FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

convenes the

ONCOLOGIC DRUGS ADVISORY COMMITTEE

The verbatim transcript of the ODAC Meeting held on Friday, June 2, 2006, at 10:00 a.m. before Kim S. Newsom, CCR-CVR, Certified Court Reporter in and for the State of Georgia, at the Omni Hotel at CNN Center, Atlanta, Georgia.

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Legend of the transcript:

[sic]	Exactly as said
[phonetic]	Exact spelling unknown
[inaudible]	Inaudible or simultaneous speech
--	Break in speech continuity

P A R T I C I P A N T S

(By Group, in Alphabetical Order)

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(Continued)

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(Continued)

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P A R T I C I P A N T S

(Continued)

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P A R T I C I P A N T S

(Continued)

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P R O C E E D I N G S

10:02 a.m.

DR. MARTINO: Good morning, ladies and gentlemen.

This is an ODAC meeting. The committee will discuss the following new drug application, (NDA) 21-986, proposed trade name Sprycel™ (dasatinib) tablets from Bristol-Myers Squibb Company, with proposed indications for (1) the treatment of adults with chronic, accelerated, or blast phase chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib, and (2) the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia and lymphoid blast chronic myeloid leukemia with resistance or intolerance to prior therapy.

At this point I'd like to ask all of you to either turn off your cell phones or to put them on vibrate, but do whatever you need to see to it that you don't interrupt the proceedings.

And the next item of business, I would like the committee members to introduce themselves, your name and where you are from, please. And we will start on my left, please. You need to press the microphone. Once it turns red you ar on.

DR. BERMAN: Dr. Ellin Berman, Memorial Sloan-

Kettering Cancer Center.

DR. KARANES: Chatchada Karanes from City of Hope Cancer Center.

DR. GOLDMAN: I'm John Goldman from the Hammersmith Hospital in London, but currently I'm working in the Hematology Branch of the NHLBI, NIH, in Bethesda, Maryland.

DR. REAMAN: Gregory Reaman, the Children's Hospital, Washington, D.C., and the George Washington University.

MS. HAYLOCK: Pamela Haylock, oncology nurse, University of Texas Medical Branch in Galveston.

DR. LEVINE: Alexandra Levine, University of Southern California, Norris Cancer Center.

DR. BUKOWSKI: Dr. Ronald Bukowski, Cleveland Clinic, Taussig Cancer Center, Cleveland, Ohio.

DR. ECKHARDT: Gail Eckhardt, University of Colorado Cancer Center.

DR. MARTINO: Silvana Martino, Medical Oncology, The Angeles Clinic and Research Institute in Santa Monica.

MS. CLIFFORD: Johanna Clifford, Executive Secretary to the ODAC, FDA.

DR. HUSSAIN: Maha Hussain, University of Michigan.

DR. HARRINGTON: David Harrington, Dana-Farber Cancer Institute.

DR. RODRIGUEZ: Alma Rodriguez, M.D. Anderson Cancer Center in Houston, Texas.

MS. BROWN: I'm Paige Brown, and I am the FDA patient representative.

DR. MORTIMER: Joanne Mortimer, University of California, San Diego, Moores Cancer Center.

DR. GOODMAN: Vicki Goodman, FDA Medical Officer.

DR. KAMINSKAS: Ed Kaminskas, FDA Medical Officer.

DR. FARRELL: Ann Farrell, Acting Deputy Director.

DR. JUSTICE: Robert Justice, Division Director, FDA.

DR. PAZDUR: Richard Pazdur, Office Director, FDA.

DR. MARTINO: Ladies and gentlemen, we are missing one member, Dr. Maldonado, who is the industry representative which is a standing member to this committee; and the reason for his absence is airline problems.

The next item on the agenda is a reading of a conflict of interest statement from Ms. Johanna Clifford.

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

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

In accordance with 18 USC Section 208(b)(3), Dr. Ronald Bukowski has been granted a full waiver for unrelated consulting for a competitor for which he receives less than $10,001 per year.

Dr. Maha Hussain has been granted full waivers under 18 USC Section 208(b)(3), and 21 USC 355(n)(4) for stock ownership in six competitor firms. Two are worth less than $5,001; two are worth between $5,001 and $25,000 per firm; and two are worth between $25,000 and $150,000 per firm.

Elizabeth Paige Brown has been granted a waiver under 21 USC 355(n)(4), an amendment of the Food and Drug Administration Modernization Act, for ownership of stock in a competitor valued at less than $5,001.

Because this stock interest falls below the *de minimis* exception allowed under 5 CFR 2640.202(b)(2), a waiver under 18 USC 208 is not required.

Waiver documents are available at FDA's dockets web page. Specific instructions as to how to access the web page are available outside today's meeting room at the FDA information table. In addition, copies of all the waivers can be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A30 of the Parklawn Building.

Dr. Bruce Cheson has been recused from participating in this meeting today due to his involvements with the product at issue.

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

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

Thank you.

DR. MARTINO: To those of you seated around the table, please recognize this is a larger table than usual and the microphones are at a distance from you, so please get yourself close to the microphone so that everyone can hear you when you are called upon to speak.

Next, Dr. Rick Pazdur will make some opening remarks.

DR. PAZDUR: Thank you, Silvana.

Welcome to Atlanta. This is the first time an ODAC meeting is being held outside of the metropolitan Washington, D.C., area. So if you have a love affair with the Gaithersburg Hilton or the Silver Spring Marriott or whatever it is, I feel your pain. But so be it.

[Laughter]

DR. PAZDUR: Our objective in holding this ODAC meeting in Atlanta at the time of the annual ASCO meeting is to provide a venue allowing greater access to these important meetings to our FDA stakeholders. These stakeholders, including patients, patient advocates, academic and community oncologists, and the regulated industry are usually present at the annual ASCO meetings, and we hope this change in venue will allow many the opportunity to view these

important ODAC meetings who may be prevented from traveling to the immediate Washington, D.C. area. Ultimately we hope this opportunity will provide the American public a more comprehensive understanding of the regulatory process at the United States Food and Drug Administration.

Today we will be discussing NDA 21-986, dasatinib for the treatment of CML. The sponsor is requesting two indications: The treatment of adults with chronic, accelerated, or blast phase chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib; and two, the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia and lymphoid blast chronic myeloid leukemia with resistance to prior therapies.

The Agency has accepted durable responses in hematological malignancies for the approval of both chronic myelogenous leukemias -- that is, accelerated approval -- and acute leukemia, granting it regular approval based on complete hematological responses.

The FDA granted imatinib or Gleevec® accelerated approval for chronic, accelerated, and blast crisis phase of CML based on durable major cytogenetic responses and major hematological responses in single-arm trials. These patients were previously

treated with interferon alpha. There were three single-arm trials with over a total of 1,000 patients enrolled. Accelerated approval was subsequently converted to regular approval after the submission of longer follow-up data of the single-arm trials.

The questions posed to the committee after hearing both the sponsor and the FDA's presentation will focus on the risk/benefit relationship demonstrated in both the imatinib-resistant population and the imatinib-intolerant population. The number of patients and the duration of follow-up may differ from the sponsor and the FDA presentation since additional patients and follow-up data have been analyzed by the sponsor after data submission to the FDA. Deliberations by the committee should focus on all available data.

A separate question will be asked regarding the approval of dasatinib for Philadelphia-positive ALL, an indication that Gleevec® or imatinib does not have. For the treatment of acute leukemias the Agency has accepted durable complete response rates for regular approval. And what we would be asking you, if dasatinib has demonstrated sufficient evidence to warrant regular approval in either the imatinib-resistant or the intolerant Philadelphia-

positive ALL population.

I'm next going to turn my attention to a very mixed issue in my heart, and that is that several of our members are leaving and I have plaques to present to them. And I said mixed emotions because we have really used them quite extensively, and they have developed I think very close working relationships with many at the FDA. Although they will be leaving the committee, you probably will be seeing them back in either advisory roles to this committee, or we will be using them at the FDA in additional capacities. But they will be officially leaving the committee.

The three members that will be leaving the committee after serving since July of 2002 are Dr. Silvana Martino, Dr. Bruce Cheson, and Dr. Greg Reaman. And we really thank them for their service to the committee and their ongoing services to the FDA throughout the year.

I'd first like to recognize our chair, Dr. Silvana Martino, who is a specialist in breast cancer and has chaired the ODAC committee for the last two years. As stated previously, she is Director of the Breast Cancer Section at The Angeles Clinic and Research Institute in Santa Monica, California.

Silvana has, I think, provided excellent leadership of this committee. She has always been available to the FDA staff to provide consultations to us and to bounce off ideas in a very professional and positive manner.

And for that, Silvana, I would like to thank you both from a professional point of view but often from a personal point of view, and like to give you this plaque in acknowledgment of your services to the ODAC committee. Thank you very much.

[Applause]

DR. MARTINO: It hasn't always been a pleasure to do this job, but it has been an honor. But in reference to this wonderful plaque, jewelry would have been nice as well.

[Laughter and applause]

DR. PAZDUR: I don't have a comeback for that.

The second person that will be leaving the committee is Dr. Bruce Cheson, who is Professor of Medicine and Head of Hematology at Georgetown University, Lombardi Cancer Center. Dr. Cheson specializes in leukemia and lymphoma research, and has provided to the Agency numerous consultations outside of the ODAC meetings on end of phase two meetings and official and unofficial consultations

with the members of the staff. We really highly regard his help. And here again, it is with mixed emotions that I give him this plaque, but I am sure he will be back in other capacities serving the FDA.

Bruce, thank you very much for your service.

[Applause]

DR. CHESON: Well, it's certainly with mixed emotions that I leave this because it's not often that we have the opportunity to do something that's really important, and this committee really does that. And as the curmudgeon of the group, hopefully I wasn't too quiet at those times. But as Dr. Pazdur said, and to quote our California friend, I'll be back.

[Laughter and applause]

DR. PAZDUR: The third physician that will be leaving the committee is Dr. Gregory Reaman, who is Group Chair of the Children's Oncology Group and Professor of Pediatrics at George Washington University School of Medicine and Health Science. Greg has helped us in many aspects, and has not only been a member of this committee but has also served on our Pediatric Oncology Committee. He has been available, again like the other members of this committee, in helping us with end of phase two

meetings, difficult questions that we have regarding exclusivity, and other pediatric issues that the Agency faces. Again, it is with mixed emotions that I give Greg this plaque, but I am sure this is not the last that we have heard or will be working with him.

Greg, thank you very much.

[Applause]

DR. REAMAN: Thank you very much. And to echo Dr. Cheson, it's not with mixed emotion; it is with sadness that I leave the committee because it is a rare opportunity that you really get to do something as important as this. And thank you for the opportunity, and I hope to be back.

[Applause]

DR. PAZDUR: Well, we'll begin this session, but I just would like to say after having heard the deliberations here in our votings, et cetera, if you still need more of the FDA after this two-hour session there will be another session tomorrow that we will be putting on. It's called "Dasatinib from Bench to ODAC." It's part of an educational session, and we'll go over some of the deliberations of this meeting. Its aim from the FDA perspective is basically to give others an idea of what goes on at

the FDA with a specific application. And I will invite many of you, if you're still here, to attend that meeting bright and early at 8:00 o'clock. It will be in Building B, Level 5, Thomas B. Murphy Ballroom 3.

Thank you very much, and I'll turn the proceedings over to Silvana.

DR. MARTINO: Thank you, Dr. Pazdur, but I will remind you this is not a two-hour meeting. You have the pleasure of being in our presence for four hours.

[Laughter]

DR. MARTINO: We now will turn to the sponsor's presentation of their data. Dr. Donna Morgan Murray will introduce her panel.

And for the committee, while the doctor is getting ready, the point at which questions will be posed both to the sponsor as well as the FDA is after each of them have had the opportunity to present their data, and so recognize that there will not be interruptions of the speakers for clarification of points until after both the FDA and the sponsor have spoken.

DR. MURRAY: Good morning. My name is Donna Morgan Murray.

We're pleased to present to you today the results

of the development program for dasatinib, an oral multi-targeted kinase inhibitor. BMS requested approval for dasatinib for the treatment of chronic myeloid leukemia, or CML, and Philadelphia chromosome-positive acute lymphoblastic leukemia, or ALL, based primarily on the results from six studies that demonstrated the safety and efficacy of dasatinib. These studies suggest that dasatinib is an important therapy for patients for whom other therapies are either not available or are unsatisfactory.

For BMS's presentation today, Dr. Neil Shah will describe the rationale for using dasatinib to treat CML and Philadelphia-positive ALL. Next, Dr. Claude Nicaise will review the clinical program for dasatinib. Then Dr. Hagop Kantarjian will provide a clinical perspective on the data. Finally, I will summarize our conclusions.

We have a team of clinicians and scientists from BMS who are available to answer questions from the committee today. In addition our consultants, Dr. Shah from UCSF and Dr. Kantarjian from M.D. Anderson, are available to answer questions. Both are investigators in the dasatinib program. Dr. Shah is an expert on the mechanisms of resistance to

imatinib, and Dr. Kantarjian's expertise is in the understanding and treatment of CML.

Chronic myeloid leukemia is a continuum of disease, and a subject's characteristics and prognosis are different at each phase. Imatinib is effective at treating newly diagnosed CML as well as accelerated and blast phase CML. However, resistance to imatinib and intolerance to imatinib are issues of increasing clinical importance. Treatment options are limited after failure of imatinib or in patients who are intolerant to imatinib.

In our presentation today you will see data demonstrating hematologic and cytogenetic responses in patients with a long history of leukemia who are heavily pretreated with imatinib, interferon, and other chemotherapeutic agents.

We will show data demonstrating the efficacy and safety of dasatinib for the treatment of adults with chronic, accelerated, or blast phase CML with resistance or intolerance to prior therapy including imatinib. We will also show data demonstrating the efficacy and safety of dasatinib for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia and lymphoid blast chronic myeloid leukemia with resistance or intolerance to

prior therapy.

Our data demonstrate durable and complete hematologic and cytogenetic responses across all phases of CML and ALL. The safety results we will describe demonstrate a favorable benefit/risk profile for dasatinib.

Dr. Shah will now beginning the technical presentation with a discussion of the scientific rationale for using dasatinib to treat CML and Philadelphia-positive ALL.

DR. SHAH: Good morning.

The pathophysiology of chronic myeloid leukemia is well understood at the molecular level. The hallmark of CML is the Philadelphia chromosome, a reciprocal translocation between chromosomes 9 and 22 which results in the formation of the BCR-ABL fusion gene. BCR-ABL is an active tyrosine kinase that is critically important to the pathogenesis of human CML as has been confirmed by the clinical success of imatinib, a small molecule BCR-ABL selective kinase inhibitor.

Treatment with imatinib results in an initial high response rate in patients with CML. However, despite this initial efficacy, a substantial number of patients suffer relapse or progressive disease

across all phases of CML. With 42 months of follow-up, 16 percent of chronic phase CML patients who received imatinib as initial therapy had evidence of disease relapse or progression. In chronic phase patients who had previously been treated with interferon, 26 percent had relapsed or progressed with 48 months of follow-up. The majority of accelerated phase patients have relapsed or progressed after four years, and relapse is nearly universal in blast phase patients. Importantly, for most patients with imatinib resistance or intolerance, few if any effective therapeutic options exist.

The molecular mechanisms responsible for imatinib resistance are largely understood. Most commonly, resistance results from clonal outgrowth of leukemic cells harboring BCR-ABL kinase domain mutations that impair the ability of imatinib to efficiently bind to BCR-ABL. A second mechanism involves overexpression of BCR-ABL through either genomic amplification or acquisition of additional Philadelphia chromosomes. Lastly, there is a minority of resistant cases that do not show evidence of either BCR-ABL kinase domain mutation or overexpression. The molecular pathways responsible for these cases are likely numerous and

varied, and presumably act independently of BCR-ABL.

More than 40 different BCR-ABL kinase domain mutations have been identified in clinical samples to date. These mutations confer varying degrees of resistance to imatinib *in vitro*. The most commonly detected imatinib-resistant mutations have been engineered into cell lines in our laboratory and tested for sensitivity to novel compounds. Dasatinib is a SRC-ABL multi-kinase inhibitor that inhibits the growth of cells harboring all imatinib-resistant forms of BCR-ABL tested at low concentration levels with the exception of the T315I mutation.

Additionally, dasatinib is approximately 300 to 400 times more potent than imatinib at inhibiting the growth of cells that harbor non-mutant BCR-ABL. Dasatinib selectively inhibits the growth of BCR-ABL dependent bone marrow progenitors in colony-forming unit assays. In this experiment, bone marrow progenitors from a healthy volunteer were not affected by dasatinib, whereas colony formation of bone marrow obtained from both an imatinib-sensitive and an imatinib-resistant CML patient was substantially reduced in the presence of dasatinib.

In summary, dasatinib offers significant therapeutic promise for imatinib-resistant or

intolerant cases of CML. Its potent preclinical activity suggests that dasatinib will be clinically useful in the majority of imatinib-resistant cases which are most commonly the result of BCR-ABL kinase domain mutation or overexpression.

In addition, dasatinib may represent a viable treatment option for patients who cannot tolerate imatinib. The ability of dasatinib to selectively suppress BCR-ABL positive hematopoietic progenitors *in vitro* suggests that it is not innately myelotoxic. Dasatinib therefore offers significant promise to improve treatment outcomes in patients with CML.

