recognize the issue is full approval.

Dr. O'Brien.

DR. O'BRIEN: I think it is clearly yes. To speak to what Dr. Perry said, I mean I think we are doing the community oncologists a bit of a disservice. Adjusting drugs because of myelosuppression is not rocket science. Everybody in oncology does it, it is not very hard to do.

This is a drug that is oral, so you haven't given 5 days of IV and now you are stuck with whatever the consequences are. You hold the drug and then you determine when to resume it, and potentially resume at a lower dose.

The reason I voted no on No. 2 is because I think the obvious question is could 5 mg be as efficacious with less toxicity. On the other hand, I am so struck by the efficacy, and I do think that this is a toxicity that is not that difficult to deal with, that I think it is much more important to get the drug out there.

DR. MARTINO: Dr. Hussain.

DR. HUSSAIN: I guess to me, the

risk-benefit ratio, the answer to this would be a no, but I would point out this. A 7 percent death rate is the hands of investigators who are using the drug on a prespecified study is a very high rate by experienced investigators.

So, now you are going to put it in the market and expect the person who has never ever used it before to figure out how to dose reduce. I would argue for chemotherapy. There is a long track record of what to do.

This agent seems to be different, at least from what I could see, and the fact the people who have been using it under the study, despite that, had 80 percent dose reductions, 40 percent SAEs, and 7 percent death rate would indicate that even in the experienced hands, it is a difficult drug to use unless you characterize it better.

DR. MARTINO: Dr. Mortimer.

DR. MORTIMER: I think most antineoplastic drugs are approved on the basis of a select population, who are previously untreated often, and when the drug gets out into the community, what

happens is patients that we ultimately treat with these agents have been pretreated, have had prior irradiation, and we have to learn to modify them.

I think the case is the same here. I mean the data is incredibly compelling. I think it would be a disservice to the patients not to have this drug available, and I, like Dr. Perry, like to think that we are able to know how to modify doses.

DR. MARTINO: Dr. Perry.

DR. PERRY: Thank you. If I would recall to the committee, capecitabine, gemcitabine, navelbine, a long list of drugs have been approved, have been used by the community, and we have had the doses reduced to what we find is clinically effective.

I think the company has made a compelling case for the efficacy of this drug. I think the toxicity is what is expected in this patient population given their age and bone marrow disease, and I am not surprised to see myelosuppression. I think I can handle it.

DR. MARTINO: But I am not sure the

question is whether you can handle it. I am going to trust that you actually could. I think the question is whether others can handle it.

DR. PERRY: Well, I am considering myself the lowest common denominator.

DR. MARTINO: Ah, but some of us would argue with that very low position. Some would agree.

Are there other comments? Dr. Bukowski.

DR. BUKOWSKI: I agree with those last two comments. I believe this drug is efficacious, there is no doubt that the data is compelling, and we always face these agents when they enter the clinic for the first time with regard to dosing, especially in populations that are older, impaired organ function, et cetera. These are things that are learned.

Now, that doesn't mean it is right. It would be nice to have this nailed down before we go in, but the data are so compelling here that it is hard to say no to this drug at the present time. That's my view.

DR. MARTINO: Dr. Carroll.

DR. CARROLL: I am going to take the patient perspective. I am a long-term survivor of MDS. I have had it for 15 years. What frightens me is that we have 15,000 new MDS patients a year. That number is growing, and those are NIH statistics.

Not only is the age lowering, but we even have infants that are now picking up MDS. I personally have had over 700 units of blood. That is a unit of blood every week.

Now, any drug that eliminates or reduces the number of transfusions for an MDS patient is lifesaving. Every unit of blood carries iron, which causes iron overload. When you start receiving blood on a weekly basis, it is very, very difficult, if not impossible, to keep your ferritin levels down to a safe figure where you are not going to cause organ damage.

Many patients that are on blood transfusions also develop antibodies, and this is as a result of being transfusion dependent. This

makes it more and more difficult to match their blood. This eventually leads to the day when they can no longer get matched blood and death ensues.

