD1839 treated arm and the placebo arm with respect to secondary endpoints including response rate and time to progression in both the studies.

Now Dr. Williams will summarize the FDA presentations. Thank you.

Summary

DR. WILLIAMS: Thank you, Dr. Sridhara.

[Slide]

Again, I will summarize the FDA findings with this slide, which I promise to return to. I must admit that we are following the presentation principle of repeating our main point here. AstraZeneca claims that ZD1839 provides symptom improvement in study 39, but FDA finds this claim is unconvincing without a control arm.

FDA and AstraZeneca agree there is a 10 percent response rate in 139 patients with refractory non-small cell lung cancer, and that there is no benefit of ZD1839 when

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added to chemotherapy in the first-line treatment of non-small cell lung cancer.

[Slide]

The last question, which would be the central question for our deliberations will be summarized on this slide. Again, you have seen this before and you will get a chance to answer this after lunch for yourselves.

Can symptom improvement claims in this application be adequately assessed without a control arm? Given a finding of no clinical benefit from ZD1839 in large randomized trials in the first-line treatment setting of non-small cell lung cancer, is the 10 percent response rate in refractory non-small cell lung cancer reasonably likely to predict clinical benefit of ZD1839 in the treatment of lung cancer?

Lastly, two points for discussion, first, thousands of patients have received ZD1839 for treatment use under an expanded access program. Please discuss how FDA should approach expanded access with ZD1839.

Lastly, regardless of whether the application is approved at this time, additional clinical trials may be planned for ZD1839 in lung cancer. Please discuss your recommendations for trial design.

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That concludes the FDA presentation. As I understand it, we get to eat lunch before asking and answering questions.

DR. PRZEPIORKA: Thank you, Dr. Williams. Yes, indeed, this will complete the presentations and the morning session. We will adjourn at this time until 1:10 p.m. and start with questions for both the company and the FDA prior to discussion of the questions. Thank you.

[Whereupon, at 12:25 p.m., the proceedings were adjourned, to resume at 1:20 p.m.]

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

Questions from the Committee

DR. PRZEPIORKA: I would like to start the afternoon session by clarifying some ground rules for our discussion, if I may. This morning we had a presentation by the sponsor and a presentation by the FDA. This afternoon we will open the second session with questions from the committee to the sponsor and to the FDA. For the purposes of making transcription a little bit simple, I would ask that the members of the committee try to address their questions to a specific individual according to the list of speakers we were given, and if that individual cannot answer the question and needs to defer, please indicate verbally to whom you are deferring the question so that the transcriptionist knows who will be speaking.

I will try to keep questions from the committee to the FDA or to the sponsor rather than having additional presentations made. So, when you are asked the question, please limit your answer to the question that has been asked. I will actually start, while people are still taking their seats, by asking the first question to Dr. Blackledge, please.

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The most obvious question that I can come up with was observing that the demographics of the individuals during the open public hearing did not match the demographics of non-small cell lung cancer in the country, I was wondering if there was additional information on the breakdown of the subgroups of adenocarcinoma regarding response rates and bronchoalveolar carcinomas specifically.

DR. BLACKLEDGE: Thank you, Madam Chairman. It is certainly true that we saw a majority of women respond in our trials, but it wasn't only women who responded. Both men and women responded.

I think it is important to remember that the situation with non-small cell lung cancer has changed dramatically over the past few years. Adenocarcinoma is now the most common subgroup of non-small cell lung cancer. I would like to ask Dr. Frances Shepherd to comment on the incidences of adenocarcinoma and its effect, if I may.

DR. SHEPHERD: That is entirely true. It is Dr. Shepherd speaking. There has been a marked demographic shift over the last ten or more years so that adenocarcinoma now represent anywhere from 50 percent to two-thirds of lung cancer in the Western world.

First of all, I think there is a lot of danger in doing a lot of sub-sub-subgroup analyses in this relatively

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small data set, but since it is being done we might as well carry on in that vein and I think that we should look very favorably on the fact that we have an agent that targets what is now the most common form of lung cancer in North America. I don't think that this should be looked on as a negative aspect of the results of the trial but, rather, a positive aspect.

DR. PRZEPIORKA: The answer to the question there then is the response rate specifically in bronchoalveolar carcinoma?

DR. BLACKLEDGE: Well, in our trials we didn't specifically break out bronchoalveolar carcinoma from adenocarcinoma so it is within that group.

DR. PRZEPIORKA: Dr. Cheson?

DR. CHESON: Bruce Cheson. I don't think it matters who I address it to, Dr. Sandler or yourself. Based on the requirements for the interval since prior therapy and based on the fact that a number of patients improved symptomatically, what was the median amount of time since prior therapy, and how can we be assured that the fact that a lot of these patients felt better wasn't because they were recovering from the toxicities of their prior therapy?

DR. BLACKLEDGE: I would like Dr. Kay to answer this question, please, who was the physician for trial 39.

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DR. KAY: Andrea Kay, AstraZeneca, trial physician. It is true that about a quarter of the patients who enrolled into the trial had a duration of less than 30 days from their last chemo dose but 75 percent did not; 75 percent were greater than 30 days.

DR. PRZEPIORKA: Dr. Carpenter?

DR. CARPENTER: One of the things we heard a lot of discussion about was the true eligibility for this study. As these inclusion criteria are listed, it seems possible that the sponsor may have interpreted these differently than the FDA did. As I read these, it says 2 previous chemotherapy regimens must have included a platinum and docetaxel; that they must have progressed on therapy. But the FDA seems to have interpreted this to mean progressed on first-line or second-line therapy, and the sponsor seems to have interpreted this to mean progressed on some therapy and have had the first two. What I am interested in knowing is how was eligibility really decided during the course of the study?

DR. BLACKLEDGE: Well, the precise words of the eligibility criteria were agreed between ourselves and the FDA. Now, the people who really had to deal with the eligibility criteria were the investigators and I would like to ask Dr. Natale to comment further on that because he, and

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other lung cancer investigators that we have here, had to interpret those data.

DR. NATALE: Thank you. Dr. Ron Natale. Let's think for a moment about what I view as a very rigid definition by the FDA regarding patient eligibility and what it really means. It came as a surprise to all of us. Their definition, first of all, is that patients had to have progressed on a first-line platinum regimen. Those are the patients who don't respond to the treatment or have a short-lived response and progress during their 3 or 4 cycles of chemotherapy. Those patients rarely live long enough to receive a third-line treatment, number one, and, number two, there has never really been any proof that rechallenging those patients with platinum, patients who have responded then progressed 30, 60, 90 days later--there is no evidence that they are platinum sensitive because the FDA has said patients who don't progress during treatment are, therefore, platinum sensitive. Yet, there is no data in the literature to support that. In fact, all physicians who care for cancer patients know that once you have used a platinum regimen up front it does not work subsequently.

Point number two is that they then applied that definition to the second-line treatment which, in most cases, was second-line docetaxel. In second-line docetaxel

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if a patient progresses during the first, second or third cycle of treatment they rarely live long enough to go on to receive a third-line treatment. Remember, the goal of the study was to look at the efficacy of this agent in the third-line setting.

So, again, they have given us a rather strange, very restrictive definition that does not apply. If we look at patients who received docetaxel in second-line trials, the ones that were reviewed by the FDA about two years ago, in Dr. Shepherd's trial, and we have Dr. Shepherd here fortunately to support this, there was only one responder in patients who were platinum refractory. This is second-line docetaxel. I think this again reflects the fact that this very restricted patient population does not respond to subsequent treatment. Some of them did respond to subsequent treatment with IRESSA. In fact, the response rate was 10.4 percent according to the FDA's calculation.

In Dr. Facella's study we can't really tease out that information specifically but we do know that in Dr. Facella's study 25 percent of the patients had performance status of 2. None of them responded to second-line docetaxel.

Finally, regardless of how many subsets you try to claim in this 200-and-something patient population, the

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response rate is always 10 percent. So, these strained definitions of refractory, resistant and sensitive don't apply to a novel biologic agent.

DR. CARPENTER: But what I am asking is this, as I read these inclusion criteria, it does not specifically state that they have to progress on first- or second-line therapy; it says failed therapy because of disease progression. What I am asking you is how were these things interpreted as the trial went on.

DR. NATALE: Investigators who entered patients into the study, and we have several of the major accruers here including myself, we know that patients who had received a prior platinum regimen and then progressed at some time during or after the treatment, and then got a second-line therapy and progressed during or after the treatment were eligible for the study.

DR. CARPENTER: Thank you.

DR. PRZEPIORKA: Dr. Kelsen?

DR. KELSEN: I have a question for Dr. Cohen. Can I talk to the FDA as well? So, the first question is for Dr. Cohen and then I think I have a question for the sponsor.

You expressed concern about the fact that the response rate didn't seem to drop in patients who received

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more prior therapy or less prior therapy. I think this might follow-up on a comment we just heard. But this agent has a different mechanism of action so I, personally, didn't find that quite so troubling. I wonder if it isn't like hormonal therapy in women with breast tumors who may have had multiple prior chemotherapeutic regimens or only one or two prior chemotherapeutic regimens and still will have the same response rate.

DR. COHEN: Well, I am not sure that you are correct in your response rates to hormonal therapy. It is my impression from the literature that the response rate to tamoxifen in the first-line setting is considerably higher than it is further down the road, approximately double.

DR. KELSEN: So, your concern is that even though it is a novel--

DR. COHEN: And we reviewed glevac which is also a novel chemotherapeutic agent, molecularly targeted, and the response rate in the chronic phase of disease was significantly higher than it was in the accelerated phase or the blast crisis phase of disease. So, there you have a model where stage of disease appears to be important.

DR. KELSEN: If I can follow-up, in summary then although it has a different mechanism of action, you are still expressing concerns as to the lack of an observed

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higher response rate in the less heavily pretreated patients?

DR. COHEN: That is correct.

DR. KELSEN: So, I have a second brief question for the sponsor. Looking at the first-line study, which I know you felt is not germane to this application but it certainly is an interesting although disappointing observation, I think we were all hoping to see a different outcome, what is your hypothesis as to why there was no benefit in either response rate, which was seen in this third-line therapy, or in survival in the first-line study? And what implications do you think that has for using this agent in combination with a cytotoxic drug?

DR. BLACKLEDGE: I think there are a number of hypotheses and I will ask one of my colleagues to discuss that in a minute. I think the results of this trial, the INTACT program and, indeed, the results of other trials which have emerged recently have enormous implications for the use of these kinds of agents with cytotoxic chemotherapy. For whatever the reason is, and I don't think we fully understand it yet--we certainly don't fully understand it yet, we are going to have to find new treatment paradigms, as Dr. Norton implied. But I know that

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Dr. Natale has some hypotheses, if you would like to go ahead.

DR. NATALE: Thank you, Dr. Kelsen. It is an important question. I think there are two possible explanations or hypotheses. The first answer is that, unfortunately, in all of the clinical trials that have compared three drugs to two drugs, three agents to two agents in non-small cell lung cancer we have never been able to prove that the addition of a third agent impacted on any of the therapeutic outcome endpoints at all. So, I think if one takes the view that this is an agent that has a chemotherapy-like action and we just happen to know what the target is, then I think the answer is that three drugs are not better than two drugs, yes, once again in non-small cell lung cancer.

I think we are also interested in this aspect because we all thought that the biological agents would be different, whether it was IRESSA, Avastin, SU54416 and even tamoxifen. Now we are beginning to generate the hypothesis, and you asked for one, that perhaps there is an adverse interaction between cytostatic biological agents and cycle-dependent cytotoxic agents so that they tend to perhaps cancel each other out when used in combination.

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I think one of the best pieces of evidence partially supporting that hypothesis are the results of the South West Oncology Group trial, presented at ASCA this past year, in which patients with breast cancer who were treated with chemotherapy plus tamoxifen had an inferior survival compared to patients who received chemotherapy followed by tamoxifen.