Dr. Claude Nicaise will now present the dasatinib clinical program.

DR. NICAISE: Good morning.

As presented by Dr. Shah, the activity in this population is suggested by a unique preclinical profile which includes both an increased potency against BCR-ABL and other mechanisms of action capable of overcoming resistance to imatinib. Because of this potential and an increased awareness of imatinib resistance, we focused the development of dasatinib on the treatment of CML patients who had failed imatinib because of resistance or intolerance. These patients have limited therapeutic options, and

dasatinib has the potential to fulfill this important unmet medical need.

The clinical program in support of safety and efficacy included six studies. The first study, referred to as 002, was a phase one dose escalation initially conducted in chronic CML patients. Subsequently, patients with advanced disease who have accrued in separate cohorts, a broad range of doses were tested up to 180 milligrams once a day and 120 milligrams twice a day. With appropriate dose adjustment, all patients were treated at optimal dose.

We also conducted four open label phase two studies, one in CML patients in chronic phase, Study 013; one in accelerated phase, Study 005; one in myeloid blast phase, Study 006; and one that included Philadelphia-positive ALL patients and lymphoid blast patients, Study 015. All phase two studies included patients who were resistant to imatinib as well as patients who were intolerant of imatinib.

We also conducted a randomized phase two study in which a comparator group consisted of patients dosed with imatinib 800 milligrams per day. This comparator was selected based on evidence from three small studies demonstrating that escalating the dose

of imatinib allowed a rescue of patients who failed imatinib at the dose of 400 to 600 milligrams. The crossover to the alternative treatment was allowed.

In all phase two studies dasatinib was given at the dose of 70 milligrams twice a day, a dose selected based on both preclinical and clinical data. Dasatinib exposure of approximately 45 nanograms per ML at steady states exceeds the drug concentration required to inhibit BCR-ABL. In addition, complete inhibition of the phospho-CrkL, the biomarker of the inhibition of BCR-ABL, was achieved at doses of at least 100 milligrams per day and was more durable with the BID schedule. Finally, in the phase one study, most major cytogenetic responses were achieved at the dose of 70 milligrams BID with an acceptable safety profile in these patients' population.

Primary and secondary resistance were defined at the maximum tolerated dose of imatinib. Resistance criteria included the absence of hematologic or cytogenetic response at specific time points. Secondary resistance was also based on hematologic and cytogenetic progressions.

Criteria for intolerance are listed on this slide and comprise hematologic and non-hematologic criteria. Intolerance was defined in patients who

responded to imatinib and had to discontinue treatment because of intractable toxicities, which in most cases consisted of liver and skin toxicities. In all cases imatinib could not be resumed.

Intolerance also comprised patients who had to discontinue imatinib prior to achieving a cytogenetic response because of hematologic or non-hematologic toxicities. Those patients were unable to have an adequate trial on imatinib at the therapeutic dose of at least 400 milligrams per day.

In addition, patients who had unquestionable resistance to imatinib also became intolerant of imatinib when dose escalation was attempted. Those patients were included in our studies and analyzed as a resistant population.

Response criteria are summarized on this slide. They were similar to those used in the imatinib registrational studies. In all six studies, efficacy was based on hematologic and cytogenetic responses. Hematologic response is required to be maintained for at least four consecutive weeks.

The definitions of complete hematologic response in chronic phase and in advanced disease as well as no evidence of leukemia in advanced disease were almost identical. Each require normal white blood

cells, absence of blasts and promyelocytes in the blood and bone marrow, basophils below 20 percent, normalization of myelocytes and metamyelocytes in the blood, as well as the absence of extramedullary disease.

In advanced disease specific criteria were set for platelets and neutrophil counts. Those criteria for complete hematologic response and no evidence of leukemia were consistent with those of complete hematologic response in chronic phase patients. In all analyses, complete hematologic response and no evidence of leukemia will be grouped as major hematologic response. Standard cytogenetic response criteria were used with complete and partial response grouped as major cytogenetic response.

There were 529 patients in the phase one and phase two studies, which are the primary basis for efficacy evaluations. Altogether we have assessed efficacy on 226 patients with chronic phase CML, 118 in accelerated phase, 97 with myeloid blast, and 88 with lymphoid transformation including Philadelphia-positive ALL. In addition, we will present the preliminary data on the first 36 patients consecutively entered and treated in the randomized trial.

As this table illustrates, all patients had a long history of leukemia and were heavily pretreated. Most had received imatinib at a dose greater than 600 milligrams per day, and the majority were resistant to imatinib. Prior therapy included interferon, chemotherapy, and stem cell transplant. Three quarters of the chronic phase patients had prior interferon treatment. Chemotherapy and stem cell transplants were frequent in patients with lymphoid blast transformation and Philadelphia-positive ALL. Approximately half of the patients had a BCR-ABL mutation. The last number of patients had thrombocytopenia at baseline reflecting the extent of disease, the tumor burden, and the poor bone marrow reserve.

Let's now focus on the efficacy data in chronic phase patients. Study 002 demonstrated preliminary evidence of activity with 91 percent complete hematologic response and 38 percent major cytogenetic response, which is the primary endpoint in chronic phase patients. In Study 013 we confirmed these results in 127 imatinib-resistant patients. With a minimum of 24 weeks of follow-up, 87 percent of the patients achieved a complete hematologic response and 31 percent had a major cytogenetic response which was

complete in 22 percent. Two patients in Study 013 lost hematologic response. The longest duration of response was 20 months in Study 002 and nine months in Study 013.

As illustrated on this chart, the major cytogenetic response rate was similar in all groups of prognostic interest including prior interferon, prior therapy with high dose imatinib, and patients with BCR-ABL mutations.

A total of 67 imatinib-intolerant CML patients in chronic phase were included, eight from Study 002 and 59 from Study 013. Sixty of these 67 patients were intolerant to imatinib because of non-hematologic toxicities consisting of severe skin toxicity or liver toxicity in more than two-thirds of these patients. All but two patients achieved a complete hematologic response. In both studies three-quarters of the patients achieved a major cytogenetic response, with a complete cytogenetic response rate of 56 percent in Study 013 and 63 percent in Study 002. There was no loss of cytogenetic response in either study.

In both studies, as shown in these bar graphs, major cytogenetic responses were similar in all patients and in those previously treated with

interferon.

All imatinib-intolerant patients are currently alive, free of progression, with a follow-up extending up to 20 months. In imatinib-resistant patients the progression-free survival in Study 002 depicted in blue and Study 013 depicted in green were similar. In Study 002, with most patients being followed for more than one year, being free of progression at six months predicts for a favorable outcome. In Study 013, although the follow-up is shorter, most patients remain progression-free at six months.

We have conducted a preliminary analysis of the randomized phase two study based on the first 36 patients consecutively enrolled and treated with a minimum of three months of follow-up. Patients in this study were less heavily pretreated. The highest dose of imatinib was 600 milligrams per day. There were few BCR-ABL mutations, and those were mostly seen in the dasatinib group.

At the time of this analysis, complete hematologic response rates were similar in the two groups. Both major cytogenetic response and complete cytogenetic response rates were higher in the dasatinib-treated patients than in those who received

imatinib at 800 milligrams per day.

This study allowed for a crossover for lack of response after a minimum of three months or intolerance at any time. Eleven of the 14 imatinib patients crossed over, six of them because of lack of response. There were only two crossovers in the dasatinib group, one because of intolerance and one because of lack of response.

Let's turn to the 118 patients in accelerated phase CML. Efficacy is presented regardless of imatinib status, as only 12 imatinib-intolerant patients were treated and results were consistent in the two populations.

As shown on these slides, the results are consistent between Study 002 and Study 005. The major hematologic response rates were 55 percent and 59 percent with most patients achieving a complete hematologic response. Major cytogenetic responses were seen in 27 percent and 31 percent of the patients. With a minimum follow-up of six months, one patient in Study 005 lost hematologic response and two lost cytogenetic response. The longest duration of response was one year.

In Study 005 shown in blue, more than 80 percent of the patients remained free of progression at six

months, with the longest follow-up of 11 months. In Study 002 shown in yellow, most patients remained progression-free after six months, and the longest follow-up was 13 months.

Efficacy in myeloid blast crisis was assessed in 97 patients. They are summarized for all patients, as only seven patients were imatinib intolerant. These were consistent across both studies, with a major hematologic response rate of 30 and 32 percent. In both groups most hematologic responses were complete. At least 30 percent of the patients had a major cytogenetic response. With a minimum of six months of follow-up, there were only two losses of hematologic response and six of cytogenetic response. In both studies duration of hematologic response greater than six months were documented.

Progression-free survival was similar in both studies. Importantly, in Study 006 shown in blue, half of the patients remained progression-free at six months, with the longest follow-up exceeding ten months.

Efficacy in lymphoid blast CML and Philadelphia-positive ALL was assessed in 88 patients. In Study 002 there was preliminary evidence of activity in 10 patients, five lymphoid blast and five Philadelphia-

positive ALL, with a major hematologic response rate of 50 percent. In Study 015 there were 42 lymphoid blast and 36 Philadelphia-positive ALL patients. Major hematologic responses were seen in 31 percent and 42 percent of those patients. It also included 31 percent of complete hematologic response in Philadelphia-positive ALL patients.

Major cytogenetic responses were also documented in more than half of the patients in both groups. Loss of hematologic and cytogenetic response in these patients occurred more frequently than in patients with other stages of CML. Although response duration was brief in some patients, we have now a number of patients with Philadelphia-positive ALL whose response is ongoing with durations greater than four months.

The median progression-free survival was 2.8 months in patients with lymphoid blast CML, depicted in white, and 3.3 months in patients with Philadelphia-positive ALL, depicted in blue. In both groups a small proportion of patients remain progression free at six months.

All patients in the phase two program were assessed for the presence of a BCR-ABL mutation at baseline in a central laboratory. We identified 34

unique mutations in 197 patients. Substitution of nine amino acids accounted for 68 percent of BCR-ABL mutations, and these nine mutations are illustrated on this slide. Major hematologic responses and major cytogenetic responses have been documented with all of the most common BCR-ABL mutations with the exception of the T315I mutation, which is consistent with the preclinical data presented earlier by Dr. Shah.

In summary, in chronic phase patients we observed a high rate of major cytogenetic responses in both imatinib-resistant and imatinib-intolerant patients. Responses were durable, and currently response greater than one year have been seen in resistant and intolerant patients. In Study 002, responses at six months was predictive of long-term benefit.

In advanced disease patients we have observed a high rate of major hematologic responses in accelerated and blast phase CML patients and in Philadelphia-positive ALL patients. These were high-quality responses. In Philadelphia-positive ALL, 31 percent of the patients achieved a complete hematologic response. In blast phase patients we have patients who are disease-free for more than six months, which contrasts to the expected survival in

this group of patients.

I will now review the safety in the clinical program. This assessment is based on 511 patients treated with dasatinib using the BID schedule, mostly at the starting dose of 70 milligrams twice a day. All studies have a minimum of eight months of follow-up.

Myelosuppression, mostly thrombocytopenia, was the most common finding in the phase one study. It occurred to various degrees in patients treated at doses above 50 milligrams per day. Fluid retention, in particular pleural effusion, was also identified. These events were the most important findings in the phase two studies, as I will describe now.

Thrombocytopenia and neutropenia were common, and as I will discuss later they were reversible and manageable. As shown on this slide, in chronic phase patients severe thrombocytopenia was seen in almost half of the patients. It was greater than 80 percent in patients with advanced disease. By contrast, none of the 32 patients with solid tumor treated with imatinib in a phase one study developed significant thrombopenia or neutropenia despite receiving doses of 70 milligrams BID or higher.

These results correlate with the preclinical data

that demonstrated that dasatinib selectively inhibited the bone marrow progenitor cells from CML patients but not from healthy volunteers. This strongly suggests that the myelosuppression in the CML program is linked to the activity in this population.

These graphs summarize the time to thrombocytopenia. It is displayed in orange when it is less than four weeks, in blue if it is between four and eight weeks, and in purple if it is greater than eight weeks. In chronic phase patients severe thrombocytopenia most often occurred during the second month of treatment. In blast phase patients it frequently occurred earlier, during the first four weeks.

Toxicities associated with myelosuppression included bleeding and infections. They were infrequent in chronic phase patients and somewhat more common in advanced disease patients. Among all 511 patients who are described in the far right column, drug-related gastrointestinal hemorrhage was seen in a total of 52 patients. Almost all GI hemorrhage were associated to severe episodes of thrombocytopenia. There were three episodes of CNS hemorrhage, two of which were fatal. There were 28

episodes of febrile neutropenia, most of them in patients with lymphoid blast and Philadelphia-positive ALL. In addition, 28 patients had severe infections, half of which were pneumonia.

As mentioned earlier, thrombocytopenia and neutropenia were reversible. They were managed by dose interruptions, dose reduction, and supportive care. Although myelosuppression was less severe in chronic phase patients, dose interruption and dose reductions occurred more frequently than in advanced disease patients, especially those in blast crisis who were mostly maintained at the target dose. When they occurred interruption due to myelosuppression was usually brief, and recovery usually occurred within one to two weeks.

Platelet transfusions were required in 22 percent of chronic phase patients and approximately two thirds of the advanced disease patients. Red cell transfusions were also common in advanced disease patients. Approximately a third of the patients with advanced disease received hematopoietic growth factor, mostly G-CSF but also erythropoietin. Their use was less common in chronic phase patients. Across all studies there were only five patients who discontinued treatment because of severe

myelosuppression.

Fluid retention was the most common drug-related non-hematologic adverse reaction. It occurred in 44 percent of the patients. Diarrhea was reported by 35 percent of the patients and was severe in 4 percent. Rash occurred in a quarter of the patients and was usually minimal in severity. Other most common drug-related adverse reactions are listed in this table and consisted mostly of GI intolerance, headache, and dyspnea, which was often associated with pleural effusion. As a result, in the right column demonstrates these adverse events were rarely severe.

Fluid retention has been commonly reported with other tyrosine kinase inhibitors including imatinib and is usually associated with the inhibition of PDGFR. With dasatinib superficial edema was seen in approximately a quarter of the patients with similar incidence across all stages of CML. They primarily consisted of peripheral edema, and less frequently face edema.

Pleural effusion was reported in 108 patients. There was some other evidence of fluid retentions including pericardial effusion, congestive heart failure, pulmonary edema, cardiac dysfunction, and pulmonary hypertension. There was minimal evidence

of cardiotoxicity, but in most patients there was evidence of fluid overload. These events were reversible.

The incidence of pleural effusion ranged from 18 percent in chronic phase patients to 30 percent in blast phase patients. Pleural effusions were also more severe in blast phase patients, with 13 percent experiencing a grade three event in this group of patients. Occurrence of pleural effusion was progressive over time. Some occurred as early as the first week of treatment, others as late as one year.

Pleural effusions were mostly managed by medical interventions, dose interruptions and reductions. Seventy-seven percent of the 108 patients who developed pleural effusions received diuretics, and a third received corticosteroids. Transient dose interruptions occurred in 44 percent of the patients, and a dose reduction in 7 percent. Interruptions were usually of brief duration.

Invasive procedures, including thoracentesis, were required in 18 percent of the patients. Altogether, with mostly noninvasive measures, pleural effusions were adequately controlled, and only four patients permanently discontinued dasatinib because of pleural effusions.

As illustrated on this slide, other manifestations of fluid retention were mostly managed by medical intervention, dose interruptions and dose reductions. Seventy [sic] percent of those 44 patients received diuretics, and 25 percent received steroids. In addition, in very few specific cases either nitrates, ACE inhibitor or beta blocker were also given. Thirty-nine percent of the patients had dose interruptions, and four patients had a dose reduction. Two patients with pericardial effusion required pericardial window. Six patients discontinued dasatinib: three due to heart failure, two due to cardiac dysfunction, and one due to pulmonary edema.

Preclinical evaluations for cardiac repolarization show moderate risk for dasatinib as illustrated by the data in the hERG assay. Although there was no issues with cardiac repolarization in animals, extensive evaluations were conducted in the clinical program where serial ECGs were performed at baseline and during treatment.

As shown on this slide, the mean QTc prolongation in clinical trial was minimal. Changes in QTc were neither dose nor exposure related. We identified a small number of outliers with either transient QTc

greater than 500 milliseconds or transient increase in QTc greater than 60 milliseconds. In addition, nine patients had an adverse event of prolonged QTc, but only one of them discontinued dasatinib. There was no arrhythmia associated with long QT, such as torsade de pointes, and there were no deaths attributable to QT prolongation.

We assessed laboratory abnormalities, in particular changes in liver enzyme which were an important toxic effect of imatinib. There were increases in AST and in ALT in over half of the patients, but in most cases they were transient and spontaneously reversible without treatment interruptions or modification. Grade three or four increases in ALT or AST or bilirubin were associated with progressive disease or other concomitant conditions.

Similarly, there were few cases of increases in creatinine, and they were unlikely related to drug toxicity. Sixty-two percent of the patients had hypocalcemia, which was severe in 10 percent of the patients. All incidents with asymptomatic and never led to treatment modifications.

A total of 94 patients were intolerant of imatinib: 67 in chronic phase CML, 12 in accelerated

phase, 7 in myeloid blast, and 8 in lymphoid blast or Philadelphia-positive ALL. The safety profile of dasatinib in those patients was similar to what we saw in the entire population. Myelosuppression and fluid retention occurred at similar frequency and severity compared to the imatinib-resistant patients.