So, again, anything that reduces the number of transfusions or eliminates it is lifesaving. So, even 6 months or a year, I can't tell you what that does to just the quality of life, to be able to go 6 months or a year without a transfusion, spending 7 or 8 hours in a hospital each week, when you have a disease that is life-threatening, and for many patients, they only have 2 to 4 years.

So, to date, there is no cure for MDS, okay, except maybe for successful bone marrow transplant. Making patients transfusion independent is the next best thing, and for MDS patients, there is only one drug out on the market that has been approved by the FDA, and it is not as effective in reducing the number of transfusions for the number of patients that this clinical trial seems to show.

DR. MARTINO: I do need to remind the

audience, as well as the group, that we basically are not dealing for a therapy that anyone that has a diagnosis of MDS would be getting. That is not the point to this application. It is a very specific type of patient we are talking about here. It is those with a very specific cytogenetic pattern.

So, let's not lose track. This is not a drug that is being promoted for everybody. So, we need to think of it in that somewhat limited context.

At this point, I trust all of you have your own views in mind. Unless there is a burning discussion point which has not been heard before, I would like to put the question to a vote.

Again, this is the question. Do you feel that this agent today merits full approval?

I will start on my left. State your name first and then your vote.

DR. CARROLL: Dr. Robert Carroll. An emphatic yes.

DR. O'BRIEN: O'Brien. Yes.

DR. FLEMING: Fleming. No, and let me provide rationale.

DR. MARTINO: Doctor, I am sorry, but I don't really need to hear your rationale. Your vote is trusted by this committee.

DR. FLEMING: But the FDA makes decisions, not advisory committees. Isn't the most important thing we do on an advisory committee is to provide rationale?

DR. MARTINO: Then, keep it extremely brief for me, please, because the time is short and we are not done.

DR. FLEMING: All right. In brief, the risk-benefit analysis that we have here might, in fact, lead to a justification of approval. In essence, the public is entitled to not only a timely, but also a reliable assessment of benefit to risk, as well as understanding of, within reason, what are doses that will allow us to achieve favorable benefit to risk.

When I reviewed these data, my initial impression before I got to the end was these setup

proof of principle that ideally position us to do a trial, that looks at 5 against 10 against control, that trial is in place.

If, in fact, this approval occurs today, it is likely to, if anything, delay. If nothing else, it takes away the sense of urgency from the sponsor. It will delay the completion of the study that will truly provide us far more reliable insights about benefit to risk, as well as potentially negatively impacting the developments in other areas.

So, ultimately, looking at the public's right to reliable, as well as timely assessments, I believe the answer that we really need is coming from that Phase III trial. Based on these current data, it establishes plausibility. Hence, my answer is no.

DR. MARTINO: Thank you, and I actually appreciate that.

Dr. Hussain.

DR. HUSSAIN: Hussain. No.

DR. DOROSHOW: Doroshow. Yes.

DR. BUKOWSKI: Bukowski. Yes.

DR. CHESON: Cheson. I was going to say what Dr. Fleming said with the additional comment of there will be an expanded access program available, so we will not be depriving patients of this drug while we are identifying a safe and efficacious dose.

So, my answer is no.

DR. ECKHARDT: Eckhardt. Yes.

DR. GRILLO-LOPEZ: Antonio Grillo-Lopez. If I had a vote, I would vote yes.

DR. PERRY: Perry. Yes.

DR. RODRIGUEZ: Rodriguez. Yes.

DR. MARTINO: Martino. No.

DR. MORTIMER: Mortimer. Yes.

DR. LEVINE: Levine. Frustrated, but yes.

MS. HAYLOCK: Haylock. Yes.

DR. REAMAN: Reaman. No.

DR. MARTINO: And the tally is 10 yes, 5 no.

The last question relates to the issue or protecting the fetus.

At this time, lenalidomide, a thalidomide analogue, does not have adequate nonclinical studies to assess reproductive developmental safety. Should a risk management program with a goal of no fetal exposure to Revlimid be instituted until the nonclinical reproductive developmental safety assessments are addressed?

Rick, it sounds to me like the company does have some thoughts of putting a program in place, so do you really want a vote on this?

DR. PAZDUR: I don't think we have to vote on this, because I think here again, we have made our point relatively clear. We want more information given the past history with this class of drugs. We will be insisting on something. This brings us in step also with their European colleagues.