DR. KELSEN: Thank you.

DR. PRZEPIORKA: Dr. Pelusi?

DR. PELUSI: My question is geared to either Dr. Blackledge or Dr. Cella. In terms of quality of life, which I know that we are all very much interested in, a question arises in terms of the other things that could influence quality of life, especially anemia. In this patient population with their previous treatment that is of great concern. Would we not have, or do you not have the data that would show us what was going on with hemoglobins that might affect fatigue, cognitive function or shortness of breath to go along with your quality of life data?

DR. BLACKLEDGE: I will ask Dr. Cella to comment on the quality of life story generally. I wonder if Dr. Kay could actually comment specifically on the anemia.

DR. PELUSI: And while Dr. Kay is coming up, if I could ask in terms of the epo if we know if they were

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started on that after their previous chemotherapy or if they were placed on it during?

DR. KAY: Andrea Kay, trial 30 physician, AstraZeneca. We did not collect anemia specifically to look at it with regard to quality of life. We collected anemia in the safety data and, indeed, a very small proportion would be less than 5 percent. So, it is not one of the common AEs. Likewise, the need for blood transfusions was rare and the use erythropoietin was incredibly rare, again in less than 5 percent of the patients. So, we did not feel that that would strongly influence the outcomes in our questionnaire.

DR. BLACKLEDGE: Perhaps Dr. Cella could comment more on the actual questionnaire itself.

DR. CELLA: I am David Cella, from Northwestern University and a developer of the FACT instrument that was used in the trial.

Thank you for your question. I will try to somewhat restrict my response. There is a lot I would like to say about the FACT but I will reserve that for the curiosity of the committee, if you are curious. As you know, the use of erythropoietin is not approved for people who are not getting chemotherapy so its use would be off-

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label. We heard it was very rare. So, that seems unlikely to be a major player in the story.

In addition, we know from erythropoietin trials that selectively there is an improvement in fatigue relative to other symptoms and concerns, and we didn't see that here in this trial. The improvement in fatigue seemed comparable to the improvement in the other lung cancer-related symptoms. So, I don't think it is a major candidate for concern.

DR. PRZEPIORKA: Thank you. Dr. Blayney?

DR. BLAYNEY: Thank you. I have three questions directed toward the sponsor. First, Ron Natale implied in his presentation that the use of adjuvant medications decreased during time on trial. Dr. Cohen said that that information wasn't collected.

Secondly, I am having trouble sorting out that this is really, truly a different study population, that the responders are different than the typical lung cancer patients whom we see, and perhaps some of that could be clarified. It seems to me there is confusion between the interval of the diagnosis and going on study and relapse and going on study. You have about two years of diagnosis that go on study, so if there is a number of patients who were

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metastatic when they went on study, if you could give us that number.

Finally, in the safety data, how are we going to use this in patients who may have metastatic disease and compromised liver function and renal function?

DR. BLACKLEDGE: Let me deal with your last question first and then I will ask Dr. Kay and, if necessary, Dr. Ochs, study physicians, to comment on your other points.

We have looked at mild to moderate renal impairment and there is no evidence of any problems there. We have obviously not looked at it in severe liver impairment, but in the patients who have been treated in the trial program and in the expanded access program, patients with mild to moderate hepatic impairment have no evidence of any unfavorable interactions with IRESSA. I will hand it over to Dr. Ochs to talk about the symptoms.

DR. OCHS: Dr. Ochs, AstraZeneca. With respect to the concomitant medications, the data that was previously presented to you was a comparison of the frequency of additional symptomatic care agents that were added to the patients comparing the symptomatic versus the non-symptomatic patients.

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At one time we had provided the FDA with data concerning those patients who had had a marked increase in a single symptom such that they had a 2-point out of a 4-point possible change in their scales. When you look at the concomitant medications looking at those, of those 31 patients that were identified, in my medical judgment reviewing the onset of the medication, the type of the medication, the duration of the symptom improvement, there were, at best, 5 patients for whom I could say that there was even a potential for some benefit for the supportive care medication.

DR. BLAYNEY: Thank you. To the issue of duration of disease before going on study, it seems like if somebody had an operation, was disease-free for a long time and then relapsed quickly, got 2 therapies and went on study, that patient is quite different than somebody who had 20 months of chemotherapy, 10 months of a platinum regimen and 10 months of docetaxel regimen and then went on your study. Those are quite different populations and I can't tell who your responders are. Could you help me?

DR. BLACKLEDGE: I will ask Dr. Ochs to comment on that.

DR. OCHS: Twenty-five percent of the patients who were enrolled in this trial had Stage 1 to 3A disease at the

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time of their original diagnosis. One of the things we did look at, and compared it predominantly by histology--because a statement has been made that adenocarcinomas are slower growing which is difficult to understand since adenocarcinoma and squamous-cell have exactly the same prognosis in the advanced-disease setting--in fact, what happened was that the adenocarcinoma patients did have the longest interval between the time of diagnosis to when they came on the IRESSA study but it largely accounted for the interval between when they had their diagnosis of lower-stage disease until they developed advanced disease.

When you compare the interval of time on therapy with the first therapy, the second therapy and the third therapy, there really is no difference. I might point out that the second patient that Dr. Natale showed, the patient who had 6 cm of disease with other metastatic sites with unmeasurable disease, that PS 2 patient was the longest patient on this study who is 50 months from diagnosis to the time she came on study, and that patient obviously had a significant symptom improvement and improvement in performance status. Again if you compare the numbers, they are fairly similar.

DR. PRZEPIORKA: Dr. Fleming?

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DR. FLEMING: I have a question for Dr. Cohen and Dr. Sridhara to make sure I am interpreting the data correctly. We have had a lot of discussion about whether response rates are independent of the number of prior regimens where you had progression. I am using as a source of my information the FDA document, page 66, Table 27. In that document it is indicated that in the 16 trial, of the 39 responses that occurred, 29 occurred in the cohort where there had been no progression on chemotherapy.

What is important is to have the denominators. So, using the table on page 63, it appears that in the cohort where there was no progression on chemotherapy there were 20 responders in 136 for a response rate of 21.3 percent. In those that progressed only on first-line and only on second-line response rates respectively were 6/38 for 16 percent and 3/18 for 17 percent.

But the group of particular interest, those people that progressed on both first- and second-line chemotherapy, there were 17 of those patients of which only 1 responded for a 5 percent response rate. This is including the Japanese cohort that has a higher response rate. Am I interpreting these numbers correctly?

DR. COHEN: Yes, I think so. I have the same table that you are referring to and I think you are right.

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DR. FLEMING: So, in essence, it says that the most relevant people from the 16 trial are the 17 people who progressed on both first- and second-line. There are 17 even if you include the Japanese cohort; only 1 responded. You have only a 5.6 percent response rate. So, this study would seem to say the response rate is very unimpressive in this third-line cohort if you focus on the 17 most relevant people from study 16.

DR. PRZEPIORKA: Dr. Redman?

DR. REDMAN: Just a clarification because of the implication of the quality of life. When was the first time point in the Phase II trial for response evaluation? Was it at 4 weeks or 8 weeks?

DR. BLACKLEDGE: It was at 4 weeks, and the radiographic evaluation was carried out after the patients had filled in the quality of life form on that day. So, the patients did not know whether they had responded or not when they filled in that quality of life form.

DR. PRZEPIORKA: Dr. Varricchio?

DR. VARRICCHIO: For the statisticians involved in this, I am curious to know, the sponsor said there was 80 percent compliance with this trial, but they didn't state how compliance was defined. But, then, when we had the FDA presentation it looked like 25 percent persisted to the end

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of the trial. I am curious about the attrition and how were the missing data points handled in the statistical analysis, especially for the symptom management part.

DR. BLACKLEDGE: Perhaps I can make this clear. Of the possible forms that could have been filled in, 85 percent were. Now, as it was made plain earlier, once a patient had progressed, once they had achieved the endpoint of the trial, they no longer filled their forms in and, therefore, the numbers naturally fell at the same rate as we saw patients failing therapy. So, we saw the median duration of response which actually correlates very tightly to the number of forms being filled in at any one time.

DR. VARRICCHIO: I am still concerned about what you considered the endpoint then? Where was the comparison point? Because if you are persisting to those 25 percent that made it to the end, those are probably the best patients. The ones who fell out sooner because of recurrence, what happened to their data?

DR. BLACKLEDGE: I would like Dr. Cella to comment on this. He devised the score and helped to set us up.

DR. CELLA: David Cella, from Northwestern. If I could just clarify why there is the disparity that you pointed out, Dr. Sridhara presented a slide that showed the proportion of patients who from the point of entry continued

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to produce data. She mentioned it but it wasn't particularly highlighted. That excluded from the numerator but included in the denominator anybody who didn't complete the form because they were off study. The purpose of this trial was to evaluate the symptom response to being on IRESSA. So, by protocol design that was worked out between the company and the FDA, patients, when they progressed, were taken off study, which included not performing any more quality of life evaluations. So, the 84 percent number, the compliance number, is the proportion of people who had expected--the way it is typically done in the field, the proportion of expected evaluations that were, in fact, received. So, 84 percent of the expected evaluations by protocol were received. That is not the 25 percent. That is overall across the duration of the study.

I asked for a very conservative sensitivity analysis to be done, imputing for all those 16 percent of missing data elements a zero score, meaning the worst possible score in the LCS which virtually no patient ever provides; it rarely happens. We computed that and the benefit remains among the responding patients. You continue to have an average improvement of over 2 points in the responding patients.

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DR. VARRICCHIO: Before you leave, just to clarify that in the field what is frequently done is to follow patients for at least 30 days after discontinuing medication, and I just wanted to clarify that these patients did not have anything further done after discontinuing medication so there was no follow-up for 30 days?

DR. CELLO: There was no follow-up for 30 days. There isn't a standard approach to this. The protocol called for final assessment at discontinuation of drug.

DR. PRZEPIORKA: Dr. Fleming?

DR. FLEMING: You raised a very key point. Essentially what we are hearing is that the analyses that are being presented to us are what is the symptom relief conditionally given that you haven't progressed, which really isn't a fully interpretable result. It doesn't really maintain an intention-to-treat type of analysis. Those people who tend to do more poorly are systematically pulled out. So, as Dr. Sridhara has pointed out, there is very significant "missingness" here. You have 25 percent missing. You have 50 percent, I think you said, missing by 8 weeks. Part of that missing is due to progression so we get a result that is conditional. Given that you haven't had a downhill course in progression, what are your symptom

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results? And, that is a very biased analysis for the entire cohort.

Secondly, what we just heard was imputing on the 16 percent. That wasn't imputing on those that progressed; that was imputing on those that hadn't progressed but had missing information. This is a very significant amount of "missingness" and it is not unrelated to the number of factors that the FDA had raised that raise serious concerns about interpreting the symptom data.

DR. PRZEPIORKA: Dr. Brawley?

DR. BRAWLEY: A couple of questions. The symptom improvement LCS score that the FDA presented, they had a summary score there and some of the sums don't quite make sense to me. Is it possible that we could just go through it for a second? For example, you could have a summary score from the 7 things and 4 was very much. This is page 2 from the FDA presentation. If you said I have been coughing, you scored that at zero for not at all, which to me would be a very positive thing. But if you said--help me figure this out. It seems like you would score zero for some very positive things and 4 for some very negative things.

DR. SRIDHARA: Can I answer that? I think I mentioned that, you know, of those 7 items, 4 of them as you

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read them, yes, you are right, zero means that there are no symptoms and 4 means that they had the symptom. But for those 4 items, they were inverted when computing the total LCS score. So, for all 7 of them zero meant no symptoms.

DR. PRZEPIORKA: Dr. Brawley, do you have any other questions?