In patients who were intolerant of imatinib for reasons other than myelosuppression, we found minimal evidence of cross-intolerance between imatinib and dasatinib, specifically none of the patients discontinued imatinib because of skin toxicity or liver toxicity, developed similar liver or skin toxicity of a grade three or four. Three patients developed grade three nausea, diarrhea or fatigue as they previously had done on imatinib.

In summary, dasatinib is clearly associated with a toxicity that might be expected from a drug with its mechanism of action and in a patient population with a complex hematologic malignancy. Nevertheless, the toxicities were generally manageable and reversible.

The most notable of these toxicities was myelosuppression. It was severe and predictable in patients with heavy tumor burden and highly potent targeted therapy. It was most often managed with

dose interruption, dose reduction, and supportive care including transfusion and use of hematopoietic growth factors. When properly managed, myelosuppression rarely led to severe complications such as bleeding or infections.

Fluid retention was also common and mostly consisted of pleural effusion, pericardial effusion, and a number of other presentations, all of which were linked to primary fluid overload. Fluid retention was managed by diuretics or corticosteroids, dose interruptions and dose reductions. Very few patients required invasive procedures or treatment discontinuation. There was minimal evidence of hepatotoxicity, and most of the other adverse events were mild or moderate in severity.

In the next presentation Dr. Kantarjian will put the dasatinib result into context of the unmet medical need for the populations included in our studies.

DR. KANTARJIAN: Good morning. I will now put this experience into context of its relevance for patient care in CML today and the benefit/risk ratio.

The initial phase one study of dasatinib showed encouraging results and efficacy in patients with CML

who had exhausted all treatment options. This led to the rapid development, implementation, and completion of the trials presented earlier by Dr. Nicaise.

The first group of patients treated had chronic phase CML resistant to imatinib, and they had limited therapeutic options with a poor prognosis and an estimated median survival of about two years. That survival is even worse in the presence of mutations, particularly the P-loop mutations where the estimated median survival is less than one year.

Very few patients are eligible for allogeneic stem cell transplant. Escalated dose imatinib may be an option, but as you've seen most of the patients had already received imatinib at 800 milligrams a day. In addition, the preliminary experience from the comparative trial suggests that dasatinib may have benefit over imatinib 800 milligrams a day.

Also, in contrast with the historical experience like with hydroxyurea or interferon, dasatinib produced durable complete hematologic and cytogenetic responses which were associated with the excellent survival you've seen, with an estimated 18 month survival rate of 90 percent.

Patients with imatinib intolerance form also an important group of patients, because for them

imatinib cannot be given because of the severe toxicity, so their prognosis in the course of CML cannot be changed. There is also a considerable overlap between imatinib resistance and intolerance because many patients who are resistant to the lower dosages can become intolerant to the higher dose of imatinib.

The current program included 67 patients with imatinib intolerance, and these patients had a substantial benefit from dasatinib where we observed very high rates of durable hematologic and cytogenetic responses at least comparable to and perhaps better than what would have been expected with imatinib therapy had it been possible to deliver it.

The lack of cross-intolerance or cross-toxicity with imatinib makes then dasatinib their best opportunity to benefit from a targeted therapy that can change the course of their disease, similar to what imatinib would have done in chronic myeloid leukemia. Also, the magnitude of the benefit with dasatinib in imatinib-intolerant patients really fulfills an unmet medical need for these patients.

In CML advanced phases, both accelerated and blastic, we're mostly dealing with patients who have

progressed on imatinib therapy to CML transformation. In the accelerated phase the survival after imatinib failure is poor, with an estimated median survival of less than a year. The treatment options in this phase are also very limited, and stem cell transplant, when feasible, may be the only real alternative.

The dasatinib data presented this morning in accelerated phase showed very high rates of durable hematologic and cytogenetic responses not achievable with any other modality in accelerated phase. In addition, the estimated six months progression-free survival was 80 percent, which is very encouraging.

In the blastic phase of CML, both myeloid and lymphoid, the outcome after imatinib failure is truly small. The patients on study had exhausted all their therapeutic options including intensive chemotherapy and allogeneic transplantation, and most such patients are expected to die in a matter of weeks.

Dasatinib again induced hematologic and cytogenetic responses, but what is also impressive is the survival. In myeloid blastic phase the estimated six months progression-free survival was 50 percent, and in the lymphoid blastic phase disease-free survival beyond six months was also documented.

Those findings do not occur with rescue chemotherapy or the standard regimes available to these patients today.

Now everything I've said for blastic phase CML can also be repeated for Philadelphia-positive ALL, except that the situation is even worse and the prognosis of these patients is quite bad. Dasatinib, in my opinion, is one of the most active agents for Philadelphia-positive ALL. Remember, these patients have received already chemotherapy. They've received imatinib, and many of them have undergone allogeneic transplantation. And yet the complete cytogenetic response rate was about 50 percent, which is probably better than any single agent therapy even in front-line Philadelphia-positive ALL. The progression-free survival in this heavily-treated population at six months was 30 percent, with some patents alive beyond nine months. And again, this is unexpected with any kind of therapy in this group of heavily pretreated Philadelphia-positive ALL.

Now the outstanding efficacy of dasatinib comes at a cost of some toxicity. The two most important side effects are myelosuppression and fluid retention. Myelosuppression in leukemia, especially in CML accelerated and blastic phase, is expected and

is part of the day-to-day management of the patients. In fact, many of these patients already start with severe myelosuppression because of the leukemia invading the bone marrow. From the imatinib experience we also expected fluid retention, but that fluid retention was somewhat different from the imatinib, but remains part of the global fluid overload with a specific manifestation like pleural effusion.

During the conduct of the studies we learned more about these events. Today we know that they are manageable and reversible with early and proper intervention. For both myelosuppression in the chronic phase as well as fluid retention in all phases, dose interruptions and reductions are key components to the early management of the patients. Hematopoietic growth factors are useful for myelosuppression. For the pleural effusions we have learned that early interventions with diuretics and steroids are important components to reverse the event. When we implement these findings, treatment discontinuations are rarely necessary.

So in conclusion, as the book title says, I know this much is true: That dasatinib benefits patients with CML and Philadelphia-positive ALL who have no

other treatment options. It is one of the most active agents in chronic myeloid leukemia. It is highly effective in all CML phases following failure of imatinib therapy. It has minimal cross-intolerance or cross-resistance with imatinib, again making it a very useful agent for imatinib intolerant patients. We know that there are side effects. Myelosuppression is predictable and manageable, and other toxicities like pleural effusion are also manageable with early intervention.

Thank you for your attention.

[Applause]

DR. MURRAY: Dasatinib is an important therapeutic advance in the treatment of CML and Philadelphia-positive ALL. The data presented today demonstrate durable and complete hematologic and cytogenetic responses in patients treated with dasatinib in all phases of CML and Philadelphia-positive ALL, and in all subpopulations including subjects who are imatinib resistant or imatinib intolerant, those who were previously treated with interferon or chemotherapy, and those who were previous stem cell transplant recipients.

In summary, we conclude that the data support the proposed indications for dasatinib to treat adults

with CML and Philadelphia-positive ALL who are resistant to prior therapy.

Thank you for your attention.

DR. MARTINO: Thank you.

The next two speakers are from the FDA, and first is Dr. Kaminskas describing and reviewing the efficacy of this agent.

DR. KAMINSKAS: Good morning. I'm Dr. Kaminskas.

This is the team that is reviewing the dasatinib application. I will be presenting some aspects of efficacy, and Dr. Goodman will be describing the safety section.

I will briefly mention some regulatory aspects that pertain to this application, the clinical studies supporting the proposed indications, the dose finding study, the population study, and the efficacy results.

The proposed indication for dasatinib is treatment of adults with chronic, accelerated, or blast phase chronic myeloid leukemia with resistance to or intolerance of prior therapy including imatinib, and with Philadelphia chromosome-positive acute lymphoblastic leukemia or lymphoid blast CML with resistance or intolerance of prior therapy.

Since the application is for treatment of CML and

for imatinib resistant or intolerant patients, it is worthwhile to review briefly the approval history for imatinib mesylate, that is, Gleevec®. Accelerated approval was granted for Gleevec® on the basis of three single-arm studies of CML patients in blast crisis, accelerated phase, or in chronic phase after failure of interferon alpha therapy. A total of 1,027 patients were enrolled in these studies.

Efficacy was assessed by the rate of hematologic responses and by cytogenetic responses. The median duration of responses in the blast phase patients was about six months. In the chronic phase and accelerated phase patients the median response durations could not be defined because the follow-up period was not long enough. Full approval for Gleevec® was granted on longer follow-up, median follow-up of 29 months, of the above phase two studies.

I shall briefly define imatinib resistance and imatinib intolerance in a very simplified manner. Basically primary resistance is failure to achieve a cytogenetic or a hematologic response with imatinib therapy. Acquired resistance is defined as progression of disease after having achieved a cytogenetic or hematologic response. Intolerance is

defined as discontinuation because of toxicity, such as grade three or four non-hematologic toxicity or grade four hematologic toxicity lasting for longer than seven days, or inability to tolerate 400 milligrams or more of imatinib per day.

FDA reviewers have not detected major issues with this application. Two issues are shown above. The sponsor recommends a starting dose of 70 milligrams twice a day on a continuous basis. We think lower starting doses should be evaluated. The second issue is whether the data for imatinib intolerant population are sufficient in magnitude since relatively few such patients were enrolled in all but one study.

The submission contains the results of four single-arm studies of dasatinib: in chronic phase CML in which 186 patients were treated, in accelerated phase CML in which 107 patients were treated, and myeloid blast CML in which 74 patients were treated, and then lymphoid blast CML and Philadelphia chromosome-positive ALL in which 78 patients were treated.

In addition, the submission contains the results of a phase one dose finding study with 84 treated patients, 40 with chronic phase CML and 44 with

advanced phase CML and Philadelphia chromosome-positive ALL. In the recognized study chronic phase patients were randomized for treatment with dasatinib or with high dose imatinib.

The four phase two single-arm trials were multi-center international trials. The data cutoff for the submission was six months after the start of dasatinib therapy. The trials are ongoing and will be completed after 24-month data have been collected.

The primary efficacy endpoint in chronic phase CML patients is major cytogenetic response, which includes both complete response with no Philadelphia chromosome-positive cells and partial response with up to 35 percent of cells being Philadelphia chromosome-positive.

In advanced phases of CML and in Philadelphia chromosome-positive ALL the primary efficacy endpoint is major hematologic response, which includes complete hematologic response: basically a normalization of blood counts and bone marrows, or no evidence of leukemia which permits cytopenias due to incomplete marrow recovery. These response criteria were used in the Gleevec® application.

Now to the dose finding study. The recommended dose for the phase two studies was determined on the

basis of primary efficacy parameters, not on the basis of dose limiting toxicities and maximally tolerated dose. The following two slides show the data from the phase one dose finding study.

In chronic phase CML patients dasatinib was administered daily, either as a single dose or in two divided doses. The results were similar with both dosing schedules. Therefore, they are combined in this slide. Major cytogenetic responses occurred in patients treated with as little as 30 milligrams per day to as much as 180 milligrams per day. The highest percentages of responses occurred in patients treated with 100 milligrams and 140 milligrams total daily doses.

Advanced phase CML and ALL patients were treated with higher starting doses than chronic phase CML patients, from a total daily dose of 70 milligrams to 240 milligrams. Please note that on this slide these are BID doses. Again, the highest percentages of responses occurred in patients treated with 50 milligrams twice a day and 70 milligrams twice a day schedules. These response data suggest that 50 milligrams twice a day may result in similar response rates as 70 milligrams twice a day in both chronic phase and in advanced phase patients.

I will now turn to the efficacy results in the four single-arm trials. These trials enrolled patients with a long history of disease and with extensive prior therapy.

Patients with the longest history of disease were CML patients with chronic phase, accelerated phase, and myeloid blast phase CML. The median times from the time of diagnosis ranged from 49 months to 91 months. They had been treated for long periods with imatinib. Over one half of the patients for longer than three years had extensive chemotherapy. Most had prior interferon treatment, and about 10 to 20 percent had prior bone marrow transplants.

Patients with acute lymphoblastic leukemia and with lymphoid blast CML had shorter histories of disease, shorter exposures to imatinib, less interferon, and about 30 to 40 percent had prior bone marrow transplants.

The starting dose of dasatinib for all patients was 70 milligrams twice a day. The durations of treatment at the time of data cutoff for this submission are shown above. The median durations of treatment were longest in the chronic phase and accelerated phase CML patient populations, about five and a half months, and shortest in the myeloid and

lymphoid blast phase CML and in ALL populations, about three months.

About 45 percent of patients with chronic phase CML had a major cytogenetic response. Most of the responses occurred after 12 weeks of treatment at the first cytogenetic analysis per protocol. The responses were durable. All the responders remained in response at the six-month follow-up data cutoff. About 90 percent of patients had a complete hematologic response, a secondary endpoint.

In advanced phases of CML and in ALL, major hematologic response was the primary efficacy endpoint. The highest response rate was in accelerated phase CML at 59 percent. Patients in other phases had response rates of 30 percent to 40 percent. The responses were durable.

Median duration could not be determined in accelerated phase and myeloid blast phase patients, as all responders except one remained in response at the six-month follow-up data cutoff time. Median durations of responses were 3.7 months in lymphoid blast CML patients and 4.8 months in Philadelphia chromosome-positive ALL patients according to FDA reviewers. Major cytogenetic response as a secondary efficacy endpoint occurred in 30 to 58 percent of

advanced phase CML and ALL patients.

Lastly, I will present the response rates in the imatinib resistance and the imatinib intolerant populations. All the patients in the single-arm phase two studies, the randomized study, and the dose finding study are included. The only disease category with substantial enrollment of imatinib intolerant patients was chronic phase CML.

About one quarter of the patients were imatinib intolerant, and they had about twice the response rate of the resistant patients, 73 percent versus 34 percent. In all other disease categories the imatinib intolerant patients comprised less than 10 percent of each patient population. Responses occurred in these patients, but the numbers were too small for quantification of response rates.

Efficacy findings may be summarized in the following conclusions: Dasatinib treatment results in major hematologic and cytogenetic responses in patients with all phases of CML and with Philadelphia chromosome-positive acute lymphoblastic leukemia who are resistant to imatinib or who have limited tolerance for imatinib. The proportions of patients with responses ranged from 30 percent to about 60 percent depending of the disease phase and the

efficacy endpoint measured.

Responses occurred within the first three months of treatment and appear to be durable. The median durations of responses were about four to five months in acute lymphoblastic leukemia patients and in lymphoid blast CML patients. Median durations in chronic phase, accelerated phase and myeloid blast phase CML are longer but cannot be estimated during this length of follow-up.

Seventy milligrams twice a day is an effective dose of dasatinib, but lower doses also result in responses. Among chronic phase CML patients, imatinib intolerant patients have higher response rates than imatinib resistant patients. Imatinib intolerant patients with other phases of CML and with ALL also had responses, but too few of them were enrolled to provide valid estimates of response rates.

I will now ask Dr. Goodman to present the safety data and overall conclusions.

DR. GOODMAN: Thank you. I will now summarize the safety findings.

The safety population consists of all patients who initiated treatment with dasatinib at a dose of 70 milligrams BID, the starting dose on the phase two

studies. This population therefore includes all patients treated on the four single-arm phase two studies, all patients initially treated with dasatinib on the randomized phase two study, and patients on the dose escalation study who received an initial dose of 70 milligrams BID.

Patients initially receiving imatinib who crossed over to dasatinib on the randomized study are not included in the safety population. Patients who initially received dasatinib and who crossed over to imatinib on the randomized trial were evaluated for events occurring prior to the date of crossover.

There are 489 patients in this safety population, including 214 patients with chronic phase CML, 110 patients with accelerated phase CML, 84 patients with myeloid blast CML, and 81 patients with lymphoid blast CML or Philadelphia chromosome-positive ALL.

Overall, 57 percent of patients had a duration of three to six months of exposure to dasatinib, while 32 percent were treated for three months or less and 11 percent were treated for more than six months. The longest durations of exposure were seen in the phase one study when nearly one-third of patients received six months or more of dasatinib. This is also the only study in which any patient had 12

months or more of exposure.

A 120-day safety update was recently submitted and is still under review. The data are therefore not included in this safety analysis.

The percentage of patients by disease phase who required dose reduction or dosing interruption for any reason are shown here. Dose interruptions were required in 68 to 82 percent of patients. The median length of the first dose interruption was 12 to 14 days. Dose reductions occurred in 11 to 50 percent of patients, more commonly those with earlier stage disease.

Patients were queried for adverse events at each visit. Adverse events were graded according to NCI Common Terminology Criteria for Adverse Events, Version 3. The next three slides describe in order of descending frequency the common adverse events defined as those with an incidence of 10 percent or greater in the safety population. The most commonly reported events included gastrointestinal events such as diarrhea, nausea, abdominal pain and vomiting; constitutional symptoms such as fever, headache, fatigue, dyspnea, and anorexia; and fluid retention events such as peripheral edema and pleural effusion.

While neutropenia, thrombocytopenia and anemia

are listed in this table because they are reported in more than 10 percent of patients, these events were not universally reported as adverse events. A more accurate picture of treatment-emergent cytopenia as based on laboratory data will be presented in a later slide.

Bleeding events were common on all leukemia studies. Epistaxis, the single most common bleeding event, occurred in 11 percent of all patients. Other bleeding events are described in a later slide.