DR. MARTINO: At this point, I will bring the committee meeting to a closure. Thank you.

[Luncheon recess taken at 11:00 a.m.]

A F T E R N O O N P R O C E E D I N G S

Call to Order

DR. MARTINO: This afternoon, the committee will discuss NDA 21-877, proposed trade name Arranon by GlaxoSmithKline, proposed indication for the treatment of patients with T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma whose disease has not responded or has relapsed with at least two prior chemotherapy regimens.

I would like to begin the meeting by having the committee members introduce themselves, and we will start on my left, please.

Introductions

DR. O'BRIEN: Susan O'Brien from M.D. Anderson.

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

DR. HUSSAIN: Maha Hussain, Med/Onc, University of Michigan.

DR. DOROSHOW: Jim Doroshow, NCI.

DR. BUKOWSKI: Ron Bukowski, Medical

Oncologist, Cleveland Clinic.

DR. CHESON: Bruce Cheson, Hematologic Oncologist, Georgetown University Hospital.

DR. ECKHARDT: Gail Eckhardt, Medical Oncologist, University of Colorado.

DR. GRILLO-LOPEZ: Antonio Grill-Lopez. I am a hematologist/oncologist. I am the Industry Representative on this committee, however, I receive no support whatsoever from industry for my participation here.

DR. PERRY: Michael Perry, Hematology/Oncology, University of Missouri.

DR. RODRIGUEZ: Maria Rodriguez, Hematology/Oncology, M.D. Anderson Cancer Center in Houston, Texas.

DR. MARTINO: Silvana Martino, the Angeles Clinic in Santa Monica.

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

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

MS. HAYLOCK: Pamela Haylock, Oncology

Nurse, University of Texas Medical Branch in Galveston.

MS. EICHNER: Marilyn Eichner, Patient Representative for the FDA.

DR. COHEN: Martin Cohen, Medical Oncology, FDA.

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

DR. PAZDUR: Richard Pazdur, Office Director.

DR. MARTINO: Next, I would like Ms. Clifford to read the Conflict of Interest Statement for the committee.

Conflict of Interest Statement

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

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

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

In accordance with 18 U.S.C., Section 208, full waivers have been granted to the following participants:

Dr. Michael Perry for owning stock in a competitor valued at less than $5,001; Dr. Maha Hussain for owning stock in the sponsor of Arranon valued from $25,001 to $50,000, and for unrelated consulting for a competitor for which she receives less than 10,001 per year;

Dr. Gail Eckhardt for unrelated advisory board activities for a competitor for which she receives less than 10,001 per year; Dr. Ronald Bukowski for unrelated consulting for a competitor for which he receives less than 10,001 per year;

Thomas Fleming for an unrelated Data, Safety, and Monitoring Board activity for competitors for which he earns less than 10,001 a year from each firm, and for unrelated Scientific Advisory Board activities for a competitor for

which he earns less than 10,001 per year.

Finally, Dr. Alex Levine has been granted a limited waiver for earning stock in a competitor valued at greater than $100,000. Under the terms of this limited waiver, Dr. Levine will be permitted to participate in the committee's discussion of Arranon. She is, however, excluded from voting.

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

We would also like to note that Dr. Antonio Grillo-Lopez is participating in this meeting as the Non-Voting Industry Representative acting on behalf of regulated industry. Dr. Grillo-Lopez is employed by Neoplastic and Autoimmune Disease Research.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to

exclude themselves from such involvement, and their exclusion will be noted for the record.

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

DR. MARTINO: Thank you.

Dr. Pazdur, do you wish to make any comments to the committee?

DR. PAZDUR: No.

DR. MARTINO: In that case, I could like to turn to the sponsor and at this point, if you would introduce yourselves.

Sponsor Presentation

GlaxoSmithKline

Introduction

DR. HO: Good afternoon. I am Peter Ho, Vice President for Discovery Medicine Oncology for GlaxoSmithKline .

We appreciate the opportunity to present Arranon before the committee today.

[Slide.]

For our presentation, we will have Dr. Stephen Sallan from the Dana-Farber Cancer Institute describe T-cell acute lymphoblastic leukemia and lymphoblastic lymphoma.