DR. BRAWLEY: Just one more. Of the 40 percent who had an improvement of 1 or greater in 6 to 7 items, I am wondering how many were in that group that was in the 25 percent who got treated on this drug within 30 days of finishing treatment on another drug.

DR. BLACKLEDGE: I don't believe we carried out that precise analysis.

DR. BRAWLEY: What I am getting is that in screening we have this principle of bias, which is actually what Dr. Fleming and Dr. Varricchio have been talking about and simply stated it is that people who do well tend to do very well. I am concerned that there may be a selection bias in responders for people who have--I hate to use the word subset--lung cancer that tend to do very well even without treatment.

DR. PRZEPIORKA: Dr. George?

DR. GEORGE: I have a question about the INTACT studies, even though you didn't present a lot of information

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on them. It has to do with whether you have any information from them whatsoever about quality of life or symptom improvement.

DR. BLACKLEDGE: We have only received these data very recently and we have analyzed the objective endpoints. We have not yet analyzed fully the other endpoints.

DR. GEORGE: But you are planning on this? I wasn't familiar with these studies until I saw these disappointing results with the primary endpoints, but you do have a plan for analysis?

DR. BLACKLEDGE: We do plan to explore these studies fully, firstly, to see if we can understand why we got the results we have.

DR. GEORGE: I raise it just because that is potentially a benefit that we haven't heard anything about. We don't know one way or the other but it is just because it is too early? Is that it?

DR. BLACKLEDGE: Yes.

DR. PRZEPIORKA: Dr. Taylor?

DR. TAYLOR: I actually have three questions. Back to his on the INTACT trial, was the IRESSA given always concomitantly with the chemotherapy or was chemo given and then dropped and then IRESSA given?

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DR. BLACKLEDGE: It was given concomitantly and continued for as long as the patients were showing benefit.

DR. TAYLOR: But both were continued indefinitely?

DR. BLACKLEDGE: No, the chemotherapy was limited to a maximum of 6 courses.

DR. TAYLOR: Secondly on the quality of life, you talked about the anemia; it did not get worse. Do we know did the hemoglobin get better because they were no longer taking chemotherapy, and would that be a reason they felt better?

DR. BLACKLEDGE: We saw no major changes in any of the hematological parameters in trial 39.

DR. TAYLOR: The third one, I was struck by the number of non-smokers who presented this morning. Do we have any data on responses in smokers versus non-smokers?

DR. BLACKLEDGE: Could I ask Dr. Kay to comment on that?

DR. KAY: Andrea Kay, AstraZeneca, trial 39 physician. Overall, 41 percent of the patients enrolled in the trial were smokers in the past or currently. We did not distinguish between the two of them. Indeed, the response rate remains the same; the tumor response rate and the symptom response rate remains the same whether they were non-smokers or classified as smokers.

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DR. BRAWLEY: I have a quick follow-up. Is there any work ongoing to try to define the subset of individuals with cancer who would respond to this drug? Quite honestly, when you just say non-small cell lung cancer or even adenocarcinoma you are probably talking about several different diseases that you are treating.

DR. BLACKLEDGE: Yes, I think that you probably are. I think you need to remember that from the findings of trial 39 it is about 40 percent of the patients who get some benefit. That is, clearly, a very clear 10 percent who get a response and symptom-related response. We are looking at trying to identify whether or not there is a specific subset of patients who will respond. I don't believe that we can do it histologically at the moment. We are looking at EGFR expression. I personally believe it is going to be something more subtle than that. For example, we are carrying out gene array studies in some of our ongoing trials to try to identify patients more or less likely to respond. But I think the important thing from the patient's point of view is that 40 percent of them are going to gain some benefit from IRESSA.

DR. PRZEPIORKA: Dr. Martino?

DR. MARTINO: Thank you. I have several questions, namely things that I need to understand here.

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Can someone tell me what the actual time to response was in measurable patients? In other words, I know that you looked at 28 days and then you looked again I believe a month later. When did most responses demonstrate themselves?

DR. BLACKLEDGE: Eighty-five percent of the responses had occurred at the one-month radiographic assessment.

DR. MARTINO: The next question I have relates to when I look at this data the impression that I get is that this is not a drug that works often. In fact, most of the time, overwhelmingly, it does not work. There are a couple of subsets that you have alluded to that would imply that perhaps it is a better drug in some, and those subsets, as I see them, are women and the Japanese. Now, I have yet to hear a reasonable or intelligent explanation as to why that should be the case, and there may be one. But if there is, I would very much like to hear it because if I were a Western male with this disease I am not sure that for a response rate of less than 5 percent I would volunteer. So, I am trying to figure out what is there about either being Japanese or being female that may be different and, therefore, meaningful so that I don't sort of group all of them within this fairly low response rate.

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DR. BLACKLEDGE: Well, we obviously looked very carefully at the striking Japanese results. A response rate of 27 percent is clearly higher than we have seen consistently across the rest of our trial program. We can actually explain much of the difference in terms of the baseline characteristics of the patients who were entered in Japan. There were more women. They had better performance status and there were more patients with adenocarcinoma. All of these factors contributed, we believe, to this favorable response rate.

If we put those into a multivariate analysis, the actual difference between the Japanese and the rest of the world actually loses statistical significance. There is still a trend which we cannot explain, but it loses statistical significance when you take into account known favorable baseline prognostic factors.

DR. MARTINO: Can you deal with the issue of the female gender?

DR. BLACKLEDGE: I can't, other than to say that women are very lucky in this situation.

DR. MARTINO: Well, maybe so but it does not speak well for the men. One additional issue that I need to understand relates to this quality of life measure. It is a lovely scale in the sense that it is simple and there are

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questions that one can answer, but I am trying to figure out in my own mind what does it actually mean clinically when a 2-point difference is noted and now someone gets excited over that? I need one of the clinicians to help me understand how much improvement in practicality does this mean. I ask this question with full respect to all of those predominantly women, but gentlemen too, who also got up this morning and showed us that in their own minds there appeared to be some dramatic difference. I am grateful for their experience but I am not sure that 2 points means very much. I need someone to help me understand how properly to interpret that.

DR. BLACKLEDGE: We will do that. I think it is important to stress that the majority of the patients who gained benefit had a much greater than 2-point increase. I mean, the responders had a greater than 4-point increase, really quite a dramatic response.

I think it is also important to remember that as part of accelerated approval we want this score to be robust enough to be linked to response, but not to prove definitively that symptom control is there. If that was the case, then I think we should be looking at full approval. So, we need to have enough confidence, and we will show you

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some of the sensitivity analyses, that there is a probable predictive linkage here.

DR. MARTINO: And maybe even at 4 points someone needs to help me understand how much does that really mean because I am thinking this is on a scale of 28, and 4 out of 28, gee, that doesn't sound terribly exciting to me. So, someone help me there.

DR. CELLO: It is my pleasure. Can I start with the ECOG slides first?

Let me try to explain to you from my perspective, I am a psychometrician; I developed the questionnaire and I can speak to that. I also am a clinician. I work with cancer patients and I will also try to speak to that. But if I fall short I am sure Dr. Natale will chime in. I am David Cello, from Northwestern University.

First, let me just provide some background about how the 2-point change was developed. It goes back to the original development of the questionnaire in which we asked 15 patients and 5 experts what kinds of questions we should be asking. Then we went on to test that with 30 more patients and then again with 90 patients, separate from the previous 45. In each of those testings we would say are you sure we are asking the right questions and we would refine those questions. So, we are quite confident, from a

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thorough preliminary set of exercises, that we have the right mix of questions in the questionnaire.

Then, in order to be efficient and not have 30 or more endpoints, because there are more than 30 questions in the questionnaire, we have to decide how to aggregate those questions, and we need to do it intelligently in a way that can be justified empirically.

So, the Lung Cancer Subscale which was selected, those seven questions as the primary endpoint in this trial, we had studied over the previous ten years and determined, first in the initial validation paper in Lung Cancer, in 1995, that two to three points was about the magnitude of difference that we saw between patients with performance status 0 versus performance status 1 versus performance status 2. We then went on to confirm that--rather than, as Dr. Sridhara had mentioned to hypothesis generate, we confirmed that in trial 5592, and I will show you that in a moment.

ECOG study 5592, conducted in the mid-'90s, was a 3-arm randomized trial of platinum etoposide versus standard dose Taxol with cisplatin versus high dose Taxol with cisplatin with growth factor rescue, all patients getting chemotherapy. We wanted to determine from that trial, with the original data from our early validation studies that had

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previously been published, could we support these differences that we were seeing between patients with, say, 0 performance status and 1 performance status. We also wanted to see if we could divide patients into those that had more than 5 percent weight loss or less than 5 percent weight loss which, as you know, is another important clinical indicator in lung cancer medicine.

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So, what we did, we divided groups into patients according to their ECOG performance status to determine what is a clinically meaningful change for dividing up patient groups and then for classifying individual patients. We started by first using a separate trial, this ECOG 5592, and we wanted to determine what was clinically meaningful and we anchored to various clinical differences and changes.

The differences, the two lower bullets, ECOG performance status and weight loss simply divided the patients at baseline into those who were 0 versus those that were 1. The difference between the 0's and the 1's was 2.5 points. We divided patients who had more than 5 percent weight loss versus those that had less than 5 percent weight loss, again a difference between 2 and 3 points.

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Then we went on to look at the change score in the LCS, the seven questions, based on this trial as to whether patients were responders--these are data at 12 weeks; stable disease or progressive disease. Lo and behold, we see that same number, 2.5 points, which is the magnitude of improvement which, I might add, in trial 39 is twice that, the reason being, as was mentioned earlier, this is cytotoxic chemotherapy so even though there is some symptomatic benefit in responding patients, the side effects of the chemotherapy are driving down the score presumably. But we have that 2.5 point difference again.

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So, we are settling in on these 2 points. Now we divided patients into those who progressed early versus those who progressed later and the later progressors at 12 weeks, forecasting the fact that they would do better over time, and they had 2-point improvements.

We put all this together, along with some other distribution-based statistics looking at the standard deviation of the spread of scores in a population at baseline and in an unchanging population, and the standard error measurement, all of which settled by currently accepted criteria for clinical significance in the neighborhood of 2 to 3 points.

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So, when I was asked by the sponsor what number I would use in a prospective analysis plan, which is what they wrote, I said either 2 or 3 points. They selected 2. As you heard, had they selected 3 the results would be virtually identical because almost all of the improvements were beyond 2 points.

I just want to make one other comment about that selection of 2 because it is true that one can look at that list of 7 questions and 28 possible points and one would wonder in a given patient, as illustrated in the earlier presentation by Dr. Sridhara--here is somebody whose score was up 2 point, does that really mean something? Well, I am quite confident that a group of people, as actually illustrated on page 61 in the FDA briefing document where they compare in this trial performance status 0 to 1 to 2 and, lo and behold, the median LCS difference is 2 points between each group. I am confident that in group comparisons 2 points is a very solid number for differentiating clinically meaningful groups.

Then the question is can you reasonably classify people as changed if they move 2 points? You will make classification errors no matter where you set that number. My goal is to try to set that number at the bar where you minimize the number of classification errors. So, some

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people who posted a 2-point change will truly not have changed. Others who posted a 1-point change will truly have changed. That is inherent in classification in any diagnostic test when you look at sensitivity and specificity. So, we tried to maximize the sensitivity and specificity, if you will, and again that number is between 2 and 3 points, and we have solid data to show that.

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Now if I could show you from trial 39, if you wanted to set the bar higher and you wanted to move it all the way to 7 points, the conclusions of the trial where there is meaningful benefit in responding patients remains the case. The number would lower to somewhere in the 10-15 percent range. So, if your preference is to make what I consider to be more misclassification errors in the direction of assigning people as unchanged because they didn't change enough for your criterion, you would still have a 10-15 percent group of patients who are answering better than 1 full point on this 4-point scale, better or improved; they are saying they are getting better on every symptom to a meaningful degree in each and every one of the 7. So, this gives you an overview of what would be across the group improvement rate.