Neutropenic fever occurred in 10 percent of patients in the overall population, most commonly, though, is with more advanced disease. Neutropenic fever was relatively uncommon in patients with chronic phase disease, occurred in 11 to 12 percent of patients with either accelerated phase or myeloid blast CML, and in 27 percent of those with lymphoid blast CML or Philadelphia chromosome-positive ALL.

Hypocalcemia was the most common non-hematologic laboratory abnormality. Eight to 30 percent of patients on the leukemia studies had baseline hypocalcemia of any grade, and less than or equal to one percent had grade three or four hypocalcemia. While on study, the incidence of any grade of hypocalcemia increased to 46 to 80 percent, and the

incidence of grade three or four hypocalcemia was 4 to 22 percent. These abnormalities were least common in chronic phase patients and more common in patients with advanced disease.

There were no reports of tetany or muscle spasm associated with hypocalcemia. A seizure occurred in one patient with grade three hypocalcemia. This patient also has documented leukemic involvement of the CNS. Patients who experienced hypocalcemia were treated with calcium supplementation as clinically indicated.

The mechanism of hypocalcemia with dasatinib use is unclear. However, in non-clinical studies dasatinib inhibited parathyroid hormone stimulated release of calcium dose dependently and blocked bone resorption.

Treatment emergent grade three and four hematologic abnormalities were common among patients receiving dasatinib. Baseline grade three and four cytopenias were uncommon in chronic phase CML patients and more common in advanced phases of disease. The percentage of patients with grade three and four cytopenias while receiving dasatinib increased substantially from baseline in all populations studied. On treatment, grade three or

four thrombocytopenia and neutropenia were more common than grade three and four anemia for all populations studied.

Dasatinib has been observed to cause platelet dysfunction in *in vitro* assays as well as thrombocytopenia. Bleeding complications are also a well recognized complication of leukemia. Bleeding events of any grade were reported in approximately one-third of patients, while grade three and four events occurred in 10 percent and fatal events in 1 percent. Fatal bleeding was primarily intracranial, accounting for five out of six events with a fatal outcome. The final fatality was a pulmonary hemorrhage. Epistaxis was the most common bleeding event, followed by gastrointestinal bleeding. Other sites of bleeding included gingival, conjunctival, CNS, vaginal, urinary tract, eye, and respiratory tract.

Most of the CNS hemorrhages occurred in patients with advanced disease, with five out of the six events occurring in patients with blast phase CML or Philadelphia chromosome-positive ALL. The remaining patient was in chronic phase. While most of the cases were in patients with severe thrombocytopenia, one patient had a platelet count of 21,000 and

another had a platelet count of 56,000 prior to the event. One event occurred followed a head injury. The remainder had no known precipitating factors. The single non-fatal event was a subdural hematoma which resolved following surgical intervention.

Preclinical studies suggested that dasatinib has the potential to cause QT prolongation. Prolonged QT, listed as either an adverse event or based on ECG data, were examined in all the CML trials. Nine patients, or 1.8 percent of the safety population, had at least one episode of QT prolongation reported as an adverse event while receiving dasatinib, and seven additional patients or 1.4 percent were found to have QT prolongation of greater than or equal to 500 milliseconds on ECG as assessed by a central laboratory reading.

Two patients were reported to have five-beat runs of non-sustained ventricular tachycardia. However, there were no reports of torsades. Two patients had recurrent QT prolongation following resumption of the drug, in one case after a dose reduction. However, this patient continued on the lower dose and had no further episodes of QT prolongation.

Preclinical studies in both rats and monkeys demonstrated a potential for dasatinib to cause

cardiac toxicity. Multifocal cardiac necrosis, hemorrhage, fibrosis, and cardiac hypertrophy were seen in rats, and hypertrophy and inflammation were noted in monkeys. Twenty patients, or 4 percent of the safety population, had an event classified as congestive heart failure, ventricular dysfunction, or cardiac decompensation. Among the 20 subjects 12 had some cardiac history, primarily hypertension.

One patient died due to congestive heart failure. This was a 28-year-old man, heavily pretreated for CML including prior anthrocyclines, who had baseline mitral valve insufficiency but a normal baseline ejection fraction. One week prior to his death his ejection fraction was 30 percent. Cause of death was reported as global cardiac insufficiency and febrile pancytopenia.

Action taken with respect to study drug for cardiac failure events was dose interruption in nine patients, discontinuation in four patients, dose reduction in one patient, and no action in six patients.

Forty percent of patients experienced edema of any type, and 19 percent experienced pleural or pericardial effusions. Peripheral edema was the most common event occurring in 26 percent of patients,

followed by pleural effusion in 17 percent and periorbital edema in 7 percent. Facial edema, pericardial effusion, pulmonary edema, and edema of other types were less common. Grade three or four fluid retention events were uncommon with the exception of pleural effusion, with a 5 percent incidence of grade three or four severity.

In summary, gastrointestinal events were common across all phases of disease and included diarrhea, nausea, vomiting and abdominal pain. Fluid retention events including edema and effusions were also common, with edema of any type affecting 40 percent of all patients. Grade three and four hematologic laboratory abnormalities increased substantially from baseline in patients receiving dasatinib.

Cardiac failure events occurred in 4 percent of patients. Death due to CHF occurred in one patient. Three percent of patients had QTc prolongation reported either as an adverse event or determined by central laboratory ECG reading. Approximately one third of all patients had bleeding of any type, with epistaxis and gastrointestinal bleeding the most common. There were six fatal bleeding events, including five CNS hemorrhages and one pulmonary hemorrhage.

I would now like to summarize the findings of the FDA clinical review of this application for dasatinib.

Thirty-one to 59 percent of all patients treated with 70 milligrams BID of dasatinib achieved a response in the primarily response endpoint. Responses were also seen at lower doses in a limited number of phase one patients. Median duration of response has not yet been reached for most of the studies due to the limited duration of follow-up.

In chronic phase, accelerated phase, and myeloid blast patients nearly all patients who achieved a response remain in response at six months follow-up. In lymphoid blast CML the median duration of response was 3.7 months, and in Philadelphia chromosome-positive ALL the median duration of response was 4.8 months.

The most common adverse events included gastrointestinal events, constitutional events, fluid retention and bleeding. Grade three and four hematologic laboratory abnormalities were also very common and occurred with a higher incidence on dasatinib than at baseline. Most patients required dose interruptions or reductions due to toxicity.

Due to clear evidence of activity in CML and

Philadelphia chromosome-positive ALL, on February 6, 2006, an expanded access program was initiated on a treatment protocol for patients with advanced disease.

Thank you.

[Applause]

DR. MARTINO: Thank you.

For the next half hour or so the members of the committee may ask questions of either the sponsor or the FDA, and the manner in which we are going to do that is that you will raise your hand. We will note your name and I will call on you. I would like very little just running back and forth of conversation and interrupting of each other, so I would like to run this in a fairly orderly process.

So Dr. Mortimer, you're up first.

DR. MORTIMER: I'd like to ask the sponsor about the pleural effusions and the pericardial effusions. Were they in the same patients? Was this just sort of polyserositis? And is there any evidence that this is an immunologic process since it responded to steroids?

DR. MURRAY: Dr. Nicaise will discuss the data that we have on both pericardial effusions and pleural effusions.

DR. NICAISE: There were a fairly substantial overlap between the pleural and pericardial effusions, and actually there were 11 out of 13 patients who had pericardial effusion who also had pleural effusions.

DR. MARTINO: Dr. Levine.

DR. LEVINE: I have several questions. Number one, one of the entry criteria was resistance, cytogenetic resistance, lack of response to imatinib. How do you know that? Was there central review of the patients prior to the time that they received the dasatinib? So how was that handled?

And then a second question which is related, who looked at this? Is this central review on treatment of the bone marrow data, histologic data, and the cytogenetic data? Who did that, and was it centrally done?

DR. NICAISE: The entry criteria was essentially based on clinical criteria. The evaluation of the bone marrow was done prospectively on bone marrow collected at data entry at the central laboratory for mutations.

DR. LEVINE: Would you say that again? In other words, number one, one of the criteria for getting on study, one of the reasons to say that somebody was

resistant, was that they did not have a cytogenetic response to imatinib. So you looked at those chromosomes? Who looked at those getting on study?

DR. NICAISE: Those were done at the local laboratory by the investigative sites.

DR. LEVINE: And what about the cases on treatment? Again, is that centrally reviewed, histologically and cytogenetically?

DR. NICAISE: The cytogenetics were done locally at the institutions.

DR. LEVINE: In that case, where were those institutions? We were never told in your handout to us or in this presentation who were the centers that did this and who looked at those responses. That would be important.

DR. NICAISE: There were approximately 70 to 80 institutions around the world who were conducting these trials.

DR. LEVINE: Did you review any of them local -- you know, together? Was there any review team that looked at those together to confirm?

DR. NICAISE: The cytogenetics were not reviewed centrally.

DR. LEVINE: Was the pathology reviewed centrally?

DR. NICAISE: There was no central review other than the mutations.

DR. LEVINE: I have a few more questions.

Number one, as it relates to the hypocalcemia, as I'm sure you know there was a recent report on imatinib associated with hypophosphatemia as well, and it was thought to be mediated through the PDGF and so forth. Did you look at phosphate, and did you look at parathormone levels?

DR. NICAISE: Yes, we looked at hypophosphatemia. And if I can have slide 15A17, these are the data that we have seen in the 511 subjects. As you can see on this slide, about 45 percent of the patients had some degree of hypophosphatemia. Seventeen percent were grade three or four. We did not look at the parathormones in those patients.

DR. LEVINE: Forgive me, but another one. With the GI hemorrhage and so forth, I'm sure that's related to thrombocytopenia. But in your data here with the SIP 3A4 data, we will not be able to use H2 blockers in these patients. I assume we can use PPIs. But would you speak to that whole issue of what drugs you want to use as far as GI toxicity?

DR. MURRAY: Dr. Anne Blackwood-Chir-Chir.

DR. BLACKWOOD-CHIR-CHIR: Anne Blackwood-Chir-

Chir, Clinical Pharmacology, Bristol-Myers Squibb.

We conducted a pH effect study with dasatinib looking at both famotidine and Maalox given with dasatinib. When famotidine was given ten hours prior to dasatinib, it in fact decreased the exposure to dasatinib by 61 percent because dasatinib has pH dependent solubility. Similarly, as Maalox was given concomitantly with dasatinib, it decreased exposure to dasatinib by 55 percent. However, when Maalox was separated from dasatinib by two hours the exposure to dasatinib was unchanged. Thus, the recommendation is for the use of local antacids with a separation of two hours.

DR. LEVINE: In that case the proton pump inhibitors won't be possible either -- i.e., so it's an acid environment that's needed. I see.

Okay, another, sorry. The timing --

DR. NICAISE: If I may add a few additional comments.

Actually we looked at the issue of PPI and H2 blockers in the clinical trials in patients who were actually having GI hemorrhage. The majority of them received proton pump inhibitor, and the majority are on H2 blocker.

And if I can slide 2-12C6, this is a summary of

the actual data in the clinical trial. So there is some potential inference with the clinical pharmacology data, but it's important to recognize that 78 percent of the patients who had GI bleed were actually treated with PPI or proton pump inhibitor.

DR. LEVINE: One last one, and that is the timing of the QTc prolongation. When did that occur in the course of treatment, and also what would your recommendations be in this regard? Are you recommending that clinicians will look for this and do EKGs at certain intervals, or what do you recommend in that regard?

DR. MURRAY: Our proposed labeling does not recommend monitoring for QTc prolongation, because as Dr. Nicaise described the mean change in QTc was 3 to 6 milliseconds with an upper confidence limit of less than 8 milliseconds, which falls below the threshold for the ICH guidelines, and therefore there's a minimal risk of QTc prolongation.

DR. MARTINO: Dr. Eckhardt.

DR. ECKHARDT: I have three questions that relate primarily to the PK. I'm a little bit concerned about the dosing and had questions.

The first one would be whether there was any dose dependence to the Cmin or trough concentrations in a

drug exposure. I don't have a good feel for dose dependant drug exposure.

Secondly, I was interested in the amount of interpatient variability. I think that could be quite significant and could impact upon those exposures.

And the third question would just be whether or not there was ever any exploration of a PK-PD relationship with drug exposure correlating with either efficacy or toxicity.

DR. MURRAY: Dr. Anne Blackwood-Chir-Chir.

DR. BLACKWOOD-CHIR-CHIR: With respect to the Cmins, we've not done separate analyses of Cmin specifically. However, dasatinib does demonstrate dose dependant -- excuse me, slightly greater than dose linearity.

If I may have slide 25-1, this analysis is done by AUC rather than by Cmin. You can see in the first column the regimen. The AUC is the third column, in the column the dose ratio, and in the fourth the AUC ratio. And this demonstrates that at the doses evaluated dasatinib is just slightly more than dose proportional. The exposures are slightly more than dose proportional.

Your second question related to -- I'm sorry, if

you can repeat the second one.

DR. ECKHARDT: Just the interpatient variability.

DR. BLACKWOOD-CHIR-CHIR: The interpatient variability was moderate with coefficients of variation in the 50 to 60 percent range for most of the dose levels studied. In terms of PK-PD, we do have some data with phospho-CrkL and PK. Those data are in the process of being analyzed, however, and with the final report from the 002 Study, the dose escalation study, those data will be available.

DR. ECKHARDT: My last question would be whether or not someone has actually calculated the dose intensity. For example, over three months in a patient there's a lot of dose reductions and interruptions, and it almost looks as if a lot of these patients would fall somewhere in between 50 and 70 after all.

DR. MURRAY: Dr. Nicaise.

DR. NICAISE: Actually, we did. In chronic phase patients the average daily dose is approximately 108 milligrams per day when you do the average over the entire duration of the study. So we go from a target dose of 140 to 108, 110, so dose intensity is about, I calculate, roughly about 75 percent.

In the advanced disease, especially the myeloid

blast patients and the lymphoid blast patients and Philadelphia-positive ALL, most patients were maintained at the target dose with minimal dose reduction or interruptions.

DR. MARTINO: If I can ask a few questions.

I'd like a sense of how much time was spent in hospital for these the patients.

DR. MURRAY: Dr. Nicaise.

DR. NICAISE: I'm sorry, could you repeat the question? The time in hospital? The average hospitalization time was seven days.

DR. MARTINO: Can you also give me a sense of how often these patients were seen?

The issue I'm getting at is there are some toxicities that you've noticed as being fairly predictable. One is this fluid retention which leads to certain clinical events, and the other is the bleeding, which I'm getting this impression is primarily related to platelet count.

Now if that's the case, then I would think that those might actually be relatively preventable events. Am I understanding that correctly? Or are these surprise events that you cannot really anticipate, and that it wouldn't matter if you were a little more attentive?

DR. NICAISE: There are several aspects in your questions. One, the relationship of bleeding to thrombocytopenia, and indeed there is a fairly tight correlation between dose.

Second aspect of your question, if I understand correctly, is to ask if by reducing the dose we will decrease the thrombocytopenia and essentially prevent the dose event?

DR. MARTINO: I wasn't necessarily thinking of dose reduction. I was simply wondering whether seeing the patients more often allows you to anticipate the platelet behavior if the platelet behavior is what predicts for the bleeding events.

I mean, dose reduction certainly is one of the ways that one could do that. But I'm actually getting at a different issue, which is proper follow-up of these patients. Is there an interval at which they were seen? I'm assuming that there was. I'd like to know what that interval was.

DR. NICAISE: These patients were tightly monitored during the clinical trials, and in chronic phase patients the dose was usually interrupted when the platelet counts would drop below 50,000. But sometimes the platelet counts would continue to drop, and that's why we have seen [inaudible] which were

relatively low, and sometimes some patients, approximately -- a small number of patients had prolonged thrombocytopenia.

So yes, in that sense it's preventable in a sense that we were able to interrupt the treatment relatively early in the majority of them. That's why there is relatively few bleeding in chronic phase patients.

In advanced disease patients, on the contrary, the treatment is much more aggressive because these patients, their bone marrow which is heavily invaded by leukemic cells, and therefore maintaining these patients on treatment is important.

And I may ask Dr. Kantarjian to give you some more comments on this because this is part of the management of the advanced disease patients, and he will probably give you some insight in that.

DR. MARTINO: I'm almost trying to ask you, is there a learning curve in using this drug with these patients? In other words, as you realize that certain problems are likely to happen, is there a way to anticipate those?

And so that really is what I'm getting it, because I am disturbed by these bleeding events and by these clinically important fluid retention issues

which would strike me as, from what you've told me so far, being somewhat preventable.

DR. KANTARJIAN: You are absolutely correct about the learning curve, so let me take the two toxicities one at a time.

Let's talk first about the pleural effusions. As you know, the pleural effusions were noted in the phase one, but we became much more aware of them when there was a large number of patients. And then we started learning several things: One, you cannot predict the patients who develop pleural effusions, meaning there is no correlation with response with some of the prior events.

But the patients always start complaining of something, so they either report like shortness of breath or a dry cough. And so what we've learned is as soon as we -- and we tell them about those things, and as soon as they have those we interrupt the drug, we bring them in, we do a chest x-ray. Oftentimes we see either minimal blunting of the costophrenic angles or a little bit of pleural effusion.