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If you decided that you wanted to go to 4 points, which is what you had suggested, that would change the 39 percent LCS improvement rate down to 29 percent, still meaningful improvement if you changed the number to 4, requiring that it be repeated at 4 weeks without a significant drop.

This looks at it by response criteria so that if your number was 4, over here, which is the number you asked about, you still would have more patients, CR's and PR's, showing symptom response compared to the stable disease patients and far more than the progressive disease patients.

If I could make one other comment to Dr. Fleming's point because you raised a significant concern about the data overall, it is that I think that there is quite a bit of protection in the concern about missing data when you consider that this form of classification analysis, which is driven by current state of the measurement science as well as FDA direction--this current approach to analysis of classifying patients as improved or not actually does count everyone in the denominator in that intent-to-treat sense because if you don't provide data, you are counted as a non-improver. So, these are proportions of the overall population and I think there is some protection there. Thank you.

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DR. PRZEPIORKA: Dr. Cello, before you leave, has this scale ever been used in a randomized trial of lung cancer where one arm was either placebo or best supportive care? If so, what happened to the scores in that arm?

DR. CELLO: The answer is no. As you know, there are precious few trials in lung cancer, particularly in the U.S., where there is a placebo or best supportive care arm. So, the answer is no.

DR. PRZEPIORKA: Dr. Reaman?

DR. REAMAN: Just a question in the follow-up to the comments of Dr. Shepherd about this agent being particularly exciting in the histologic subtype of adenocarcinoma, are there any data to suggest differential expression of the EGF receptor in adenocarcinoma, and particularly in the patients entered on this trial?

DR. BLACKLEDGE: I will ask Dr. Averbuch to comment on that.

DR. AVERBUCH: Steve Averbuch, clinical research, AstraZeneca. As was mentioned earlier, EGFR is expressed across all the histological subtypes of non-small cell lung cancer. In fact, the over-expression is more frequent in squamous cell carcinoma, but it does still occur in adenocarcinoma as well.

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DR. REAMAN: But in the individual patients who responded was there any correlation with EGF receptor expression?

DR. AVERBUCH: As agreed with the FDA and as of great interest to all of us, the analysis of EGFR was identified as an exploratory endpoint. Now, that has proven to be extremely difficult in the absence of validated standardized assays. So we are currently working with collaborators to get those assays standardized. We have collected samples, about 40 percent of patients, and we are currently trying to establish those assays so that that analysis can be done. So I think there will be an answer forthcoming.

DR. REAMAN: Do you have any information on gender relationship with pharmacokinetics or pharmacodynamics of this agent?

DR. BLACKLEDGE: We have looked carefully at that and there are no gender relationships.

DR. PRZEPIORKA: Dr. Varricchio?

DR. VARRICCHIO: I think we are all kind of going around the same question. It is impressive that when it works, it really works and when it doesn't, it doesn't, and trying to see if we can get our thinking around what is it about those people in which it worked that made them

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different from the ones where it didn't. I guess I am just kind of making a request that you mine your data to see if you can find some kind of profile that would predict in which patients this is likely to work if it goes forward. It seems it is an "all or nothing" almost.

DR. BLACKLEDGE: I take your point about that. We believe it is more than an "all or nothing" because we have 40 percent of patients who have either partial response or stable disease, and 40 percent of patients who show these quite striking differences in their Lung Cancer Subscale. But there is a group of patients who are exquisitely sensitive, I agree. And, there is a further group of patients who gain some benefit, and about 50 percent of patients who really have no benefit. That is very similar to what we see with many other non-cytotoxic agents. Those are roughly the data you see with tamoxifen, 10-15 percent good response, stable disease in about 30 percent and progression in the rest. It is actually what you see with glevac. If you look at GIST tumors which express C-KIT but do not have mutations, the response rate in those patients is 10 percent. A further 30 percent benefit and the rest do not benefit.

Something is starting to come out with non-mutated receptors and these inhibitors of these receptors, and it

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looks as if it is something like that. No one yet knows why it is. We have over 100 collaborations with laboratories worldwide looking specifically at trying to identify these but at the present time I am afraid we can't give more guidance than a pathological subtype.

DR. PRZEPIORKA: Dr. Kelsen?

DR. KELSEN: Sort of following on that and Dr. Taylor's initial question about the INTACT trial, if I understand your answer correctly, in the first-line randomized study there was a period of time in which patients were getting this drug without receiving chemotherapy. That is, there was a maximum of 6 months of chemotherapy. Were responding or stable patients then continued indefinitely on IRESSA?

DR. BLACKLEDGE: Well, they continued for as long as there was no evidence of progression.

DR. KELSEN: Yes, I understand that. So, as long as they were having benefit they were continued. The placebo patients presumably received placebo indefinitely until they progressed?

DR. BLACKLEDGE: That is correct.

DR. KELSEN: Have you looked or do you plan to look at outcome from the moment that chemotherapy stopped, or do you have any data you could tell us today?

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DR. BLACKLEDGE: Well, I think you actually saw some data in the time to progression slide in one of the trials that was shown by the FDA this morning. If you actually look at that, the curves actually cross and both the 250 arm and the 500 arm start to separate from the placebo arm, which is suggestive but not proving a maintenance effect.

DR. KELSEN: When I looked at the data for survival, they looked awfully tight.

DR. BLACKLEDGE: Well, I agree.

DR. KELSEN: Could you show us those slides again just to refresh my memory?

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DR. BLACKLEDGE: There is a small amount of separation but I believe that if you are going to do a maintenance trial you should do a maintenance trial because you may well have developed resistance in combination with chemotherapy during that first 90 days or so. So, I think whilst these data might be suggestive that there might be some kind of effect there, I believe that you actually have to do a prospective trial to determine the value of IRESSA in that situation.

DR. PRZEPIORKA: Mr. Simon?

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MR. SIMON: I direct mine to Dr. Cohen, FDA. You mentioned with regard to trial 39 that 66 percent of the patients had adenocarcinoma, slow-growing cancer. I believe the sponsor may have addressed parts of that but could you address why that is so significant with regard to that trial?

DR. COHEN: Well, I think the major issue was time from initial diagnosis to time to randomization for IRESSA. The principle point that I wanted to make was that this was a selected population, that this was not the typical lung cancer population that most of us see who present with metastatic disease and die quickly.

There is considerable overlap in doubling times between histologies. If one looks overall, adenocarcinoma tends to be the slowest, but there are exceptions and some adenocarcinomas are fast growing and some adenocarcinomas are aggressive. But in this particular study it appeared that the patient population selected was those with the slow-growing tumors that were less aggressive based on their maintenance of performance status.

MR. SIMON: Did the results in those that did not have adenocarcinoma, did they differ from them?

DR. COHEN: The numbers were very low. We are only talking about 22 responders total and the majority of

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them were adenocarcinomas so that the numbers of other histologies were very small.

DR. PRZEPIORKA: Dr. Cheson?

DR. CHESON: Just a couple of minor questions. First of all, in many diseases females do better than men. If you look at myeloma or other diseases, that is a fairly consistent observation amongst the number of tumors. What intrigues me a little more is the Japanese situation, which would lead to a suggestion to look at the pharmacogenomics, which hasn't been mentioned. Is there some difference in metabolism of the product whether it be women or whether it be a cultural thing?

My question is I have been involved in designing questionnaires and questions and exams for a long time, and maybe you went over this but when you have questions that are backwards that may tend to confuse people and they put the wrong answer down. Was there some sort of protection? You know, when one is positive and is on the right and the other is negative and is on the right, is there some protection against the patient putting the wrong answer there because they thought everything--like, I do that on all kinds of forms and I find I did the wrong thing and, you know, it gets you into problems when you are trying to get over the border?

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[Laughter]

DR. CELLO: David Cello. You might not like my response, Dr. Cheson, because the reason we do that is that it actually is one of the principal teaching points of creating questionnaires, which is that the best way to keep people paying attention and not doing "I'm in a hurry doctor routine" in running down a questionnaire is to mix things up a little bit so people actually have to read the questions. So, reversing the order, if you will, reversing the frame positive and negative, sticks people on task more. It doesn't allow somebody to say, "oh, I get it, you are asking about a lot of negative things; I'm doing fine so I'm going to say a bunch of zeros," which is a problem that some instruments have. So, this is a protection against that. We can recheck that after we have the data through a measurement model using item response theory where we can determine whether any individual question misperform or whether people misperform on those questions. So, yes, there are protections.

DR. CHESON: I am not concerned about the two ends of the spectrum. I am more concerned about the ones in the middle obviously. Obviously, I am not an expert in this field so I don't know how you measure whether there is variability or not, but do you really instruct them to be

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careful that some of these are backwards, or do you make sure they read them? It is just a minor point of concern.

DR. CELLO: People are asked to read every question carefully. You can't guaranty that people won't do that. Like I say, this is a protection against the most common response bias that people show.

DR. CHESON: Thank you.

DR. PRZEPIORKA: Dr. Blayney?

DR. BLAYNEY: You mentioned that the median time to response was 4 weeks. Am I remembering that correctly?

DR. BLACKLEDGE: Yes, nearly 80 percent of the patients had shown their initial x-ray response at 4 weeks.

DR. BLAYNEY: So, what is the last responder?

DR. BLACKLEDGE: The last responder that we saw was at 16 weeks.

DR. BLAYNEY: Sixteen weeks?

DR. BLACKLEDGE: Yes, but in the vast majority the response had occurred within the first 4 weeks.

DR. BLAYNEY: So, if you wanted to put somebody on, 80 percent of the time they would declare themselves early as a responder.

DR. BLACKLEDGE: Well, I think you heard today that certainly many people start to feel better within a

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matter of days. That may be the ultimate way of choosing which patients are going to benefit or not.

DR. BLAYNEY: And which ones you are going to continue for a long time?

DR. BLACKLEDGE: Sure.

DR. PRZEPIORKA: Dr. Kelsen?

DR. KELSEN: One of the questions we have been asked to comment on regards future study design whether accelerated approval is recommended or not. A number of potential designs are possible, almost all of which I would think would be randomized to the drug versus something, placebo and a variety of treatments. What is the sponsor's feeling on the willingness of patients to enter into such a confirmatory trial in which they will be receiving or not receiving this agent if it is available widely via accelerated approval, and then if it is available widely via the extended access program?

DR. BLACKLEDGE: Well, the definition of clinical benefit that we are using is a better life, and it has been very clear from all the discussions that we have had this afternoon that symptom control seems to be a key aspect. We believe that we would be able to perform a trial looking at IRESSA versus best supportive care and looking at time to symptom worsening, and then crossing over to IRESSA. So

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this would not be a survival trial; this would be a confirmation of the benefits that are predicted in the trial which we have submitted for accelerated approval.

The alternative to that would be to carry out a randomization versus a common chemotherapy agent, say gemcitabine, which has a low response rate and, again, provide the crossover at time of symptom worsening.

Rather than my saying whether I think these are feasible, perhaps I could ask Dr. Mark Kris to comment on that and Dr. Lynch who would be potential investigators.

DR. KRIS: Mark Kris, medical oncologist from Memorial Sloan-Kettering. I think the kind of trial designs that Dr. Blackledge just mentioned would be very doable here, and I think they would allow patients access to the drug; allow us to confirm the endpoints that we have; and I think that they easily could be done.

DR. LYNCH: Tom Lynch, Mass. General. Just to echo Mark's feeling, I think one of the comments made earlier was about the rapidity of response to this agent makes it particularly appealing to look at in a crossover design, having treated hundreds of patients on expanded access and a number on trial 39, you know within 4 to 6 weeks whether there is benefit. So, ethically, morally to put a patient on a quick crossover, 4 to 6 week period

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before the crossover, I think is very doable versus not just best supportive care, but I think you actually have to do it versus placebo to be certain that what you are seeing is truly effect of the drug.

DR. KRIS: Actually, we seldom tell the patient they respond; they tell us, just as we heard this morning.

DR. PRZEPIORKA: Dr. Martino?

DR. MARTINO: The more I think about this, the more it becomes apparent to me that the real key for me as to whether this is a good drug or not is really not response rate, because response rate is very difficult to measure, particularly when you are dealing with patients who have had several previous therapies. So, the fact that this response rate is fairly unimpressive I guess is the lot of our lives in many of our tumors right now. But to me the key really, again, has to do with this quality of life issue. I am not sure that I am ready to accept that what appears to be an impressive quality of life, which is not necessarily directed at measurable response because you have this group of patients who have stable disease who appear to get something out of this. If, in fact, that is correct then this is a worthwhile endeavor. If, on the other hand, there is some other explanation, then this is not a worthwhile

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endeavor. So, to me, what it really comes down to is to what degree can I accept this quality of life information.

DR. PRZEPIORKA: Are there any other questions from the committee? Dr. Redman?

DR. REDMAN: A clarification on the response again, most of the responses occurring at 4 weeks, is that PR or is that PR plus stable disease?

DR. BLACKLEDGE: Those are the PRs that I was talking about.

DR. REDMAN: At 4 weeks?

DR. BLACKLEDGE: At 4 weeks the radiographs had shown 50 percent reduction.

DR. PRZEPIORKA: Dr. Fleming?

DR. FLEMING: A brief follow-up to some earlier discussion, in the FDA briefing document, bottom of page 14, top of pate 15, discussing some of the methodologic problems with the assessment of symptom relief, a sentence at the top of page 15, "there are also methodologic issues, including early progressors being censored." Could you clarify in your analyses essentially what that means, what you are reviewing?

DR. SRIDHARA: We didn't really go into details of who progressed, but as I showed in that graph, by week 1 there was 25 percent who were not there. So, yes, those are

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the only ones who were available for assessment of quality of life.

DR. FLEMING: So, in the analyses that you were able to validate that we are looking at for symptom relief, progressors were censored?

DR. SRIDHARA: Yes, but the denominator was everybody.

DR. PRZEPIORKA: Dr. Blayney?

DR. BLAYNEY: This is a question that is sort off the topic of response but could you clarify the relationship between AstraZeneca, the sponsor of this product, and Cedar Sinai Comprehensive Cancer Center, the major accruing organization, just for the record?

DR. BLACKLEDGE: I am happy to do so. Cedar Sinai Cancer Center is part of Salek Healthcare which employs a number of independent physicians. I don't know if Dr. Natale wants to comment further on that.

DR. NATALE: Salek Healthcare is a subsidiary of AstraZeneca that is completely independently managed. The physicians, including myself, who work in the Cedar Sinai Comprehensive Cancer Center are private practicing physicians who entered patients onto this clinical trial. My salary does not come from AstraZeneca. They don't influence my salary or my bedside practice.

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DR. PRZEPIORKA: Dr. Varricchio?

DR. VARRICCHIO: Just in terms of sort of where do we go from here and our comfort level with this data, the fact that there is no control group is one concern to knowing what is going on. But also we were told that the subjects were on quite a few concomitant medications that would address the symptoms in and of themselves. That data was not collected nor reported on the frequency of use and what was going on in terms of the people who were responding positively to a reduction in symptoms--what was going on with the other medications they were taking. So, I think, you know, if there is a next step, it should be a controlled trial and keeping track of the concomitant medications as well.

DR. PRZEPIORKA: Dr. Kelsen?

DR. KELSEN: A very brief question, it is clear you have been thinking a lot about the next step, no matter what is decided today, as far as a confirmatory trial. I am struck by the comments about how rapidly patients could be accrued to such a trial and that you would not have a question about accruing the patients. So, how large would that trial be and how fast can you do that to obtain the information that would then answer the questions that have been raised today?

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DR. BLACKLEDGE: Well, we haven't absolutely established the size or the power of the trial. We have an efficient recruitment mechanism and we would obviously try to recruit it as rapidly as we could, but we don't have any actual specifics as yet because we haven't agreed on trial design.

DR. PRZEPIORKA: If there are no further questions, we will go on to the next section where we will address the questions. The format will be to first discuss the questions before we take a vote. Before we start that part, I would like to again remind everyone here that we sit in advisement to Dr. Pazdur and Dr. Temple and I would like at this point to ask if either of you have any further instructions to the committee before we undertake the questions.

DR. TEMPLE: Actually, I just have one question because it is important to us later. The view was expressed that it would be easy, even if the drug were available, to randomize people in third-line therapy to, I guess you would call it, early treatment versus slightly later treatment. Could somebody elaborate on that? Obviously, if the drug is not available you could probably do that trial, but people seem to think that would be no problem and I just wondered why everybody thought it wouldn't be a problem.

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DR. LYNCH: I think the biggest point is that the time frame you are looking at is a relatively short time frame, and this would be a study that is important to do to be able to distinguish the robustness of the quality of life data. Because of the importance of this study and because of the fact that you are only asking patients for a 4- to 6-week crossover, I think it is a study that actually is a doable study, particularly early on.

DR. TEMPLE: Despite the feeling that we heard expressed here that the improvement in symptoms and all of those things is so very dramatic? This is an important question. One can only speculate obviously since you haven't done it yet, but you think people would be willing to enter such a trial even though the drug was commercially available?

DR. LYNCH: I would think so.

DR. FLEMING: On a related point though, this is probably raising a really key issue because what I am hearing there is a crossover that they propose would be occurring very rapidly in time, and by crossing over if, in fact, you did that very rapid crossover you really would be getting much more limited true comparative information and, obviously, you would be very substantially compromising any opportunity to really see if there is a survival effect, but

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even for progression or longer term or durable symptomatic relief comparisons you would be compromising that. So, I wouldn't think that the most informative crossover design would be one that would cross somebody over if they didn't show immediate symptom relief after the first assessment. That really wouldn't answer the question that we need to answer.

DR. TEMPLE: Well, it was really offered as a way to verify the symptomatic benefit.

DR. FLEMING: You raise a very good point. If this is available it is certainly going to be more difficult to do what would really be the more informative assessment as to whether or not there is truly clinical benefit. It would be easier to do something that would be very marginally informative, which would be crossing somebody over very rapidly in time.

Committee Discussion and Vote

DR. PRZEPIORKA: I think we are going to have actually more extensive discussion, but first I want to hear from Dr. Temple and Dr. Pazdur about anything else.

[No response]

Well, we have a number of issues that are set before us and the first question from the FDA is the FDA believes the relevance of the sum improvement data discussed

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above cannot be adequately evaluated with a randomized, blinded study with an adequate control arm. The two doses of ZD1839 show no difference in efficacy and are thus not adequate. Do you agree? Dr. Varricchio, do you have any opinions regarding this question in particular?

DR. VARRICCHIO: I think that it is a soft claim of efficacy of symptom management in this situation. Obviously something is going on but you don't know why and what might have caused the improvement in symptom management. So, I feel to really have a strong basis for saying that this drug is the cause of the improvement in symptom management you do need a randomized, controlled trial with a real no drug arm, not this drug arm. Whether it is placebo or best standard care, that can be discussed.

DR. PRZEPIORKA: Mr. Ohye?

MR. OHYE: I would like to make first a general comment, if I may. I would like to compliment the sponsor for carrying out these trials because I know they are difficult, and also embarking on the expanded access. I think that is very humanitarian and the committee should go on record to say well done.

I also think the FDA has done a good job in finding every blemish, every freckle, every micro-pimple in

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the trial, and that is their job because they have to look at this with an abundance of caution.

My general comment is I think when we look at all these questions we have to look at the fifth question that was proposed, accelerated approval, and we have to think in terms of the requirements for accelerated approval that were so adequately or so well explained to us on page 3, third slide by Dr. Williams. We have to look at the standards there and we have to bear in mind that the evidence that we have to have is do the data show that it is reasonably likely to show a clinical benefit, not that it has to be proven beyond reasonable doubt.

I think it goes without saying that we have met some of the other criteria that were dealing with a serious, life-threatening disease and that the question is whether it is reasonably likely to predict a clinical benefit. I think the data are very much in favor in that area. Thank you.

DR. PRZEPIORKA: Dr. Redman?

DR. REDMAN: I guess I will ask the biostatisticians, can you state with the information that is present that it did not have a negative impact, a negative aspect? Is that no?

DR. FLEMING: Well, there are many issues here that we are going to be discussing and, as has already been

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pointed out, there are serious limitations in interpreting these data in the absence of randomization. The data establish some level of plausibility that there could be a quality of life impact and, to the extent that it establishes that, it makes it more implausible that it is a negative effect. But, in fact, the risk for biases here, as we will articulate shortly, are so substantial that one would have to be very cautious about what you interpreted when you are saying is there adequate evidence of causal positive influence of intervention on these quality of life measures.

DR. PRZEPIORKA: Dr. George?

DR. GEORGE: Just a comment, I would like to come back to something that Grant mentioned in his slides that I think is very important and we can't lose track of. That is, the evidence for accelerated approval is not different than for ordinary approval. That is, we have to look for substantial evidence, and that is what I keep coming back to. Because of these potentials for serious biases in these studies I have a real problem coming to the conclusion that it is substantial evidence. My feeling is that obviously something is really going on. It is just too bad that we didn't have the direct randomized comparison so we can really know what the magnitude of that is. So, I just

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thought we ought to keep that in mind. I thought Grant had a very good point about that.

DR. PRZEPIORKA: Dr. Varricchio?

DR. VARRICCHIO: Just a thought that has occurred to me listening to this, if this drug did not have such a user-friendly toxicity profile we might not be considering some of the things we are considering. This is kind of low risk in terms of the toxicity profile, and maybe we are creeping out further out on the limb than we might if the drug had a more serious toxicity profile.

DR. PRZEPIORKA: Dr. Blayney?

DR. BLAYNEY: I would like to say two things. One, if this drug was more toxic, like in the ECOG study, it ought to be reflected in a decrement in the symptoms score. So, there is some reassurance, in my mind, that the lack of toxicity is reflected in the improvements here.

Like Dr. George, I am convinced that there is a signal here. We have wrestled in the past with very similar sorts of problems. It looks like there is a signal. A lot of people tell me that there is a signal, and I think this drug ought to be available. I am wrestling, and perhaps I shouldn't--that is your problem, wrestling with the regulatory and statutory burdens placed by the legislative

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branch on a government agency. So, that is where I have come down.

DR. PRZEPIORKA: Dr. Temple?

DR. TEMPLE: This question is the main one in which you come to grips with the plausibility of the symptom benefit. So I have to ask a question just in response to something that went before. There isn't any doubt that there is an effect. We don't have any doubt that there is an effect on a surrogate, that surrogate being tumor shrinkage. Nobody has challenged that; we don't disagree with the numbers. The whole question is whether that is reasonably likely to predict clinical benefit.

We have been offered by the company the option to believe that the evidence they have of symptomatic improvement is at least a basis for thinking it might correspond. So I have to ask my question. We are very accustomed to being suspicious of unblinded quality of life assessments as a general matter. One of the points that was made, although I must say not as strongly as I would have made it if I were the company, is that much of the symptom benefit is apparent before anybody knows whether there has been a tumor response. That is comparatively unusual, and we would be very interested in knowing whether that affects

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anybody's thinking about this or not because we are going to have to come to grips with it.