So then there are two ways of treating them. Most of the investigators have used diuretics. At our institution we've realized that short courses of steroids are highly effective. So we do prednisone,

40 milligrams daily for two days, then 20 milligrams daily for two days. We repeat the chest x-ray, and the large majority, by that time, they are asymptomatic and the chest x-ray normalizes quickly, and we resume at the lower dose.

So there was a learning curve, and now we know that if we intervene early for the pleural effusions that's not a problem.

Let's take the bleeding events now. The GI bleedings, as you correctly pointed, are related to the thrombocytopenias in the large majority of instances.

Now the patients with CML blastic phase or accelerated phase, what we've tended to do is treat them through the myelosuppression like we do for acute leukemia. Because if we start then the leukemia -- if we stop, then the leukemia comes back and the patients are going to die. So what we do is try to treat them through the process. We give them supportive care measures, platelet transfusions and so on. If they achieved a complete morphologic remission or a hypoplastic bone marrow, no evidence of disease, then we interrupt and we let the platelets recover.

In the chronic phase, as Claude has mentioned,

once they achieve -- in the first part of the trial we do the blood counts once a week, and then if there are no issues we go to every two to four weeks. If the platelets get to reach at the level of 50,000 or below, then we watch them more closely. If they go below 50,000 we interrupt, and then we watch for the recovery above 80,000. If that recovery is within two weeks, then we resume the same dose. If it takes longer than two weeks, then we reduce the dose. If an event happens more then once we also reduce the dose.

So these are simple management approaches that we've learned over time, and we've used them in the past -- not the effusion, but the myelosuppression, we've use similar procedures for the imatinib trials in the management.

DR. MARTINO: Thank you.

Dr. Hussain.

DR. HUSSAIN: I have three toxicity-related questions.

The first one of them is across all trials, is it fair to assume or to conclude that the death rates related to therapy was only the one percent?

DR. MURRAY: Dr. Nicaise.

DR. NICAISE: Across all trials there were six

deaths that were related to therapy.

DR. HUSSAIN: So what percent was that?

DR. NICAISE: Six out of 555 patients, was just one percent.

DR. HUSSAIN: Okay. And the second question is what percent of patients discontinued therapy due to toxicities?

DR. MURRAY: Dr. Nicaise.

DR. NICAISE: I'm sorry, may I ask you to repeat the question, please? I could not hear it.

DR. HUSSAIN: Sure. Across all trials, what percent of patients discontinued therapy due to toxicities?

DR. NICAISE: Discontinued therapy because --

DR. HUSSAIN: Therapy due to treatment-related toxicities.

DR. NICAISE: Fourteen percent of the patients discontinued trials because of toxicity altogether, 14 percent. Thirty-four patients out of 511 discontinued the trial because of toxicity, for a discontinuation rate of toxicity of 14 percent.

DR. HUSSAIN: Fourteen percent.

And the final question, and this is probably for Dr. Kantarjian, and that is can you put the overall toxicities, because they are concerning, and for

those of us who deal with solid tumors we don't see this kind of pattern of toxicities, which I would appreciate that you are quite -- well, I should say you are used to seeing. But could you put the toxicity profile of this agent across all trials in the context of the disease and in the context of therapies that would have been administered to these patients?

DR. KANTARJIAN: Hagop Kantarjian from the Leukemia Department.

So the drug is safe. There are two kinds of toxicities that we see.

The first one is the myelosuppression, and with the myelosuppression what we do usually, if they are in the chronic phase, we interrupt and dose reduce; and that's quite manageable. In the transformation we take more risk in terms of continuing the drug until there's a complete metamorphologic remission.

The pleural effusions is the toxicity that is new in this setting. But as I mentioned, at our institution we look for early signs of the pleural effusions, such as a dry cough or shortness of breath. We instruct the patients. We bring them very quickly, or we give them instructions to stop the drug and get a chest x-ray. And then we

institute the management -- the diuretics, the steroids -- and then we resume at the lower dose.

So in our experience the drug is safe, and I really believe the benefit-to-risk ratio is extremely worthwhile in that population setting.

DR. MARTINO: Dr. Rodriguez.

DR. RODRIGUEZ: Yes. With regards back to the pharmacodynamic issues in the question of -- my question is why you selected the 70 milligram versus the 50 milligram BID dosing, because on slide 17 your pharmacodynamics and inhibition data showed that 100 percent was equally effective as any doses higher, if I understand your information here, and your phase one trial responses seem to suggest that. So I was curious about that.

Secondly, just as a clinician, if I understood the information correctly again, on an average patients had to discontinue the drug for 10 to 12 days. It suggests that perhaps a pulsed or intermittent schedule might be safer and equally effective, and I wonder if you have any preclinical data to that effect?

DR. MURRAY: Dr. Nicaise to answer the first question, to provide our rationale for the dose selection of 70 milligrams BID.

DR. NICAISE: We selected the 70 milligram BID, as I indicated in my presentation, for different reasons, the clinical and preclinical data; and I will essentially focus on some of the clinical data.

First of all, we have looked at the inhibition of the phospho-CrkL, and what we have seen is that we have complete inhibition of the phospho-CrkL at doses of 100 and 140 milligrams per day. This inhibition was relatively transient given at the QD schedule, and it was extended to the entire duration of the dosing interval at the BID schedule. So that allowed us to choose the BID schedule over the QD.

Also, the inhibitions [inaudible] was seen at 100 percent at the 100 milligram dose. It was more complete and actually more reproducible from one patient to another at the 140 milligram per day.

The second thing that we have looked at, the dose response that we have seen in the phase one, and there are several ways to do the analysis. You have seen some of the data presented by the FDA. I will show you a different analysis that we have done, which is Slide 23-4.

And what we have done is to look in the phase one trial where the patients could adjust their dose escalating from a certain dose, and look at what dose

did they achieve the major cytogenetic response. So we did not look at which dose they started, but we looked at which dose they were when the cytogenetic response was documented. And as you can see on this slide, most of the cytogenetic responses were seen at the 100 and 140 milligram per day. If we look at the BID schedule, in a very, very small number they were seen at 140 more frequently than at lower dose.

So this has helped us to address this, and this was the rationale for selecting the dose of 70 milligrams BID, because at the time there was adequate evidence of the safety at that dose level with essentially no difference in terms of immediate toxicity within a month of follow-up in those patients who were treated at 70 milligrams BID or 50 milligrams BID. There was no evidence of a dose response.

Now the question that is raised by the FDA is a very important question, which is the starting dose of 50 milligrams BID or 100 milligrams total dose per day. And we recognized that this was a very important question as we were developing the drug, and we have actually initiated a clinical trial to address that particular question.

This is a trial that is actually looking in

chronic phase patients at four different dose schedules, which are 50 milligrams BID, 100 milligrams QD, 70 milligrams BID, and 140 milligrams QD. That trial will allow us to address the question whether -- if we can sustain the activity that we have seen by starting at the lower dose and at the same time reducing the toxicity.

Based on the data that we have it's probably premature to draw any conclusions, because the phase one study and the phase two study do not allow us to draw that conclusion, although we know that there is some indication that the lower dose may be more efficacious, and the patients actually in the trial were maintained at the lower dose because most of them had the dose reduction.

DR. MARTINO: Dr. Goldman.

DR. GOLDMAN: I have just one comment that may require a response.

I think if you just look at the chronic phase patients and the way the data were presented, I think the prognosis for patients who become resistant to imatinib has been unduly pessimistic. Once a patient is resistant to imatinib that does not automatically mean the disease will progress to an advanced phase, and I think the tie-up between the observation of a

kinase domain mutation and the probability of progression to advanced phase is weaker than perhaps one realizes, according to data we've presented and others.

So there is in fact very few presented or published data in relation to the use of, say, hydroxyurea, interferon, homaharataneme [phonetic] in patients who are resistant to imatinib, in chronic phase patients who are resistant to imatinib, and their survival may not be all that bad. They may still be in chronic phase and they may stay in chronic phase.

So the need for a totally new drug for that logic alone is not entirely cogent. But I absolutely concede that the chromosomal data that you presented in chronic phase are very convincing. That's my comment.

My question relates to something rather different, and that is I'm not very clear as to the reasons why doses were interrupted versus reduced. What actually were the criteria that enabled the clinician to decide between interruption and reduction, and what were the criteria that led to resumption of full dose, say, 70 milligrams twice a day in chronic phase?

DR. MURRAY: Dr. Nicaise.

DR. NICAISE: In the phase two protocols the criteria for interruptions were the occurrence of a thrombocytopenia below 50,000 or a neutropenia below 1,000, and the treatments were to resume after recovery of a platelet count above 50,000 or a neutrophil count above 1,000. So these are the criteria that were set. In case of recurrent hematologic toxicity, then reductions could actually occur.

So when you look altogether in the clinical program, and if you look specifically in the chronic phase patients where you have raised the question, approximately 80 percent of the patients had a dose interruption. So at one point or another they started treatment, usually for approximately one week, but only 60 percent of the patients actually had to reduce their dose from 70 milligrams twice a day to 50 milligrams twice a day.

So there is a difference between the dose interruptions, and the dose interruptions, they are not automatic.

DR. MARTINO: Dr. Bukowski.

DR. BUKOWSKI: I have two questions.

One is related to the cardiac toxicity that you

noticed, four percent of patients had congestive heart failure you reported. Was there any evaluation of cardiac function in these patients -- in other words, pretreatment and then during therapy?

And the second question relates to the statement you made about the etiology of the pleural effusions or the fluid retention being related to PDGFR inhibition. Could you clarify if you have data that supports that?

DR. MURRAY: Yes. I'll ask Dr. Nicaise to address both questions, on the cardiac toxicity and on the etiology of the pleural effusions.

DR. NICAISE: The cardiac toxicity, actually relatively few patients had an echocardiogram that were done. And in approximately half of the patients who had an echocardiogram done because of congestive heart failure, the left ejection fractions remain normal.

The interesting thing -- and I think that in my presentation I told you that this was largely linked to a fluid overload -- it's related to the fact that these congestive heart failures and some of the cardiac dysfunction that have been reported occur relatively early in therapy, and most of these patients are treated with diuretics as they are

diagnosed, quote/unquote, as congestive heart failure or whatever. They lose weight. They lose water. And after a few days they feel much better, they resume therapy, and they continue therapy uninterrupted subsequently. And these are the data that have been shown earlier, is that even though they are diagnosed with, quote/unquote, a cardiac event, in the majority of them there is minimal actions taken other than transient interruptions and treatment with diuretics.

Now if we want to address your second question, and if I have slide 13C2, the mechanism of fluid retention with some of the tyrosine kinase inhibitors -- and there was a recent editorial, I think it's in JCO -- is likely attributable to the inhibition of the PDGF beta receptors. And the data are coming from essentially two potential difference sources. The first one was a publication in 1999 that demonstrated the PDGF beta regulated the interstitial fluid homeostasis in mouse model, and disregulating this is linked to essentially interstitial fluid retention.

The second one is that in recent years there is a number of drugs that have been in development, monoclonal antibodies that have been in development

that are known to inhibit to a certain degree the PDGF receptor. Imatinib is one, dasatinib is one, but other tyrosine kinase inhibitors are similar to that and are known to have fluid retention.

But the most interesting one is probably a monoclonal antibody called CDP-860, which is a specific inhibitor of PDGF beta. And in the phase one trial of that particular monoclonal antibody, seven out of eight patients developed ascites and pleural effusions to a very high level within a few days after the initiation of therapy, which is concurrent and consistent with the data that have been described in linking the fluid retention, the fluid overload, to the PDGFR inhibition.

DR. MARTINO: Dr. Karanes.

DR. KARANES: Yes. This is related to the dose response again, but is in relation to the clinical response in terms of hematologic response or major cytogenetic response.

In a patient that didn't have any interruption or maintained the regular dose versus the one that received reduced dose, do you have any data to show that the one that didn't have reduction of the dose had better response?

DR. MURRAY: Dr. Nicaise.

DR. NICAISE: We looked carefully at these data, because the common sense would say that it's important to be on the drug to respond to therapy. And indeed, this is what we have found. Interruptions of small duration have relatively no impact on the response, hematologic or cytogenetic response.

So when we look at these data we show that, and we saw in the clinical trial that if the dose interruption is less than four weeks there is no difference between the cytogenetic and the hematologic response in those patients who had short interruptions relative to those who have no interruptions. On the contrary, if the interruptions are greater than four weeks, in most patients, especially in the chronic phase, there is a decrease on the level of activity.

We also looked specifically at the issue of dose reductions, and we have seen that at the 70 milligram BID, the 50 milligram BID, and to some extent even at 40 although the data are difficult to interrupt, the activity is maintained even in patients who had to reduce the dose at 50 milligrams twice a day.

In addition, what we have also shown -- and this is also related to dose -- is in those patients who

were not responding at 70 milligrams BID, if we were escalating the dose to either 90 or 100 we were still able to rescue some patients and induce response in some of those patients.

DR. KARANES: Thank you.

Can I ask another question? For the fluid retention is there any factor that you can use as a predictor so that we can monitor those patients more carefully?

DR. NICAISE: Actually, unfortunately we have not identified any predictor for that. We have looked at the baseline characteristics of those patients including their disease characteristics, some of the other prognostic factors, and there was no evidence that any one in particular would predict for the occurrence of pleural effusions. And unfortunately, we cannot say that they are more frequent in one population than in another.

DR. KARANES: Thank you.

DR. MARTINO: Dr. Berman.

DR. BERMAN: I have a few questions.

First, as it relates to the CrkL phosphorylation as a rationale for the phase two studies, were these done in CML cell lines or in fresh patient samples?

DR. NICAISE: I'm sorry, I could not hear the end

of the question.

DR. BERMAN: The CrkL phosphorylation studies, were these done in cell lines or in fresh patient samples?

DR. NICAISE: The phospho-CrkL?

DR. BERMAN: Yes.

DR. NICAISE: Maybe I can ask Dr. Shah to answer that question.

DR. SHAH: Yes. The phospho-CrkL analysis was performed four hours after initial dose of dasatinib in a peripheral blood sample from the patients.

DR. BERMAN: Okay.

Second question, you had a lot of mutational data on these patients, and in the patients who had lymphoid blast crisis or Ph-positive ALL and myeloid blast crisis the responses were short-lived.

Did you look at the cells following treatment? Were the same mutations present when the disease progressed, or did new mutations develop?

DR. MURRAY: Dr. Nicaise.

DR. NICAISE: In the phase two trial we are in the process of looking at these data, and I don't have the data at this point.

DR. BERMAN: Third, to me it's hard to relate inhibition of PDGFR and the pleural effusions. And

you showed some data on slide 49 where the time to event ranges from one day to 343 days. It would seem to me that you would see the pleural effusions cluster shortly after starting therapy if PDGFR inhibition is in fact the cause.

DR. NICAISE: We have seen some of the pleural effusions occurring relatively early during the treatment. But actually they can occur at any time, and there is no time point, and most common occurrence at the early stage of therapy than at later stage of therapy. So at this stage our best response to that is that there is no difference in time point that we have observed at this point.

DR. BERMAN: But again, it would seem that to see this almost a year out after starting therapy doesn't point the finger at PDGFR inhibition.

DR. NICAISE: That's possible. That's the best explanation that we have. This is what has been seen and reported with other tyrosine kinase inhibitors, and we have not identified any other parameter that would trigger the fluid retention or the pleural effusion other than the PDGFR inhibition.

DR. BERMAN: Another question related to that, it seems what Dr. Kantarjian is describing is very similar to what's seen in patients who take all-trans

retinoic acid for acute promyelocytic leukemia -- that is, a leaky capillary syndrome that is treated with a short course of Decadron in that case. Is that in fact what you're going to be recommending at the first sign of these pleural effusions?

DR. MURRAY: Dr. Nicaise will address the question on our recommendations for managing pleural effusion.

DR. NICAISE: So as we have learned through the phase two program about the pleural effusions, it has become apparent that indeed it may be very similar to capillary leak syndrome, and that these patients are usually symptomatic before developing these pleural effusions, either a cough or dyspnea.

So our recommendation at this point in time is to, when patients present with one of these symptoms, to do a chest x-ray, to assess whether there is preliminary edema or any sign of fluid retention including pleural effusions; if those signs are identified to stop treatment, initiate therapy with corticosteroids and diuretics until the situation is under control; and subsequently to resume therapy at one dose level.

These are new findings that we have as we move towards the interpretation of the clinical trial, and

these hypotheses have not been tested in a prospective way. But these are recommendations that we will make in our clinical trials.

DR. BERMAN: And then just two quick questions about the hypocalcemia that you saw. Was this at all related to phosphate levels or albumin?

DR. MURRAY: The question is, does the hypocalcemia relate to the phosphate levels or the albumin?

I apologize for continuing to repeat the questions, but we are having a hard time hearing.

Dr. Nicaise.

DR. NICAISE: I apologize. I'm having a very, very hard time to hear.

So is hypocalcemia related to hypoalbuminemia?

DR. BERMAN: Yes.

DR. NICAISE: Actually, when the hypocalcemia that I described, which is approximately 50 percent altogether and 10 percent grade three or four, are uncorrected hypocalcemia, if you correct for the albumin level there's a reduction of 10 percent, which are approximately 40 percent hypocalcemia all grades and 6 or 7 percent grade three or four.

DR. BERMAN: Then the other question was the QT prolongation. Was that related to hypocalcemia, or

is that a direct effect on Purkinje fibers?

DR. NICAISE: Actually, in the nine patients who were reported to have a QT prolongation as an adverse event, not the patients who were having sequential EKG, but the nine patients who had an adverse event of QT prolongations, eight of these nine had some level of hypocalcemia. And actually these were transient, and actually only one of these patients had actions taken. But it's possibly related to that.