DR. PRZEPIORKA: If I could just paraphrase what you just stated, what we need to actually ask ourselves is, looking at the symptom improvement data in isolation, there may not be enough there to say this is really real. But in terms of looking at the symptom improvement data together with the response data, does that make a more plausible story?

DR. TEMPLE: Yes, and just one more point. Usually in refractory disease we have a history of accepting tumor response data as reasonably likely to correspond. The problem here is that in the first-line therapy where that question was tested--nothing; no hint; no nothing. So, that makes it a somewhat unusual problem and the potential that you might believe a little bit in the symptom data. The question is, and Tom has been raising this, how should one believe in that. I was particularly interested in one feature of it which is that the symptom response appears to be reported before anybody knows there has been a tumor response and I wondered if that made people think one way or the other about it.

DR. PRZEPIORKA: Dr. Reaman?

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DR. REAMAN: That certainly was very important for me, but equally important was the fact that there was a cessation of collecting symptom response data when patients progressed. So I don't know how you balance out those methodologic shortcomings.

DR. PAZDUR: Let me just follow-up to Bob's question. Many of the drugs that we have gotten in for accelerated approval on a single-arm basis do not even have any attempt to look at quality of life data or symptom control. How would the committee view this in a refractory disease setting if we were simply dealing with a 10 percent response rate here, with the given confidence intervals, and that is all we had, period? Is that reasonably likely to predict clinical benefit if we didn't have the first-line data?

We have approved drugs, for example CPT11, as Grant pointed out, with a very similar response rate. I am not going to cut hairs here between a 10 percent response rate and a 12 percent response rate or a 15 percent response rate. Obviously, we felt comfortable enough giving accelerated approval to that drug. We didn't have the first-line data of CPT11 at the time of approval but, nevertheless, we felt comfortable enough to go ahead with that approval.

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So, pretend we didn't even have the symptom benefit analysis, would a 10 percent response rate be predictive, or reasonably likely to predict clinical benefit? And, then a question for you that we frequently get from sponsors is how low can you go?

[Laughter]

DR. PRZEPIORKA: Is that question number two, if I read question number two correctly? Let's finish one first and immediately go there. If there are no other questions, let's go ahead and take the vote. The question is, to rephrase this, the symptom improvement data discussed above cannot be adequately evaluated without a randomized trial. Do you agree? We will start with Dr. Martino. Please state your name before giving your vote.

DR. MARTINO: Silvana Martino. Yes, I do agree.

DR. PAZDUR: Could you repeat that?

DR. PRZEPIORKA: The data cannot be evaluated adequately without a randomized trial. Do you agree?

DR. MARTINO: Yes, I agree that it cannot be evaluated. I understood you correctly. Thank you.

DR. BLAYNEY: Doug Blayney. No, I disagree.

DR. VARRICCHIO: Claudette Varricchio. I agree.

DR. BRAWLEY: Otis Brawley. I disagree.

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DR. PELUSI: Jody Pelusi. I disagree but I would put a little caveat in here. It would be really helpful to see those patients who then went off study, to really show us their quality of life data as well to help us balance that.

DR. REAMAN: Gregory Reaman. I agree.

DR. PRZEPIORKA: Donna Przepiorka. I agree.

DR. FLEMING: Tom Fleming. I agree but I would like to actually expand a little bit on the rationale. I think interpreting symptomatic response data in this type of a setting is treacherous. It has long been recognized to be treacherous. The FDA has given a very clear articulation of all of the reasons.

I would like to expand briefly on some of them. It is an open-label trial. Placebo effects clearly exist. The fact that there are some immediate improvements may well be due in part to therapy; undoubtedly are due in part to a placebo effect and not necessarily a true treatment effect. We don't know what the contributions are by ancillary care. I am bothered by the fact that we are not really doing an intention-to-treat analysis. We haven't truly looked at what is the symptomatic response across the board in all patients. Why is it not relevant to know what the symptom response is when someone progresses? Why do we stop

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assessing it at time to progression? To really understand this we should be fully assessing this.

Then we get into these analyses about trying to provide credibility of response by looking at correlation with symptoms and vice versa and with survival. We have been down these pathways for 25 years in oncology research, recognizing how fallacious this reasoning may be. Response may simply be a marker for intrinsically better patients who would have had a better symptomatic outcome even without treatment.

Essentially, when we look at a marker, let's say it is tumor response and a clinical endpoint, as I believe symptom improvement would be if we showed it, looking at whether there is a correlation is a necessary condition but not a sufficient condition for validity as a surrogate, meaning that if there isn't a correlation then one really does have a difficulty in being able to interpret whether or not, in fact, one basically would say it can't be a valid surrogate. But if there is a correlation between response and symptomatic improvement it just gets you in the door. It just means that there is now at least a possibility and, in fact, maybe only a limited possibility that it truly is representing treatment effect.

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Essentially what has long been recognized is when you have a class of agents and you are looking at validating a surrogate, you really need to have studies that look at the treatment effect on the marker and the treatment effect on the clinical endpoint to really understand, for that class of agents, if the effect on the marker is reliably telling you about the effect on the clinical endpoint.

As we will say shortly, the sponsor did a remarkable job on the INTACT trials. I am very confused if they didn't have an intention of using those trials as the basis for establishing clinical benefit why the reliance in accelerated approval was just basically on the 39 trial. Why didn't we have a control arm, in essence, to be able to validate that there truly is a treatment effect on the symptom response?

So, the bottom line is these data may well provide clues and encouragement for doing a properly controlled trial, certainly though, they can't be interpreted as providing adequate evidence to establish that treatment is actually influencing symptom relief, or even, the words the FDA has used, providing substantial evidence for such.

DR. REDMAN: Scientifically, I think the answer to the question is yes, but also with the caveat based on the

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toxicity profile that the drug surely didn't have a negative impact on quality of life.

DR. KELSEN: David Kelsen. I agree.

DR. CARPENTER: John Carpenter. I think I disagree but that is only a partial disagreement. I don't think these numbers are really adequate but I am very influenced by the degree of improvement in symptoms without any knowledge of the response data.

DR. CHESON: I am Bruce Cheson. I still have this feeling that when patients are off their chemotherapy they start feeling better and some of them just don't start feeling better within a month but they feel better over a longer period of time. With this study design, I think that the number of patients influenced by that is not discernible given the information we have. So I agree.

DR. TAYLOR: Sarah Taylor. I agree.

MR. SIMON: Tom Simon. I disagree.

DR. PRZEPIORKA: Of the 14 votes, 9 agreed and 5 disagreed.

I think Dr. Pazdur has already adequately stated the second question for us. Given the lack of clinical benefit in 2 large studies of ZD1839 in combination with standard first-line chemotherapy, is study 39 response rate of 10 percent in 139 patients with resistant or refractory

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non-small cell lung cancer reasonably likely to predict ZD1839 clinical benefit? Dr. Carpenter, do you have comments?

DR. CARPENTER: John Carpenter. I am not too influenced by the Phase III results here because you are giving an anti-proliferative drug with 2 drugs that depend on cell proliferation for their efficacy. It is very much like giving hormonal therapy and chemotherapy for breast cancer where the response rate doesn't go up, and if you give them together they will change the outcomes. I think the model may be fairly true here so I would negate those 2 Phase III studies and say that what they tell us is that we didn't know how to study this drug, and I think everybody will agree that the most robust evidence all afternoon is that when you give this along with chemotherapy people don't do any better. There was no serious discussion of that.

I think if we are going to undertake this right, we are going to have to look at the early studies just based on their own as a single agent. It seems to me that it is clear there is some prediction. What we don't get, because of the inadequacy of the trial data we have here, is how strong that signal is. But it is very clear that some people are getting better and some people are getting

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clinical benefit and at least nobody, so far, has picked out a way to identify those.

I would submit to the company that if you look at who gets better on this drug, besides doing all the fancy gene analysis, if you took a simple immunoperoxidase stain and picked out slow-growing tumors everybody who gets better on this drug has a long and natural history in a tumor that grows slowly, and if you hypothesis were that people in the lowest quartile do better on this drug, you might figure out who gets better on this drug pretty quickly, and without doing too many elegant genetic studies.

So, I think there is a signal. I think that 10 percent is hard as far as the response rate, and I think it is reasonably likely that that predicts clinical benefit. Given the inadequacy of the data we have, I would say yes.

DR. PRZEPIORKA: Dr. George?

DR. GEORGE: Maybe I can delay some of my comments until item 4 when I guess we are going to discuss additional trial designs because that may provide some information about what we think about this first-line trial as providing evidence in this case. But I want to point out that it is certainly possible that an agent such as this, with a low toxicity profile could, indeed, provide clinical benefit as measured by symptom improvement or quality of life and have

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absolutely no effect on survival. If that were true then, of course, that is a clinical benefit. It is not survival benefit but I think sometimes the question is phrased as if we always mean survival and it is clear in the regulations and the way things are stated that it is not just overall survival. In fact, in this trial I asked the question earlier whether we had any information about quality of life or symptom improvement even in that first-line therapy and we have no evidence of that whatsoever at this point. So, it is clear that there is no survival benefit so it is certainly possible.

Now, the question of whether it is reasonably likely to predict such things, then we run into an area of metaphysics and I can't give a probability of what reasonably likely is, but it is clearly possible that it could.

DR. PRZEPIORKA: I will just weigh in with my two cents here. I don't know of anyone with non-small cell lung carcinoma whose cancer went away by itself or developed a PR by itself. So, very clearly there is activity here, and very clearly 10 percent is substantial as a third-line agent. I don't know that you could say for all non-small cell lung cancer. I think that is where some difficulty may

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arise, but very clearly there are patients who have derived clinical benefit from treatment with IRESSA. Dr. Cheson?

DR. CHESON: The response troubles me I guess. You can take the hematology out of the doctor but not the doctor--you know, we deal with tumors that respond so it is a bit problematic. But just looking as someone who has done clinical research for a number of years, you would be hard-pressed to find a study in which the Phase III data, particularly response rates, were better than the Phase II data. So, this 10 percent, with confidence intervals going down to 5.6, may actually be optimistic in the grand scheme of things. So, that gives me significant room for pause about substantial clinical benefit. I thoroughly agree that some people really have had astounding benefit but what is that going to be when the drug is used to treat tens of thousands of patients?

DR. PRZEPIORKA: Dr. Kelsen?

DR. KELSEN: I agree with Dr. Pazdur's original comments, or I will try to answer his original comments. A 10 percent activity in third-line therapy in a variety of cell tumors, and colorectal is a really good example, is meaningful. Whether it is a surrogate for a higher level of benefit is difficult to say today, but it is a surrogate for activity and this drug does have activity, and the

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risk/benefit profile for this agent is substantially better than the risk/benefit profile for irinotecan and oxaliplatin.

DR. PRZEPIORKA: Dr. Fleming?

DR. FLEMING: Certainly there is evidence here that there is biologic activity. The question is how impressive is that evidence and how reliable is it to indicate true clinical benefit? We have two studies. We have the 16 study and we have the 39 trial, and the 16 study--just going back to what the team had intended, they were trying to discern between a 5 ruling out a 5 as an inadequate response rate, against a 20 percent response rate. So, according to their statistical criteria they needed to see a 13.3 percent response rate for success. They had less than that in the trial looking in the non-Japanese patients.

As we had discussed earlier, if you focus on those people that, in fact, truly were first- and second-line progressors there was only 1 responder. So, there is very limited information in that 16 trial about whether there is really an interesting or impressive response rate in third-line. We are left with the data in the 39 trial and essentially we are looking at the basis of that as 22 responses with, as Bruce was pointing out, confidence

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intervals that go down to 5 percent. In fact, if you follow the protocol it is 97.5 percent confidence intervals that go below that.

Then, as the FDA has pointed out, there are a lot of favorable characteristics in these people who responded. So, how impressive in the context of this trial are these responses? It appears, as has been presented to us, that the strategy that was in place here several months ago, prior to the release of the INTACT trials, was that the INTACT trials were going to give us the truth. Essentially, they were marvelous studies, absolutely fabulous studies conducted by the sponsor randomizing a thousand people per trial, getting 750 deaths per trial giving, in pair-wise comparisons, 500 deaths.

Essentially, these types of studies are incredibly informative and reliable in their assessments allowing us to detect, with reliability, even a 25 percent reduction or what would correspond to an improvement in survival from 10 months to 13.3 months.

What do the data show? The data show estimates that are slightly unfavorable, about a 10 percent increase in death rate in the 14 trial and no difference in death rate in the 17 trial. If you put this data together from these two studies, what you get is a remarkable level of

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precision. You have a thousand deaths per pairwise comparison to assess.

So this is not just a matter of, we didn't achieve statistical significance. This is a matter of these studies nailed with great precision exactly what the true effect is going to be in first-line. Essentially, what that true effect is is a loss of one week in overall survival on a ten-month median for the control arm, a loss of one week at 500, a loss of two weeks at 250, with a precision two standard errors of within five weeks.

What that means is these agents could be as unfavorable as reducing survival by six weeks and as favorable, best-case scenario, three-week improvement which is one-quarter the level of benefit that would correspond to what the study had sensitivity to detect.

So I am left with a philosophical debate. These studies clearly conclusively establish providing consistent and compelling evidence that there is no effect on survival, not just that we have failed to achieve significance. There is no effect in the global population on survival. Response rates and TTP were also negative.

What is the relevance? Clearly, it is always true that if you are really interested in survival effect in third-line that first-line results could give either false-positive or false-negative conclusions, false-positive being

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maybe you have an effect earlier on on survival if you deliver IRESSA earlier in time. If, in fact, the studies had been positive, would the sponsor be asking us to step back and reexamine their relevance to third line because you had agreed they would be relevant up-front.

Yes; in fact, they could also be false negatives and that is the question that is validly being asked now. But hindsight is twenty-twenty. To say, in retrospect, gee, we can explain now why these results are providing compelling evidence of no-survival effect, aren't relevant to the third line, I would argue we should be incredibly cautious about that interpretation. That is clearly a data-driven interpretation.

Yes; it may be true, but the bottom line is there clearly is relevance to those data and those data have to be factored in significantly. With that being factored in, it provides a great influence, I would argue on whether response rates in twenty-two responders in the uncontrolled 39 trial is compelling.

DR. PRZEPIORKA: Dr. Carpenter?

DR. CARPENTER: I think I would look at the Phase III slightly differently but only from an interpretation standpoint. They show, as well as I can imagine, that if you add these two drugs together, the way they did, that there is simply a vanishingly small chance

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that there is any real improvement. Would you agree with that?

DR. FLEMING: I agree.

DR. CARPENTER: I think the question is limited by the way we asked it and so I don't think they tell us, necessarily, what the drug does in front-line therapy. They just tell us that the way we asked the question, or the way they asked the question, that we feel confident that, if you do it that way, there is no advantage to adding this drug. But I wouldn't, for a minute, conclude that if you asked the question differently with a different type of study that you would, necessarily, get the same answer.

DR. FLEMING: You mean adding IRESSA first-line to a different combination; is that what you mean?

DR. CARPENTER: I am talking about separating the IRESSA from the chemotherapy. I think what they did was to combine them as if it were a third chemotherapy drug and, like other third chemotherapy drugs, it didn't work and we feel pretty confident that it didn't.

What I am saying is that answers that we have are limited by the way the questions were asked.

DR. FLEMING: Just to clarify. Yes; I do agree that, in essence, we are limited to the interpretation of what these studies were designed to address. When the result is negative, to step back and try to assess why is

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very relevant. But to say they are not relevant to third-line is stepping back too far.

DR. CARPENTER: I may have not stated my question right. Excuse me.

DR. PRZEPIORKA: Dr. Brawley.

DR. BRAWLEY: One possible design of the trial would be, for example, to take individuals treated with first-line chemotherapy who respond who have a very high likelihood of relapse and then giving them IRESSA at that point to see if it sort of prevents relapse or prevents recurrence. That is a question that has not been addressed and it may--there is some scientific reason to believe it actually might work.

But they really have not--I mean, the drug's clinical benefit, in my mind, can be very different from does the tumor respond. So I think I have given you what my answer to No. 2 is going to be.

DR. PRZEPIORKA: Dr. Pazdur.

DR. PAZDUR: I wanted to kind of go over this question before you vote on it because I think there are several things here that the committee has to understand. First of all, when we are asking this question, this is tantamount to should the drug be approved on accelerated approval. It is Question No. 5 of the sponsor. So you could just skip that Question No. 5. This is it.

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We were rolling around on our merry way here in our Division with this 10 percent response rate and the symptom benefit. We believed that basically we weren't going to be taking a look at the symptom-benefit work per our previous discussion but we did look at this 10 percent response rate.

Then we were kind of floored when the two large studies came into play. This is really what Tom was getting at here, that this is the point of the question. We are not asking about a 10 percent response rate. As I told Dave Kelsen, we approved a drug with a 12, 15 percent response rate. We already have that history of doing it. That is not the question here.

The question is in the context of these two other trials. If we didn't have these trials, we probably wouldn't even be here. We would have already approved the drug on our merry way. We have this data here. We can't just ignore it. We have to take a look at the whole data package when we look at the approval of the drug.

The question here is not the 10 percent response rate. It is in the context of these two other trials that are front-line trials. The observation that this drug does not work with chemotherapy is an observation. It is not an explanation, and I have not heard from the sponsor a viable explanation of why these trials have failed.

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If they would like to get up now and give it, I would like to hear it. George?

DR. BLACKLEDGE: Well, Dr. Pazdur, I can hypothesize as well as anyone else. It is very clear that whatever effects you are seeing with doublet chemotherapy, you cannot, it appears, add to. That appears to be the case, whether it is another chemotherapy agent or whether it is a novel agent of this kind.

I don't have the explanation yet, and I don't think anyone else does. All I can say is that it does seem to be an emerging pattern for both chemotherapy agents added as a triplet and also for novel agents added as a triplet.

Whilst I don't think we can ignore the data, I do think that it looks an extraordinarily different situation from where we have clearly seen agents, noncytotoxic agents, giving real benefit as monotherapy in various different situations when they haven't shown any additional benefit in combination.

So I am not sure I agree with Dr. Fleming completely. I think that, whilst you must take these data into effect, use as a monotherapy for clinical benefit and for response which leads to clinical benefit is a very, very different situation.

DR. PAZDUR: One of the problems that I see with that answer, George, when you take a look at this drug when

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it is favorable to your situation, you may look at it as a chemotherapy drug. When it is not favorable to your situation, you take a look at it as a special agent here which is somewhat perplexing to me.

I am fully aware of the doublet, triplet information in lung cancer. The question here, we have no other situation that I know in medical oncology, and I am having a tremendously difficult time trying to figure out why, in a first-line setting, you would not have some effect here.

Obviously, AstraZeneca has gone on an extensive development program not only in lung cancer but in a myriad of diseases with chemotherapy and this agent, I assume, based on some preclinical rationale, we got the results of this trial. It has thrown a tremendous monkey-wrench here. What is the explanation? That is the essence of this question and that is what needs to be discussed here, not the 10 percent response rate.

We have approved drugs. I don't know how low is low and how low you can go, but this is the issue here of the 10 percent rate, albeit it might even go down to 5 percent. I don't care. The question is these first-line data being there and that is the issue and that is the crux of why we brought this drug to the committee.

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DR. FLEMING: Could I add just briefly to Dr. Pazdur's question for the sponsor to respond to. If the sponsor didn't anticipate that the two first-line studies would, in fact, provide the validation of the surrogate effects, justifying the accelerated approval, what was the strategy since, essentially, the accelerated-approval strategy indicates that postmarketing studies would usually be under way.

So, if you prospectively, before you saw the results of the first-line trial, already knew that those first-line results weren't going to be relevant to efficacy in third-line, what third-line comparative randomized studies were already under way as the basis for validating this accelerated approval in third-line?

DR. BLACKLEDGE: We had no randomized third-line studies underway. The reason for that is that when we planned Study 39, we discussed extensively with our investigators about possibilities of randomization. They advised us that, certainly within the context of the United States, that would be extremely difficult to carry out.

In addition to that, the studies that we carried out in third-line were validation of the Phase I data that we saw where we unexpectedly saw responses and it seemed logical to carry out a Phase II in that setting. That is the basis that we went forward with accelerated approval.

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Now, we are clearly faced with a difficult situation. I don't think any one of us expected the results that we saw in the INTACT studies although, in fact, if you look at other data that has emerged since we started them, maybe you might have expected that we wouldn't see that effect.

I don't believe it invalidates, however, the response that we see and the strong suggestive evidence, but not proven evidence, of a clinical benefit linked to those responses.

DR. FLEMING: Just in completing the response, then, to this response, your approach in the INTACT trials was remarkable. You did a remarkable effort to come forward with outstanding trials to establish whether or not there were effects on survival and other clinical endpoints in first line.

As a result, it seems to be a paradox that you have mounted the accelerated approval in third-line based on the 39 trial without any backup plan for how you were going to, in fact, be able to validate as accelerated approval requires, it surely leaves me to think you actually were anticipating a favorable result in INTACT that would serve as a basis for validating and, in which case, if we then took that logic to the limit, we would say, you did view

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that there would be relevance to what you see in third-line in the first-line trials to the third-line indication.

DR. BLACKLEDGE: We have never linked the third-line submission with the first-line submission. Clearly, if there was a positive result, we would have been very pleased with that and so would the patients. But this is not the only clinical-trial program that we are carrying out. We are carrying out trials with monotherapy in adjuvant situation.

We have maintenance studies going on and we would be more than happy, as we have described earlier, and as our investigators have described earlier, to attempt to validate the data that you have seen today from Trial 39 in a randomized setting.

DR. PRZEPIORKA: Dr. Carpenter?

DR. CARPENTER: John Carpenter. Since we seem to be pressing in on this question of should we approve this drug or not, I wanted to get a couple of comments in if it is okay. I think that we could all speculate on the reason that the third-line therapies don't--I mean, the first-line therapies don't validate the results seen as a third-line drug. But that may be because of the mechanisms of action of the drugs and they would be counterproliferative.

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That is an hypothesis but it certainly is a testable one. It seems very clear that slowing indolent tumors are the ones that get better here.

If this drug--and I will be very favorable towards this drug with the limited evidence that we have, partially because there is no viable competitor in this situation. But I think there is a whole flood of studies that could be done to elicit out the way to use this drug. You could study performance-status-2 patients and test this versus anything since nothing else works very well.

I think there is a study of vinoralbine in older patients. That is certainly doable. You can use it in a short period before front-line chemotherapy with a crossover. You could use it as an adjuvant with a placebo control after frontline chemotherapy and sort this out. All these things are easily doable.

You can do the proliferation assay and see if you can predict who gets better on this. All those are easily doable studies. So I think I am going to come out in favor of making this available with the proviso that a bunch of studies about just how to use this drug need to be done and should be done.

DR. PRZEPIORKA: So, Dr. Pazdur, I think your question is not just is there any evidence for clinical benefit for this drug, but do the results of the two

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randomized trials actually suggest more or less that the results that we see in the single-arm study makes a difference.

I have to actually weigh in with Dr. Carpenter. I think it is very clear there is clinical benefit in the single-arm study, but I think the questions being asked in the randomized studies are completely different questions. Although we don't know why, I am not sure we actually know that the inhibition of the kinase is actually the mechanism of action that this drug uses because there doesn't seem to be any correlation with EGFR expression.