DR. MARTINO: Thank you. I know there are a few others of you that want to ask questions. However, I need a break, therefore you're getting a break. I'd like you back here in 15 minutes.

[Break from approximately 12:21 - 12:37 p.m.]

DR. MARTINO: The next portion of this meeting is the open public meeting. We have three speakers who have asked to address the group. There is a microphone in the middle of the auditorium which is the one that will be used by the public speakers. Ms. Clifford will announce the speakers, but before she does that I need to read a statement to you from the FDA:

Both the Food and Drug Administration and the public believe in a transparent process for

information gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship you may have with the sponsor, its product, and if known its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, the FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement it will not preclude you from speaking.

MS. CLIFFORD: Our first speaker is Ms. Musa Mayer.

MS. MAYER: Let me begin by saying I have no conflicts of interest to declare and that I paid for my own travel expenses to this meeting. I'm an

independent patient advocate, although I do collaborate and consult with different organizations.

Since my own recovery from stage two breast cancer 17 years ago, I've been working to help women who are living with metastatic breast cancer, the incurable and progressive form of the disease that is responsible for the death of 40,000 American women each year. I don't need to tell you that the development and approval of new drugs is a lifeline for these women and their families. That's what led me to my work as a patient representative and consultant with the FDA over the past few years.

As you know, at every meeting of the Oncologic Drugs Advisory Committee a patient advocate sits as a voting member. It has been my honor to serve a number of times as a patient representative to ODAC, thanks to the FDA's Office of Special Health Issues and their excellent training program for advocates. Today, as ODAC visits ASCO, I'd like to say that it has meant a great deal to me, and I believe to other patient advocates, that our voices are heard in these deliberations and that FDA actively solicits and values our input.

While FDA has been vocally and repeatedly attacked at ODAC meetings and elsewhere in recent

years for its lack of compassion for cancer patients, I wanted to take this opportunity to state publicly that there are many cancer advocates and advocacy groups who understand the crucial importance of high quality evidence in the compassionate care of cancer patients at all stages of disease, and who realize that it's only through maintaining the highest standards that we will get treatments that really work. We also care about getting treatments to patients who need them at the earliest possible moment through expanded access programs and accelerated approvals.

When I began my work as an advocate in the early 1990s, it was widely believed in the breast cancer community that high-dose chemotherapy with bone marrow or stem cell transplant was the treatment of choice. Though few understood it at the time, that belief was based on inferior evidence from uncontrolled trials by comparison with historical controls. Because they were told it was their only hope, tens of thousands of women with locally advanced and metastatic breast cancer demanded access to and received this highly toxic, unproven treatment outside of the randomized trials set up to test whether it really worked.

As sometimes happens, emotional appeals and heart-rending stories won out over reason and science, over hard looks at evidence or lack of evidence. As a consequence, the randomized controlled trials designed to determine efficacy took years longer to enroll than they should have. By the end of the 1990s, when the randomized trials finally reported their results, bone marrow transplants were proven to be no better than standard chemotherapy but far more toxic.

Of course, our intentions had been good. We thought it was compassionate to argue for access to this investigational treatment prior to good evidence of its safety and efficacy. But it was not. Thousands of women suffered terribly as a result and many died. We all lost women we loved. Families were impoverished. If only we had waited. But there were no controls, and desperation and hope ruled the day. This horrendous experience taught my generation of breast cancer advocates the hard way that we needed to care more about levels of evidence, and that if we were to serve the needs of our constituents with true compassion we had to do more than push for early access.

Today I am hopeful because new targeted

treatments, like the one you are reviewing here today, are beginning to change the face of cancer. So in a time of innovations undreamed of only a decade ago, reflecting on the past may seem irrelevant to some, but it is not. Progress, far from consisting in change, depends on retentiveness. Said philosopher George Santayana, "Those who cannot remember the past are condemned to repeat it."

Thank you.

MS. CLIFFORD: Thank you very much, Ms. Mayer.

Our next speaker is Carolina Hinestrosa.

MS. HINESTROSA: Good afternoon. I have no conflicts of interest to report. My organization, the National Breast Cancer Coalition, receives some educational grants from pharmaceutical companies, and the information is available in our web site; as per board-approved policy, just a limited amount of support.

Again, my name is Carolina Hinestrosa. I am a two-time breast cancer survivor, and I'm the Executive Vice President of the National Breast Cancer Coalition. I am pleased to have the opportunity to speak before ODAC about the importance to consumers of preserving scientific rigor in clinical research and the role of clinical trials as

we seek to find real answers about cancer and translate them into real prevention and real cures.

The National Breast Cancer Coalition has been fighting for improvements in breast cancer research since our inception in 1991. Our core values for research -- integrity, impact, accountability, respect, beneficence, justice, shared decision-making, and flexibility -- put the patient at the center of the research endeavor, ahead of science for its own sake, of personal prestige in scientific circles, and of commercial gain. NBCC works under the philosophy of evidence-based health care. We need to learn what really works for women with and at risk for breast cancer, and all women need access to current scientific evidence about the most effective care available.

Based on our core values, NBCC developed a position on access to investigational interventions outside of clinical trials. We also oppose and developed a position on the Abigail Alliance's lawsuit against the FDA that was filed by the Washington Legal Foundation. Investigational treatments made available outside of clinical trials undermine the trial system that is a pillar of evidence-based healthcare and ultimately delay the

answers patients desperately need. Interventions must be based on high-quality evidence, and appropriately designed randomized clinical trials are the gold standard to evidence.

In this country we lose an average 111 women each day to breast cancer. Every death is a tragedy. NBCC is committed to working to find the causes, prevention and cures for this disease so it can be eradicated. We are impatient to find answers so no one runs out of treatment options and no more lives are lost. We're frustrated by the slow pace of discovery of truly effective interventions. Unfortunately, despite media and institutional hype about breakthroughs, history tells us that most experimental drugs do not turn out to be effective or they provide only incremental benefit.

As a patient-centered organization, NBCC believes it is important to create reasonable expectations for patients about experimental therapies. We must not foster a climate where patients believe that access to investigational interventions is their best hope, when in fact it is most often false hope. The harsh fact is that after conferring under well-designed and properly conducted phase two studies, the true impact on both efficacy and safety are not known, and their

use by individuals outside the study conditions provides little useful information.

The lawsuit that I referred to before undermined the clinical trials process. We all know that allowing patients to obtain any investigational therapy outside a trial removes the incentive for patients to participant in studies and undermines accrual efforts. Inability to enroll patients creates a major barrier for investigators evaluating the safety and efficacy of the intervention.

Musa referred to the example of bone marrow transplant, so I'm not going to talk about it. I was going to before I heard her speak.

NBCC supports strengthening the FDA's role to encompass a clear and rigorous path to demonstrate efficacy and safety. Ultimately that is the best protection for patients.

In addition to undermining the effort to determine true efficacy and safety, all trial access to investigational interventions raises serious issues of fairness. The availability of these therapies is often limited by practical and economic constraints. Individual patients sometimes gain access through single patient INDs, a practice also known as compassionate access. These patients are

usually well-connected. They have access to physicians who have the ability to develop a protocol for them and are willing to implement it. This is not the case for most patients with cancer.

The off-trial process involves a great deal of time and expense for clinicians, regulators, and investigators, while unfortunately there is little chance of benefit to the patient and no chance we will learn anything to help other patients. We believe that resources devoted to fight breast and other cancers must be allocated fairly based on the best evidence available.

This is the first time the Oncology Drug Advisory Committee has its meeting during the annual meeting of ASCO. ODAC fulfills a critically important role in evaluating data concerning the safety and efficacy of marketed and investigational human drug products for use in the treatment of cancer. I am somewhat concerned that the credibility of the process could be compromised when stakeholders that stand to gain financially from ODAC's decisions are in such proximity in abundant numbers. I encourage ODAC to carefully assess the benefits and potential drawbacks of a meeting simultaneously with ASCO to avoid the perception of bias and undue influence.

Thank you.

MS. CLIFFORD: Thank you very much for your comments.

Our next speaker is Ms. Bev Parker.

MS. PARKER: Thank you for allowing me to present this statement. I have no conflicts of interest to disclose.

I'm Bev Parker, a three-time breast cancer survivor. I represent Y-ME National Breast Cancer Organization. The mission of Y-ME is to ensure through information, empowerment, and peer support that no one faces breast cancer alone.

It's important to Y-ME that patients have access to the medications or drugs that work best for them to combat breast cancer, reduce the risk of recurrence, and overcome side effects. Breast cancer patients want the very best care and access to the very best treatment. We know this at Y-ME because we hear from more than 40,000 breast cancer patients and survivors each year on our 24-hour hotline. When news of a new potential drug is announced many patients contact us. They want to know whether it will work for them and whether they will have affordable access to the treatment.

Therefore, we commend the FDA and ODAC for

establishing the accelerated approval process for new cancer treatments. This regulatory process has given cancer patients access to new drugs as soon as they are proven effective, benefiting not just patients but the whole cancer community.

However, it concerns Y-ME that before FDA approval some new treatments or drugs would be made available to patients outside of a clinical trial. We do understand the emotional climate of affected patients and their families, but we insist on high levels of evidence in drug development for cancer. Cancer patients should not be given false hope with unproven treatments. We must have the best science available, and that can be achieved only by well-designed clinical trials.

For those patients who believe they have exhausted all of their options, the FDA allows compassionate use during phase three or, in certain cases, during phase two trials. To do so earlier has both the potential of weakening the integrity of the FDA as a scientific body and being detrimental to patients in the long run. Accrual to ongoing clinical trials and the marketing approval of the drug could be delayed, in turn harming the best access for the greatest number of patients.

For breast cancer patients and all patients, Y-ME requests that the FDA continue granting approval to cancer drugs based on science and good clinical trial evidence. We encourage the FDA to implement regulations for an expanded access program for unapproved drugs that would benefit the greatest number of cancer patients.

Thank you.

DR. MARTINO: On behalf of the committee I'd like to thank all three of our public speakers.

Does the FDA wish to respond to our second speaker in terms of why this meeting is being held in conjunction with the ASCO meeting?

DR. PAZDUR: First of all, one of the, as I mentioned in my introductory comments, one of the reasons why we made a decision to have this meeting here in Atlanta is to provide a venue to have people that would not have an opportunity to come to Washington to participate in these meetings. This is primarily a logistic issue. There many people here, both from an international perspective as well as a national presence, that don't have the opportunity to make it to Washington, D.C., for a meeting. Hence, we thought it would be appropriate to have a venue that is outside of the Washington metropolitan area.

DR. MARTINO: Thank you.

Next, there were some of you who had questions that we did not get to before the break. If the sponsor can retake the podium.

Dr. Eckhardt, I believe you were next.

DR ECKHARDT: Yes. I had a question for Dr. Kantarjian, and that is I'm still sort of stuck on this dosing issue between 50 and 70. And one of the questions I would have would be, as a clinician, is there a reason?

One of my concerns revolves around the constant hearing of interruptions and reductions of the 70 milligram dose, and certainly with kinase inhibitors that can be concerning that you can lose the activity.

On the flip side, the question is whether as a clinician you would be comfortable with dosing at 50 and proceeding with dose escalation? Or is there a reason that you feel that it's a better approach to actually start at the higher end of toxicity and then use reductions as needed?

DR. MURRAY: Dr. Kantarjian.

DR. KANTARJIAN: From the data we have today, we feel that the 70 milligrams orally twice a day is an effective dose and is manageable. So like with any

other drugs, for example, recently linolenamide was approved at 10 milligrams a day, but we know that 80 percent of the patients had to have dose reductions. So whenever we get into a drug it is sometimes naïve to think, well, this is the dose that we are recommending, and that's going to be the final dose.

I'm going to give two examples in leukemia which are close to this one. The first one is with Gleevec®. Six years into the treatment we still do not know whether the dose is 400 or 800 milligrams a day, and we're arguing about it. Another less close example is RIC. RIC has been with us for 30 years, and yet the dose ranges in the schedule are anywhere from 1 gram to 15 grams per meter square per course.

So from the data that we have from the trials, we know that 70 milligrams twice a day is effective and safe, but we recognize that there is the possibility that the 50 milligrams twice a day may be as effective and associated with less side effects. So the company has already completed large-scale trials comparing the twice daily with the single dose and the 100 versus 140. So it's a four-armed randomized trial of 50 milligrams twice a day, 100 milligrams daily, 70 twice a day, 140 daily. Those studies are completed. We're just waiting for the maturation of

the data. And if we feel that there is a better dose schedule -- for example, the single dose or the 100 as opposed to the 140 -- then things can be adjusted.

At this stage I think there are so many patients that do need this drug, and I do feel that the efficacy versus the risk ratio is very worthwhile. And 70 milligrams twice a day is effective and manageable.

DR. MARTINO: Dr. Shah, would you please provide your perspective as well?

DR. ECKHARDT: Sorry, I just wanted to make the comment that in fact imatinib, though, is dosed starting at the lower end with dose escalation as tolerated.

DR. SHAH: I would just like to first, I think, follow on what one of the public speakers said, and that is trying to avoid mistakes of the past.

The decision to go with 400 milligrams of imatinib was based on initial response rates that looked very good and acceptable toxicity. When it became apparent to us in the field that resistance was driven by mutations, many of which are actually sensitive to higher concentrations of imatinib *in vitro*, that decision to go with a lower dose initially seemed not to have been the wisest, using

20/20 hindsight.

So my feeling is that with targeted agents this is going to be a very difficult issue, I think with all targeted agents. When I think about epidermal growth factor receptor inhibitors, Tarceva®, which has shown more activity than IRESSA®, is actually a dose closer to the MTD. Now I don't know that that's necessarily responsible for its greater efficacy, but it certainly suggests as much.

Thinking again forward about what we may face with dasatinib and dasatinib resistance down the line, it's entirely possible that there will be mutations that cause resistance to dasatinib that may be sensitive to a higher dose, and one could almost make an argument that we should be trying to dose closer to an MTD which has not even yet been established.

So in my clinical practice I've come to appreciate the importance of really individualizing doses for patients. Certainly some patients respond to less doses of dasatinib. I've also seen patients require higher than 90 milligrams twice a day to achieve cytogenetic response.

So given the complexities, I feel that 70 milligrams is a very reasonable starting point.

DR. MARTINO: Dr. Reaman.

DR. REAMAN: Just to follow up again on the pleural effusions and the plan for recommendation for the use of short-course steroids in its management, since that was done in the earlier trials, was there any evaluation of the potential effect of concomitant meditation on responses, particularly in patients with lymphoid blast crisis?

DR. MURRAY: Dr. Nicaise, question is was there any effect on safety and efficacy of --

DR. REAMAN: Not safety, but efficacy.

DR. MURRAY: On just efficacy.

DR. REAMAN: And are you sure that going forward that you're making the right recommendation?

DR. NICAISE: At this point there is no evidence that there is any interactions with concomitant medications on the safety of the drug, on the safety profile that we have observed.

DR. REAMAN: My question doesn't relate to the safety profile of the drug, but to whether or not the activity that was seen was a result of dasatinib or a result of steroids in patients with lymphoid blast crisis.

DR. NICAISE: Oh, I'm sorry. I apologize. I did not hear the question.

I think that it's safe to say that the activity was related to the activity of dasatinib because steroids were not used early in the treatment of those patients. They were used eventually later on for a short course of therapy when they were already in response. The average time to achieve a response in lymphoid blast crisis is less than four weeks.

DR. REAMAN: And the other question relates to the fact that there was a difference in response rates between imatinib resistant and intolerant patients. The resistant patients I can understand, but can you give a better clarification or description of what constituted intolerance to imatinib from the standpoint of eligibility of patients enrolled in these trials, and whether or not there was an effect on response in those patients?

DR. NICAISE: Actually, let me start by the resistant issue and come back to the intolerance, to better understand the difference in the populations and at the same time the difference in responses that we have seen.

The resistant patients were essentially patients who were treated with imatinib at doses up to 800 milligrams, responded and then progressed. They are actually in a late chronic phase, and they are

essentially a fairly poor prognostic group of patients.

The intolerant patients comprise two groups of patients which are divided essentially equally. One group of patients are patients who responded to imatinib, achieved a major cytogenetic response, were maintained on imatinib for their major cytogenetic response, and developed at that particular time toxicities that precluded the continuation of imatinib such as liver toxicity, grade three or four liver toxicity, grade three or four skin toxicity, which were usually recurrent even if the patients were rechallenged, which occurred in about half of those patients; and those patients had to discontinue imatinib when they were actually responding. At that time these patients lost their response to imatinib and were put on dasatinib, and these were patients who were potentially sensitive to a BCR-ABL inhibitor, and therefore they had a rescue to imatinib.

The second group of patients is a group of patients who essentially was never able to achieve a response from imatinib because they never had a fair trial on imatinib. They started at 400 milligrams, and some of them within days they had liver toxicity,

had to stop. Some of them were retreated at doses as low as 100 milligrams and could not be maintained. So in those patients a BCR-ABL inhibitor was never really tested at the appropriate dose.

So that group of patients has a much more favorable prognostic, because essentially they were either responsive to a BCR-ABL inhibitor or were never tested on a BCR-ABL inhibitor. And what you have seen is that in this group of patients the responses that we have achieved are very similar to what has been achieved with imatinib when given an interferon failure patient.

DR. MARTINO: Dr. Harrington.

DR. MURRAY: Dr. Kantarjian, would you like to comment further on that, on intolerance and benefit to intolerant patients?

DR. MARTINO: If I can simply hold you, I think -- was the answer adequate?

DR. REAMAN: [No audible response]

DR. MARTINO: Thank you.

Dr. Harrington.

DR. HARRINGTON: Thank you.

Two questions about the randomized study of dosing. First, when will it be mature enough that it can be analyzed and presented? And then second, does

the population of patients in that study align perfectly with the population that we've heard about today? Does it have -- across the phases of CML?

DR. MURRAY: Dr. Nicaise.

DR. NICAISE: The randomized study has been fully accrued, and we have now a minimum of three months of follow-up on all patients. And the three months follow-up is the preliminary endpoint in that trial, and the study will be presented tomorrow.

The second part to your questions is that the populations were not exactly similar. These are patients who were treated at 400 or 600 milligrams, while in the study that we presented in the phase two trial, most of them were treated at 800 milligrams of imatinib.

DR. HARRINGTON: So I guess I have a question perhaps for our chair, and that's whether it is in bounds to ask about the data from that randomized trial since it apparently will be shown tomorrow. Could we learn more about it?

DR. MARTINO: I'm not sure that I have an answer that I can give you. I'm assuming that ODAC has certain restrictions --

DR. PAZDUR: You should take a look --

DR. MARTINO: -- but the FDA can speak.

DR. PAZDUR: You should take a look at all available data.

DR. MURRAY: So I'll have Dr. Nicaise then walk through the data. I do want to clarify that these data are not part of the NDA so they haven't been reviewed by the FDA, although the FDA is indeed aware of the data and has seen them. But they are not part of the review.

DR. MARTINO: Right. I will allow you to do that, but recognize that time is critical here. And in fact, I'm going to give you not more than about five minutes to do that.

DR. NICAISE: Okay. I will try to do this in three minutes. And I just want to clarify that the data were not in the NDA because at the time of the submissions the trials were actually not yet accrued.

So my I have first slide 24-2. This slide summarized the data in the 150 patients that we recruited in this randomized phase two trial. There were 101 patients treated with dasatinib and 49 treated with imatinib. As you can see, the highest dose in the trial for imatinib was 600 milligrams per day, which is lower than what we had in the non-comparative studies. Overall, this was a less heavily pretreated group of patients. Pretreatment

characteristics were generally similar between the two groups, with the exceptions of the BCR-ABL mutations which were more frequent in the dasatinib group relative to the imatinib group.

May I have slide 24-3. This gives you the dispositions of the patients with a minimum of three months of follow-up in those patients. As you can see, there is a difference between the two groups with a higher rate of discontinuation in the imatinib group of 76 percent compared to dasatinib of 15 percent. The difference in the rate of discontinuations was largely linked to the progressions or no response in the imatinib group relative to the dasatinib group.

May I have slide number 24-4. We summarized the cytogenetic and hematologic response in those patients. As you can see, the cytogenetic response rates are higher in the dasatinib group, specifically the complete cytogenetic response rate which was 21 percent after three months of follow-up in the dasatinib group compared to 8 percent in the imatinib group. In those patients who would continue beyond the three months the overall response rate, the cytogenetic response rate, major and complete, were also in favor of the dasatinib compared to imatinib,

especially the complete cytogenetic response rate which was 27 percent and 12 percent.

Slide 24-5. If we look at specific subgroups of patients, we see that the difference in major cytogenetic response rate was seen in those patients who were the most heavily pretreated. Patients with prior interferon therapy, patients who have received imatinib at 600 milligrams per day, and patients with no prior cytogenetic response to imatinib, where there is a 23 percent major cytogenetic response rate to dasatinib versus none for imatinib.

The next one I present to you, which is slide 24-2 [sic], the time to treatment failure, and in this slide treatment failure is defined as either progressions or lack of response or intolerance. And the difference is in favor of dasatinib, where the majority of the patients remained on study, while in the imatinib group at the time of this analysis only 20 percent of the patients were still on study.

Slide 24-7 summarized the toxicity of the drug, and this is very consistent with what we have seen in the phase two trial. Fluid retention is the most common adverse event. It's present in 43 percent of the imatinib 800 milligram patients and 25 percent of the dasatinib patients. In imatinib it's mostly

superficial edema. In the dasatinib group we have a 10 percent, 11 percent rate of pleural effusions. There are some other differences between the two drugs in terms of adverse events, but in general they were relatively similar between the two groups.

In slide 24-8 is a summary of the myelosuppression, which is more significant in the dasatinib group compared to imatinib. We have the same type of rate of myelosuppression, thrombocytopenia and neutropenia that we have observed, around 50 percent in the dasatinib group versus 10 to 40 percent in the imatinib group.

So this is in five minutes a very quick run through the randomized trial that will be presented tomorrow.

DR. MARTINO: I'm not sure that that is what you were asking. Do you want to re-ask your question?

[Laughter]

DR. MARTINO: But that was lovely, and we do thank you.

DR. HARRINGTON: It was an impressive presentation on the fly.

My question was about the dose finding study -- not the dose finding study, but the randomized study that looked at the four different schedules and when

that would be ready.

DR. MURRAY: Okay. We have two ongoing studies that have completed accrual, but it will -- to follow them adequately the patients need to be followed for 6 to 12 months. So that data is off somewhat in the future.

DR. HARRINGTON: How far in the future?

DR. MURRAY: Since we just recently completed accrual, it would be dependent on whether the six-month data or the 12-month data would be most important to FDA. So we'd be looking at a 9- to 15-month period of time before those data would be available.

DR. HARRINGTON: Thank you.

DR. MARTINO: And I had one last question, and that is the four trials, the phase two trials that you have presented for this application, patients will be followed to what endpoint, please?

DR. MURRAY: The original primary and secondary endpoints will be followed up to 24 months.

DR. MARTINO: With that we thank you.

And at this point the committee will turn its attention to the questions that have been posed to us from the FDA, and I think that we have slides of those. I will start by reading them to you. And

since what needs to happen is a discussion, fairly succinct I would hope, and then voting on the various questions.

Question number one: The Agency has accepted durable responses in hematologic malignancies for approval for both chronic leukemias in the accelerated approval situation and acute leukemias in the regular approval setting. The FDA granted Gleevec® accelerated approval for chronic, accelerated, and blast crisis phases of CML based on durable major cytogenetic responses and major hematological responses.

Based on the magnitude and duration of responses, has the sponsor provided sufficient evidence for dasatinib's effectiveness for the following: Chronic phase CML, accelerated phase CML, myeloid blast CML, and lymphoid blast CML? And please note that the Philadelphia chromosome ALLs are not included in this question.

And so to that question I will take discussions, the same manner as before. If you would raise your hand I will acknowledge you in turn.

Dr. Hussain.

DR. HUSSAIN: So this question is to the leukemia specialists here, and then to the FDA.

What is the definition of major hematologic responses and durable? So in the context of leukemias that we're dealing with, how do clinicians define major and how do they define durable?

DR. MORTIMER: The briefing documents actually, that the company provided on page 16.

DR. HUSSAIN: Which says?

DR. MORTIMER: Which says that a complete hematologic response is a white count less than the institutional upper limits of normal platelet sets of 450,000, no blasts or promyelocytes in the peripheral smear, less than 5 percent myelocytes plus metamyelocytes in peripheral, peripheral basophils less than 20 percent, and no extramedullary involvement.

DR. HUSSAIN: Dr. Mortimer, I recognize that, but it would seem to me there's a difference if it happens in one patient versus in 50 percent of the patients.

So I go back and ask the question, what would be the rate would be considered an important rate, and then what is the duration that is considered clinically relevant?

Perhaps Dr. Karanes or --

DR. KARANES: To me the most impressed response

is in the group that is imatinib resistant. And those patients that respond respond probably at three months that show a major cytogenetic response, and when we treat CML I think we aim for major cytogenetic response. That, to me, is very impressive in this efficacy data that has been shown.

DR. GOLDMAN: Could I return to a point that I made before?

I don't think the hematological responses in any of these patients in any phase of disease is critically important in comparison with what might have been achieved with other cytotoxic or interferon or indeed a transplant. But what is of great fascination, I think to the clinician, is the degree to which the residual disease appears to have been reduced using chromosomal markers.

And it's therefore the cytogenetically, so-called major cytogenetic response, which as we've heard includes complete cytogenetic response and partial cytogenetic response, that is a thing that would not have been expected with all other therapies other than allografting. And I think that's a very convincing index of the value of dasatinib in patients judged to be resistant to imatinib.

DR. MARTINO: Dr. Levine, you want to add to

that, please?

DR. LEVINE: I agree with Dr. Goodman, and in addition I would just make another comment.

And that is in the myeloid blast crisis, that's an exceedingly difficult disease. These are patients resistant to imatinib. The fact that there are 30 percent major responses that are durable beyond six months is huge in a clinical sense. That's a huge thing. And frankly, it's not as huge in lymphoid to me, but those diseases are not well treated by us at all. So there are very few options.

DR. MARTINO: Dr. Berman.

DR. BERMAN: I would agree, especially since the patient population in the lymphoid blast crisis, myeloid blast crisis were heavily treated. I think close to 50 percent of patients had already had a stem cell transplant, so you're dealing with a refractory group of patients. I think that the data for the cytogenetic remissions is valid across the board for all the disease subtypes they looked at.

DR. MARTINO: Is there any subgroup in whom you are not impressed?

DR. BERMAN: No.

DR. MARTINO: Is that a general hematological statement from our hematological colleagues?

DR. BERMAN: Correct.

DR. GOLDMAN: Yes, I share that view.

DR. LEVINE: I do as well, and would agree that in the chronic it's much more difficult because survival doesn't mean anything here. It's the chromosomes that mean something.

And to be quite honest to the company, in future studies it would be very nice to have some central review. That was an error and shouldn't be done in future studies. On the other hand, because we're making a big deal about the cytogenetic responses, but that to me is the bottom line on the chronic cases.

DR. MARTINO: It also strikes me that the patients that have gone into a response by these definitions have stayed there for at least six months of follow-up, which is what we have at least in the briefing documents. So it does appear that there is some durability to this biology, however one achieves it.

Are there other questions, other comments?

[No responses]

DR. MARTINO: If not, I'm actually going to take a vote on this question.

And recognize that the question again is specific

and excludes the Philadelphia chromosome patients, nor does it ask for your judgment in terms of toxicity. That will follow. So the issue is very clearly, are you impressed with the level of activity that this drug has demonstrated?

And we'll start on my left. As you vote I need you to announce your name, and then a yes or no vote.

DR. BERMAN: Berman, yes.

DR. KARANES: Karanes, yes.

DR. GOLDMAN: Goldman, yes.

DR. REAMAN: Reaman, yes.

MS. HAYLOCK: Haylock, yes.

DR. LEVINE: Levine, yes.

DR. BUKOWSKI: Bukowski, yes.

DR. ECKHARDT: Eckhardt, yes.

DR. MARTINO: Martino, yes.

DR. HUSSAIN: Hussain, yes.

DR. HARRINGTON: Harrington, yes.

DR. RODRIGUEZ: Rodriguez, yes.

MS. BROWN: Brown, yes.

DR. MORTIMER: Mortimer, yes.

DR. MARTINO: It is a unanimous yes, and I thank you.

The next question is number two, and I will again read it to you:

The major toxicities that observed with dasatinib include the following: gastrointestinal and hematological toxicities, fluid retention, bleeding, and myelosuppression. Less frequent but serious adverse events include cardiac toxicity and intracranial bleeding.

Based on phase two data, does the risk/benefit profile support dasatinib's approval for the following: Again, it's chronic phase CML, accelerated phase CML, myeloid blast CML, lymphoid blast CML, and excludes the Philadelphia chromosome-positive patients.

Discussion on this item? And again, this is the question really of benefit versus toxicity, and therefore your overall assessment of is this a drug that we want to give accelerated approval to.

And Dr. Pazdur, am I correct that that is the intent, accelerated approval only?

DR. PAZDUR: Yes. If we take a look at the similar situation that we encountered with Gleevec®, the conversion to regular approval was based on submission of further follow-up data when this data becomes mature, so accelerated approval was given.

And here again, please note we're talking about the imatinib resistant population, because we're

going to be coming back to the intolerant population in the next question.

DR. MARTINO: And I thank you for that clarification.

And again, there is a separation in this question. It is purely the patients who demonstrated resistance to imatinib.

And maybe I can turn again to our hematological colleagues on the committee. Your overall thoughts as to the toxicities that have been presented and their manageability, are these a level that you consider appropriate given this patient population?

Yes, doctor.

DR. BERMAN: The drug is more complicated to give than imatinib. Imatinib was straightforward, few dose reductions along the line. This, with the potential for cardiac complications and the potential for pleural effusions, pericardial effusions, leaky capillary syndrome, is going to make it a little bit more complicated.

That said, I think it's clear, at least it is to me, that the risk benefit is far in favor of the benefit.

DR. KARANES: I agree with Dr. Berman. I think that as clinicians we need to monitor these

populations very carefully. Many times we forgot that we prescribed oral medication, and we assume that the patient will call us when they have problems. And I think that we have to be -- the guidelines have to specify how do you monitor these patients carefully in the recommendation.

DR. GOLDMAN: Yes, I think I agree with that.

There are obviously two major areas of toxicity which have caused the morbidity and mortality, and that is myelosuppression on the other hand and fluid retention on the other. But it seems that as experience is gained, prophylaxis in terms of either efforts to prevent platelet transfusions, for example, or early intervention with efforts to prevent the pleural effusions, will reduce the toxicity to individual patients. And in an oncological setting, I think it's okay.

DR. LEVINE: I would agree. As hematologists we are used to dealing with patients who have very low platelet counts, especially in this setting, and that would not be particularly difficult.

The effusions are more difficult. Certainly not rate limiting in my own view, but if in fact these pleural effusions can occur a year later and the symptom is a cough, then I would imagine that we're

going to deal with a lot of upper respiratory tract infections in chest x-rays.

So there may be some practical issues here, but certainly not issues that would stop me from wanting to use the drug.

DR. MARTINO: Can I ask the question again of the hematological members of the committee: Are there reasonable good or poor alternatives for these patients?

DR. BERMAN: The alternatives for patients with imatinib resistance or imatinib refractory disease are really that of stem cell transplant, which is really a whole different league of type of treatment. For patients with accelerated and blastic phase disease, where the timing is such that oftentimes there isn't time to actually identify a donor and do the transplant, there is really not a good alternative.

So this is a suitable -- more than suitable; it's an attractive alternative for the categories that we talked about, and I would be in favor of seeing its approval for all of those.

DR. MARTINO: Is there a disagreement amongst the hematologists to that conclusion, to that statement of alternatives?

DR. GOLDMAN: I think as I perhaps also said before, the role of allogeneic stem cell transplant for patients who are sufficiently young and have suitable HLA match donors has been a little bit downgraded in this meeting so far. And there's no doubt that in patients that are -- a minority of patients who are imatinib resistant and would have been eligible for an allograft in the pre-imatinib era should now seriously be considered for allografting, possibly in preference to dasatinib.

That's for debate, and that's very much a clinical and bedside decision. But one should certainly not exclude the possibility of allografting, which even certainly in a patient still in chronic phase, and probably in a patient, in some patients in accelerated phase, has the potential to so-called cure this disease, which may also be the case with dasatinib in due course. That we certainly don't know.

But the majority of patients who are resistant to imatinib will not be eligible for allografting by conventional criteria, and that leaves dasatinib as being very important.

DR. MARTINO: Then I'd like to call the question to a vote, and again the question is accelerated

approval in patients whose disease is resistant to imatinib.

And this time I'd like to start on my right with Dr. Mortimer. Again, your name and your vote, yes or no.

DR. MORTIMER: Mortimer, yes.

MS. BROWN: Brown, yes.

DR. RODRIGUEZ: Rodriguez, yes.

DR. HARRINGTON: Harrington, yes.

DR. HUSSAIN: Hussain, yes.

DR. MARTINO: Martino, yes.

DR. ECKHARDT: Eckhardt, yes.

DR. BUKOWSKI: Bukowski, yes.

DR. LEVINE: Levine, yes.

MS. HAYLOCK: Haylock, yes.

DR. REAMAN: Reaman, yes.

DR. GOLDMAN: Goldman, yes.

DR. KARANES: Karanes, yes.

DR. BERMAN: Berman, yes.

DR. MARTINO: The vote is unanimous, and it is yes.

You all are being very nice to me today because this is my last meeting. I'm used to at least a few good arguments around this table, ladies and gentlemen. Italians don't feel good without at least

one argument.

[Laughter]

DR. MARTINO: The third question: This relates to patients who are imatinib intolerant, and again excludes patients that have Philadelphia chromosome-positive ALL. And I again will read it to you:

Imatinib intolerance was defined as either, one, imatinib-related toxicity leading to imatinib discontinuation; or two, inability to tolerate imatinib. The number of intolerant patients enrolled per study, except for the chronic phase CML study, was than 10 percent. Based on the data presented, has the sponsor provided evidence of an effect on a surrogate endpoint, meaning major cytogenetic response, for chronic phase CML patients intolerant to Gleevec®?

And Dr. Pazdur, do you want me to take a vote to this question, because it is different from what follows?

DR. PAZDUR: [Inaudible response]

DR. MARTINO: Okay. So can we deal first with patients with chronic CML who were registered because of intolerance? Are there comments on this?