I don't know that anybody right now could actually answer your question about why the combination does not work because I don't think we have enough information available.

DR. TEMPLE: Maybe everybody said this and maybe it is clear to everybody, but we need to be quite sure. As Rick said, if all we had was the response rate in third-line, we might not even have brought it here because we have been approving drugs with reasonable response rates in refractory disease on the basis of that right along.

We were, however, surprised by a negative result in first-line which, as everybody has noted, was a complete surprise to everyone or they wouldn't have done the trials. The fundamental question is does that shake your belief that

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a 10 percent response rate is reasonably likely to predict clinical benefit, just to be clear.

That is why we are asking you, because we would ordinarily have been comfortable with that response rate. Should we not be comfortable anymore because of those trials? That is really the question.

DR. PRZEPIORKA: With all due respect to the statisticians, I think what we have heard from the clinicians, both from the sponsor and on the committee discussing is we don't think the results of the randomized trials are that clinically relevant to our opinion of the single-arm trial.

But I could take a vote and let you know for sure.

DR. PAZDUR: That's appropriate.

DR. PRZEPIORKA: So the question is, given the lack of clinical benefit in the randomized trial, do you still think that the response rate of 10 percent using ZD1839 is likely to predict clinical benefit?

Dr. Martino.

DR. MARTINO: Yes; I do. I am discouraged, but not totally devastated.

DR. BLAYNEY: Doug Blayney. Yes.

DR. VARRICCHIO: Claudette Varricchio. Yes.

DR. BRAWLEY: Otis Brawley. Yes.

DR. PELUSI: Jody Pelusi. Yes.

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DR. REAMAN: Gregory Reaman. Yes.

DR. PRZEPIORKA: Donna Przepiorka. Yes.

DR. FLEMING: Thomas Fleming. No.

DR. REDMAN: Bruce Redman. Yes.

DR. KELSEN: Dave Kelsen. Yes.

DR. CARPENTER: John Carpenter. Yes.

DR. CHESON: Bruce Cheson. No.

DR. TAYLOR: Sarah Taylor. No.

MR. SIMON: Tom Simon. Yes.

DR. PRZEPIORKA: The vote is 11 yes and 3 no.

The third question regards the expanded-access protocol. We had some discussion regarding expanded access and single-patient exemptions and single-patient protocols. So, Dr. Temple, Dr. Pazdur, if you just want to set the stage regarding specifically what that means, especially for the new members, of the committee, that might be helpful.

DR. WILLIAMS: This question becomes a little more difficult after your answer to No. 2. We will have to decide what to do with your answer to No. 2. Theoretically, supposing the drug is not approved, there is the issue of expanded access. I think the company has mentioned that they would have to reexamine to determine whether they thought it was ethical.

We had two ODACs where we discussed expanded access and we talked about the level of activity that should

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be seen, et cetera. If this were to be of such a level of activity that we would not approve it for accelerated approval, the question would be would it still be indicated to allow widespread expanded access.

I guess we could go ahead and have that discussion as you wish.

DR. PRZEPIORKA: Comments? Dr. Kelsen?

DR. KELSEN: Actually, I was initially heartened and then a little bit taken aback by two contradictory comments from the sponsor. First, I thought I heard that it would be very straightforward to perform a confirmatory trial either before accelerated approval, while the expanded-access program was open, or after accelerated approval, that, in either case, it would be quick to achieve definitive opinions to clear the air because patients would readily approve randomized to a study in which they initially did not receive the drug and then, at sometime, they received the drug.

That is what actually swayed me quite a bit because I could see you doing that before accelerated approval with the expanded-access program wide open.

Then I was a little taken aback by the answer that we got that the reason that we didn't see Phase III data right up front today, which would have clearly answered the

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question, is that it was felt that patients wouldn't accept such a randomization.

Maybe it would help if the sponsor could clarify their position.

DR. BLACKLEDGE: What I was referring to, Dr. Kelsen, was the situation two years ago when we began our trial program and the expanded-access program. We have been in regular discussions with both the FDA, with NORD, with medical ethicists and patient advocates to review the expanded-access program as we move along.

We are certainly not going to make any instant decisions and we would want to discuss the situation extremely carefully with all those people, particularly the FDA. Of course, we would want to be in a situation where we were able to carry out a confirmatory study.

We didn't speak to the patients about the original randomization. We spoke to investigators at that time. But now you are hearing from investigators who would take part in those studies that they feel, in view of the changed environment and changed need, that it would be possible to carry that out.

Now, we want to work together with all the involved stakeholders to make sure that we come to a happy resolution of this. We began the expanded-access program in the anticipation that one day we would stop it. Clearly, we

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would like to do that as soon as possible because we would like to see the drug approved with accelerated approval.

We would also like to do the confirmatory study as quickly as possible and, therefore, we would like to achieve some kind of balance so that we could do the study and yet not deprive patients of the benefit that they are gaining.

DR. PRZEPIORKA: Just a comment. I recall, in our discussions, that the program should be set up so that patients who are eligible for any studies would not be allowed in the expanded-access program. I think that is a very valid way to continue if this program does stay open. But I think it is also very important, now that we have seen the response rates and that there may be certain subsets of patients in whom the response rate is highest and others in whom there is no response, and especially there is no valid reason to use it with chemotherapy, that that is something that absolutely has to be given to the patients prior to their making a decision to take this drug.

DR. PAZDUR: Donna, we have corrected the informed consents to reflect these recent INTACT trials.

I do want to mention one thing. There are 12,000 patients on expanded-access trials which is a huge number of questions. There are a huge number of patients and there are a huge number of questions that are unanswered about this drug.

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I want to step back. This is something that we are trying to encourage sponsors to do is to start looking at other trials that could be done within the context of a more expanded research program with a particular drug. Even if they were not meant for registration or to fulfill a new indication, or even to just give us more idea about what would be a better use of this drug, specific populations, populations that this drug would not work in, rather than just giving everyone, 12,000 patients, this drug.

The best way to get information for everyone in society is for patients to be going on clinical trials. We would like to work with sponsors more to design other trials. For example, in the third-line setting, could we have used a point analysis of time to progression where patients could have gone on a chemotherapy regimen that their doctors agreed to versus this drug and cross over at the time of progression to IRESSA looking at a time-to-progression endpoint.

Everybody would get the drug. Some people would get it a little later than the others, but one would have access and get more information on this drug.

We really would like to emphasize the best way for us to get information is randomized trials and is to look at trials in a more close way. I think this would give us much more confidence in approving drugs in the long term.

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DR. PRZEPIORKA: Any other comments on Question 3? Hearing none, let's move on to No. 4. Regardless of whether ZD1839 is granted accelerated approval for treating non-small-cell lung carcinoma, additional trials may be needed. Please discuss any potential study designs that will demonstrated ZD1839 provides clinical benefit to non-small-cell lung cancer patients.

I think we had some initial ones. If anyone wants to underscore their favorite design or indication, now is the time to discuss it.

Dr. Blayney?

DR. BLAYNEY: Given what we have seen and our experience, I think it would be reasonable to ask the question, front-line in untreated patients, does this drug offer a benefit over--pick your chemotherapy. I would probably pick a good performance status, relatively good prognosis, patient population.

But I think, from my point of view, that is an ethical question to ask.

DR. PRZEPIORKA: Dr. Martino?

DR. MARTINO: I want to simply follow up on that. There is a design in front-line that has been mentioned around the table and that is actually looking at a new agent--this would be the new agent--in place of chemotherapy. I think that would allow us to, first of all,

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look at this agent up-front but, also, if it turns out to be as good as and, perhaps, better than chemotherapy, would be a nice alternative.

DR. PRZEPIORKA: Dr. George?

DR. GEORGE: Just a comment about the crossover designs that have been mentioned or the early and late IRESSA, say, in the third-line setting, there are a lot of problems with that. I just wanted to make sure everybody is aware of that, that it might be easy to get--it might be a practical issue of getting patients on the study but there is a real serious problem with--you, first of all, have to be very careful about the time to progression, making sure the blinding is working properly so you are not biased in deciding when somebody has progressed so that they can get IRESSA or something.

But just the whole issue of how soon you do that is going to cause you to be very limited in your kinds of conclusions. If that were the kind of follow-up study, I would be kind of skeptical of whether whatever came out of that would really prove or validate the clinical benefit of IRESSA.

So that just kind of bothers me. It is possible to do but it would need to be carefully thought out.

DR. PRZEPIORKA: Dr. Varricchio?

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DR. VARRICCHIO: I would to suggest that, given the hints that have come from the trials that we have been hearing about, that any subsequent trial be designed so that it could look at stratifications in the analysis that might let you be able to begin to look at predicting which subset of people this drug would be most effective to be used in.

DR. PRZEPIORKA: Dr. Fleming?

DR. FLEMING: This is a difficult issue because whether accelerated approval is granted or not, the efficacy has not been established. The issue on the table here was not whether full approval should occur. It is whether accelerated approval should occur.

So whether or not FDA grants accelerated approval, it is recognized that efficacy has not been established and there needs to be a timely conduct of adequate and well-controlled studies to achieve that evidence.

Many of us have argued for a long time that accelerated approval has many advantages and disadvantages, advantages if there is adequate evidence to establish plausibility of benefit, it provides earlier access. However, at the risk of providing earlier access to interventions that haven't been truly proven to have a favorable benefit-to-risk profile and also, at the significant risk of being able to do a timely assessment--i.e., if there is accelerated approval, we had already heard

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from the sponsor that they had reservations about mounting the Phase III comparative or Phase IV postmarketing comparator trials without accelerated approval.

Now, if there is accelerated approval with wide access, not access--an expanded access limited to those people who wouldn't be eligible for a study but to anyone who would choose to get access, is it logical to think that we are going to be able to mount a truly informative randomized comparative study to reliably assess effects on clinical endpoints.

It could be argued, well, sure we will do a crossover study. As Dr. George has pointed out, they can be very problematic in interpretation, particularly if you offer crossover at a relatively early point in time. So let's suppose, based on what I am hearing, that people are not so willing to take a failure in first-line and, in any way, argue that that should give us less confidence in third-line.

I think I would ask, then, under that logic if accelerated approval is granted, give me a third-line trial that is a randomized comparative study that will truly establish in a timely way efficacy on clinical endpoints. That is going to take several hundred patients properly randomized and followed for an adequate duration of time to

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be able to meaningfully establish the benefits at least on symptoms and, potentially, even on survival.

I have serious concerns as to how that is really, truly going to be something that can be done in a timely way as the regulations require if, in fact, accelerated approval is granted.

DR. PRZEPIORKA: Mr. Ohye?

MR. OHYE: When accelerated approval is granted, it is only granted in the United States. So there is Canada and other countries where this study can be carried out. I would also like to add that, before I retired, I was a competitor of AstraZeneca. As a competitor, I was very much impressed with the level of research that they are able to carry out because they have research centers in Sweden, which is a major scientific center, and they have research centers in the U.K. and in the United States.

So, with this worldwide capability and the brain power that they have available, I have every confidence that they would be able to come to an agreement with the agency on the appropriate study and carry it out in a timely fashion.

DR. FLEMING: And you are confident that the results that would be done in other settings would be truly relevant? We have already seen the differences in ethnicity

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with the Japanese and U.S. That doesn't cause you any concern?

MR. OHYE: I think the challenge has been set down before the company and, while I can't speak for the company, I have competed against this company and I know that their capabilities are formidable.

DR. PAZDUR: Tom, the drug is approved in Japan, so doing the trial in Japan would not be an option. The EU community; we have accepted lung-cancer trials from Western Europe and even Eastern Europe. So we feel confident in that aspect of quality of data and comparable results to the U.S.

DR. PRZEPIORKA: Hearing no further comments, I will adjourn the meeting. Thank you.

[Whereupon, at 3:35 p.m., the meeting was adjourned.]

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