DR. BERMAN: I think it's great that the number of patients that we have to study is so small. It

means imatinib is effective in the majority of patients. So yes, I think dasatinib has a role in this small number of patients.

DR. MARTINO: Ms. Brown.

MS. BROWN: Yes. I was thinking back to back when the Gleevec® approval was done, and I think I recall that the intolerance criteria was very strict and very defined.

And the reason I bring that up is because I know that there's a lot of enthusiasm in the patient community for this new drug, and I fear that the good sides of it are being really played up but the potential toxicities are not. And so that you're going to have a lot of patients saying oh, we had this same discussion when it was interferon versus Gleevec®, or that drug was up for approval. But now with this, I fear that you're going to have a lot of patients thinking that this is newer drug so it's a better drug, so all of a sudden I'm intolerant to Gleevec®. So that's just a concern I want to bring up.

DR. MORTIMER: Well, when I was thinking about this I was just wondering whether or not, if you looked at the intolerant patients and you said, well, are there other options for these patients, and

clearly the truly intolerant patient, no. I mean, there are some other ones, but I think in terms of an orally active drug. And then I think again, as a non-hematologist, the question is, is there a risk if the patient is truly not intolerant?

So perhaps we haven't defined it correctly, or there's issues about whether or not they're coming off and being called intolerant prior to truly being intolerant. And I would say no, there's really not. I think we have evidence that that drug would have activity in that population that may be defined incorrectly. So I couldn't really see a downside to this.

DR. MARTINO: Are there other comments?

[No responses]

DR. MARTINO: If not, I will take a vote. And again, these are patients who are intolerant to Gleevec® but whose diagnosis is chronic myelogenous leukemia, and not to other categories.

I will start on my left, please.

DR. BERMAN: Berman, yes.

DR. KARANES: Karanes, yes.

DR. GOLDMAN: Goldman, yes.

DR. REAMAN: Reaman, yes.

MS. HAYLOCK: Haylock, yes.

DR. LEVINE: Levine, yes.
DR. BUKOWSKI: Bukowski, yes.
DR. ECKHARDT: Eckhardt, yes.
DR. MARTINO: Martino, yes.
DR. HUSSAIN: Hussain, abstain.
DR. HARRINGTON: Harrington, yes.
DR. RODRIGUEZ: Rodriguez, yes.
MS. BROWN: Brown, yes.
DR. MORTIMER: Mortimer, yes.
DR. MARTINO: The vote is 13 yeses and one abstinence.

Same question continuing: Based on the data presented, has the sponsor provided sufficient evidence to warrant accelerated approval in CML patients again intolerant to imatinib in either the accelerated myeloid blast or lymphoid blast phase?

And I think the major issue here is simply the number of patients in these disease categories that were enrolled in the various trials.

And the question that I have of my hematological colleagues is, does that matter? Normally for me, as a clinician, if I'm thinking of a therapy if a patient is intolerant of it, whether it's my decision that they're intolerant or their decision that they're intolerant, I don't know that I necessarily

separate them out as a distinct category. But I tend to include them as patients who need a different therapy. Do we need to have this distinction? Does this category need to be separated distinctively out? That's the question I'm posing.

Dr. Levine.

DR. LEVINE: I understand what you're saying in the sense that this is a pill, and if the patient believes that they are not tolerating this pill they won't take it. And that's the answer, they will not have access to that drug. They won't take it.

The difficulty is, looking at these numbers, we're asked to define something on 13 patients. That makes it exceedingly difficult in a scientific sense. In a human sense, in a practical sense, yes, we're going to use it in those patients. So it's a difficulty between practicality and being a scientist. I think the practicality would win, however.

DR. MARTINO: It strikes me that even though those numbers are remarkably few and perhaps might have been almost left out, yet when you look at those very small numbers, if anything the response rate appears to be higher rather than lower, which one would logically have anticipated.

So is there some other reason why I should worry about these patients that I'm simply not understanding? Is there something else that I should worry about?

DR. BERMAN: My own opinion is that, even in the setting of small numbers, I think that the response rate is such that I, myself, I would certainly vote for approval.

DR. GOLDMAN: Yes, I think the only issue is the one that's already been mentioned, that somebody who may -- an individual patient may have a relatively low threshold for deciding that he or she is intolerant, knowing that there's an alternative agent to which they may respond or they may tolerate better.

So the threshold for actually defining intolerance, at least in the eyes of the patient, may be rather flexible. But that said, I think in the clinic one probably would be constrained to approve the patient's decision that they'd like to try another drug. So the answer is probably yes.

DR. MARTINO: Can I remind the group of the data that was unsolicited yet presented to us, which is a comparison of these two drugs that we're now fussing with, where if anything it looks like this is the

better of the two drugs. For me that provided a certain comfort even in a patient who might say but, but, but, I want the new drug and not the old one.

Do the rest of you have a reaction to that?

DR. GOLDMAN: I think the data that were presented to us are a little difficult to interpret, because most of the patients in both arms of the randomized study had had imatinib for some while, or the majority of patients in both arms of the randomized study had had imatinib for some while.

What is a little strange is the fact that patients who were randomized allocated to receive further imatinib within the study then became intolerant within a very short space of time of starting the new phase of their own imatinib. So I think actually the randomized study, as we heard it, is indeed a little bit difficult to explain as a formal randomization.

DR. MARTINO: Dr. Berman.

DR. BERMAN: I think when you look at the reasons why people are intolerant to imatinib it's usually not a subjective finding. It's because of a rash, it's because of liver function test. I think it's usually obvious to both the patient and the physician. And I doubt very much it's going to be a

patient who says, gee, I'm fatigued, or has a more nebulous reason for stopping the imatinib. I think it's going to be pretty obvious.

DR. MARTINO: I will then pose the question to a vote, and we will start on my right with Dr. Mortimer. Again, your name and a yes or a no.

DR. MORTIMER: Mortimer, yes.

MS. BROWN: Brown, yes.

DR. RODRIGUEZ: Rodriguez, yes.

DR. HARRINGTON: Harrington, yes.

DR. HUSSAIN: Hussain, yes.

DR. MARTINO: Martino, yes.

DR. ECKHARDT: Eckhardt, yes.

DR. BUKOWSKI: Bukowski, yes.

DR. LEVINE: Levine, yes.

MS. HAYLOCK: Haylock, yes.

DR. REAMAN: Reaman, yes.

DR. GOLDMAN: Goldman, yes.

DR. KARANES: Karanes, yes.

DR. BERMAN: Berman, yes.

DR. MARTINO: The vote is unanimous, and is yes.

Next I will turn you to question number four, which now is specific to Philadelphia-positive ALL patients.

As stated above, the FDA has approved drugs to

treat acute leukemias based on durable complete responses. The sponsor has presented data (major hematological responses) for Philadelphia-positive acute lymphoblastic leukemia patients who have experienced disease progression on imatinib and other therapies. Based on the data presented in the above tables, has dasatinib demonstrated sufficient evidence to warrant regular approval in either the imatinib-resistant or intolerant Philadelphia-positive ALL population?

And again, I will remind you this is full approval, not accelerated approval, that we are dealing with. Comments, please.

Dr. Levine, I'm going to start with you.

DR. LEVINE: So to clarify, we are now talking about a very small number of patients. So on the resistant side, 39 patients with Philadelphia-positive ALL.

My problem is again the numbers are exceedingly small. On the other hand, in a clinical sense these patients are exceedingly hard to treat, and I'm not convinced that there's anything else that we could do. And I may be upset at myself later when I read this, but I would be voting to approve this. I would want this. There are no other options to treat these

patients.

DR. MARTINO: Dr. Berman?

DR. BERMAN: I would agree.

DR. MARTINO: Dr. Karanes?

DR. KARANES: Yes, I agree.

DR. MARTINO: Dr. Goldman?

DR. GOLDMAN: I concur.

DR. MARTINO: Are there others? Yes, Dr. Harrington?

It's not that I'm looking for disagreement here, doctor.

[Laughter]

DR. HARRINGTON: I'll be glad to give you some.

So for my clinical colleagues, what is the difference between having this available as an accelerated approval, and the company needs to come back with either further follow-up or another study in this very difficult population, or full approval? Practically speaking, does it change the availability in the clinic?

DR. MARTINO: Dr. Pazdur, maybe you might want to comment on that, and why you're looking at this for full approval, which surprised some of us.

DR. PAZDUR: Yes. It's based on a precedence of looking at full approvals in acute leukemias, which

we've brought to this committee before. And the committee has approved on small numbers of patients in acute leukemias, refractory leukemias, have recommended full approval.

This is based on the feeling that has been discussed with the committee that in acute leukemias, where you have a complete response rate with resolution and normalization of counts, this constitutes clinical benefit per se -- i.e., patients do not need transfusions, patients do not need -- are not at the same risk of having infections. There's a correlation with survival.

So it's an established surrogate for clinical benefit in this setting.

DR. MARTINO: Do you need any further clarification, or are you happy?

DR. HARRINGTON: I don't need any further clarification.

DR. MARTINO: You're not happy, though, huh?

[Laughter]

DR. MARTINO: Yes, doctor?

DR. ECKHARDT: I guess my question to the hematologists would be, how would you go about designing a study that would actually take something like this from accelerated to full approval in that

disease? I think we've had this discussion before, where we think about accelerated approval, and then the problem is the randomized study just can't be completed due to patient numbers and the fact that patients really want access to the drug.

Can you think of a way that you would confirm beyond accelerated approval other than a randomized study that would never accrue?

DR. BERMAN: I'm not sure what you would randomize it against.

DR. MARTINO: Is the issue perhaps having a larger population of treated patients, even in a straight phase two environment?

DR. LEVINE: The issue is numbers of patients.

Also, on the resistant side there are no data on this table as far as major cytogenetic response. Do we know that? That would be interesting. So we have major hematologic response, 36 percent, but not the cytogenetic data on the resistant patients.

But yes, the difficulty to me is the cytogenetics and the number. I don't see the point in differentiating between accelerated and full because there isn't anything to randomize it against. I agree. So if we're going to approve it, it would make sense to do this on a full basis.

DR. KARANES: There is cytogenetic response on table one. It's the major cytogenetic response, 58 percent for Philadelphia chromosome-positive ALL.

DR. LEVINE: Thank you. That helps.

DR. MARTINO: Dr. Harrington.

DR. HARRINGTON: So I acknowledge the difficulty here of doing a randomized trial in an agent that shows effectiveness. I guess I had always assumed that an additional study or expanded follow-up after accelerated approval need not be randomized, that it could be in the larger number of patients, and it could be to validate this as a surrogate marker for survival, which I realize has been used in the past in leukemia. But with each new agent there may be a different way in which it interacts with the cytogenetic parameters.

DR. PAZDUR: One alternative would be to have an accelerated approval for this indication and then ask for further data, further accrual on a single-arm trial and submission of further data.

Remember, as we discussed with the chronic leukemias and the reason why we're giving them accelerated approval, is that we want more follow-up on these patients.

Here again, the reason why we're asking this

question, based on similar discussions that we've had in other acute leukemias with this group -- i.e., some of the pediatric leukemias -- we've given full approval based on very similar data.

DR. MARTINO: Dr. Reaman, did you have a comment?

DR. REAMAN: No.

DR. MARTINO: Yes, doctor?

DR. BUKOWSKI: It seems to me that given the rarity of this disease and the data we see here that this an approvable drug. I think to do another study would be very difficult if this drug even is out there in an accelerated fashion. So the data would seem to support approval of this drug for this disease.

DR. GOLDMAN: Does it make sense to give full approval and still ask for additional data, or is that an irrelevance?

DR. PAZDUR: Well, you could always add a phase four commitment to update the data on this. The major distinction between this accelerated approval and the full approval or the regular approval is the strength that we could have these studies done, basically. The commitment is a mandatory commitment.

DR. MARTINO: Are there other issues?

[No responses]

DR. MARTINO: If not, I will take the question to a vote. And we'll start -- where did I start last time? I'll start on my left.

DR. BERMAN: Berman, yes.

DR. KARANES: Karanes, yes.

DR. GOLDMAN: Goldman, yes.

DR. REAMAN: Reaman, yes.

MS. HAYLOCK: Haylock, yes.

DR. LEVINE: Levine, yes.

DR. BUKOWSKI: Bukowski, yes.

DR. ECKHARDT: Eckhardt, yes.

DR. MARTINO: Martino, yes.

DR. HUSSAIN: Hussain, abstain.

DR. HARRINGTON: Harrington, no.

DR. RODRIGUEZ: Rodriguez, yes.

MS. BROWN: Brown, yes.

DR. MORTIMER: Mortimer, yes.

DR. MARTINO: And the count is 12 yeses, one no, and one abstinence.

The final question, number five: Accelerated approval requires a commitment to perform a confirmatory clinical trial to demonstrate clinical benefit. Please discuss future study design to accomplish this goal. These trials could be either front-line or relapsed disease settings.

So at this point I think we're soliciting advice from the committee as to what further data they might want.

Dr. Pazdur, do you want to make a comment?

DR. PAZDUR: Yes. Basically, as I stated before, what we are interested in as far as the conversion of this application is subsequent data to be obtained from the single-arm trials.

What we want to know from you -- and this is a discussion point of view -- what other data do you feel that you would like to be seen, especially since we are contemplating an accelerated approval and can make either the submission of ongoing trials data mandatory as a subpart H accelerated approval commitment? Which of these do you see that you really feel is essential to giving you more information about this drug that you feel prescribers require? We've had a lot of discussion on dose of this drug.

DR. MARTINO: Well, it strikes me that continuing the ongoing trials, so that you do know what the duration of response is, is something that is already planned and without question necessary.

The dose question; but again, the company has addressed that question, I think, in a reasonable

manner. We'll just have to see the outcome of that.

A more direct comparison with imatinib, I think for me, would be a logical next step, a true randomization as opposed to a phase two side-by-side kind of trials.

Yes, Dr. Reaman.

DR. REAMAN: I think there's also the possibility or potential for combination studies, particularly in Philadelphia chromosome-positive ALL with this drug and other agents used to treat ALL.

DR. MARTINO: Dr. Rodriguez.

DR. RODRIGUEZ: With regards to the chronic phase CML patients, I think that the drug obviously merits perhaps even front-line evaluation given the efficacy we see even in the resistant patients.

But one concern that I have that no one has spoken about is the total duration of treatment. If these patients are reaching cytogenetic remission, one would only hope they perhaps are, do I dare say the word, cured. How long does someone who is in complete cytogenetic remission need to stay on this drug? What dose of drug? What schedule? Should it be daily, continually for life? Should it be intermittently, every other week? Should it be at a very low dose? Should it be at the standard dose?

Should it be no drug at all?

I think that in order for this drug to have application across the board for the patients with the chronic phase of the disease, we need to consider as well the quality of life of the patients and potential downstream long-term effects that we haven't foreseen at this point.

DR. MARTINO: Dr. Goldman, did I see your hand up?

DR. GOLDMAN: Well, I'm not sure about that. By analogy with the imatinib, one can only say one really doesn't know the answer. Patients have now been taking imatinib in the randomized study for five, getting on for six years. Some have become molecularly undetectable for a number of years with BCR-ABL transcripts. Whereas two years ago people were saying this drug should be continued indefinitely in responders, there has in the last few months, I think, been a feeling that it's worth studying patients who have responded well in a comparison of those who continue versus those who stop.

And I think the same will probably apply to dasatinib for patients who have good responses at the molecular level, that two or three years from now we

will agonize a little bit as to whether this drug should be -- whether one should try to raise the dose, keep the same dose, reduce the dose, or stop the dose. And we don't know.

DR. MARTINO: Dr. Pazdur, did I see some movement on your side there?

DR. PAZDUR: Yes. I was surprised when Dr. Reaman raised his hand that he didn't ask about pediatric studies. So the question to him was --

DR. REAMAN: Well, that's exactly why I asked that question. I asked about or mentioned the combination studies because certainly as a single agent it wouldn't be used, but I think there are a number of pediatric indications, including CML in chronic phase or blast crisis, in which it should be studied.

DR. MARTINO: Dr. Levine.

DR. LEVINE: I don't have anything new to say. Just to augment or underline what Drs. Goldman and Rodriguez said, I think it would be extremely important to look at molecular markers in up-front studies of this drug versus imatinib over time.

DR. MARTINO: Are there other comments?

[No responses]

DR. MARTINO: If not, I thank all of you. You've

probably made this the most simple time that I've run this committee.

Apparently the next meeting of ODAC is September 6th, which is the day before my birthday for those of you who care to acknowledge that.

[Laughter]

DR. PAZDUR: You don't get no jewelry then.

[Laughter]

DR. MARTINO: Thank you. Thank you all.

[Applause]

[Meeting concluded at 1:52 p.m.]

C E R T I F I C A T E

STATE OF GEORGIA)
)
COUNTY OF DEKALB)

I, KIM S. NEWSOM, being a Certified Court Reporter in and for the State of Georgia, do hereby certify that I have no interest, financial or otherwise, in this matter, and that the foregoing transcript, consisting of 161 pages, is a true, complete and correct record of the proceedings held before me on June 2, 2006.

This transcript is not deemed to be certified unless this certificate page is dated and signed by me.

WITNESS MY HAND AND OFFICIAL SEAL this 22nd day of June, 2006.

_____

KIM S. NEWSOM, CCR-CVR
CCR No. B-1642

[SEAL]