Dr. Richard Larson from the University of Chicago will summarize the efficacy of Arranon from the pivotal trials.

Dr. Mark Russo from GSK will present the safety experience, and finally, Dr. William Carroll from NYU will discuss the role of Arranon in the treatment of this disease before we conclude.

[Slide.]

In addition, we have with us today the following external consultants.

[Slide.]

And GSK staff to address your questions.

[Slide.]

We will present data supporting the use of Arranon in the treatment of patients with T-cell acute lymphoblastic leukemia, or T-ALL, and T-cell lymphoblastic lymphoma, or T-LBL whose disease has not responded to or has relapsed following

treatment with at least two chemotherapy regimens.

This rare indication has received orphan drug designation from the agency.

[Slide.]

Children born with the genetic deficiency of the enzyme purine nucleoside phosphorylase, or PNP, exhibit profound T-cell lymphopenia. Their T-cells cannot metabolize guanine nucleosides and accumulate toxic levels of deoxy-GTP.

This clinical observation provides the rationale for the targeted treatment of T-cell malignancies with Ara-G, a purine analogue that is resistant to PNP catabolism. This results in the toxic accumulation of Ara-GTP in their T-cells, leading to selective death, akin to that seen in patients with PNP deficiency.

Arranon is a soluble pro-drug of Ara-G that was developed by Gertrude Elian and Associates to precisely exploit this biochemical vulnerability of T-cells.

Arranon has been in the clinic since 1993, when Dr. Joanne Kurtzberg initiated the first

clinical study.

The development of an agent in this rare T-cell malignancy could only be conducted through the NCI and the cooperative groups, and we are grateful for their active partnership.

With NCI support, the Cancer and Leukemia Group B and the Pediatric Oncology Group, now Children's Oncology Group, generated compelling and consistent data in a targeted population with no suitable treatment alternatives.

This submission would not be possible were it not for the collaborative efforts of the CALGB and COG in providing their data to us for analysis and today's presentation.

GSK views it as our responsibility to patients with T-cell ALL and T-cell LBL, to the clinical investigators, and to the NCI to assemble the submission with these cooperative group data.

[Slide.]

Now, in the clinic, Arranon has fulfilled the promise of T-cell selectivity. Arranon demonstrates consistent clinical efficacy in both

children and in adults and in patients with multiply relapsed as well as refractory disease.

Its safety profile is well characterized with risks that are common to those of other therapeutics used in this disease.

Arranon exhibits a favorable overall benefit-risk profile for these heavily pre-treated patients, and as such, Arranon meets a significant unmet medical need in a rare and lethal disease.

Despite substantial progress in the treatment of leukemias and lymphomas, there is no proven effective alternative therapy available for patients with relapsed or refractory T-cell ALL and T-cell LBL.

At this stage, I would like to turn over the presentation to Dr. Sallan to review the indication.

Disease Overview

DR. SALLAN: Good afternoon. My name is Stephen Sallan. I am a pediatric oncologist from the Dana-Farber Cancer Institute. I would like to take a few minutes, if I may, to overview T-cell

acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma.

[Slide.]

As shown here, collective, these are a rare group of diseases. It is estimated there are only about 1,600 new cases per year in the U.S., and T-cell ALL and lymphoblastic lymphoma differ from one another principally in the percentage of lymphoblasts in the bone marrow.

They represent 10 percent to 15 percent of all childhood ALL and about 20 or slightly more than 20 percent of all adult ALL. Most of these diseases are in older children and young adults, and recent studies have shown that much of the biology of these diseases is age-independent.

Specifically, in the findings of notch-1 mutations found in 50 percent of patients with ALL, there was no difference at all between the adult and pediatric populations, and similarly, in studies of gene expression signatures, there was no age-related difference.

[Slide.]

Current treatment approaches consist of multi-agent chemotherapy at the time of diagnosis and for those who go on to relapse at the time of first relapse, as well.

Treatment is always at those stages with curative intent: at diagnosis with chemotherapy only, and at first relapse, with multi-agent chemotherapy whose purpose is to induce a second complete remission, and then the curative part of the post-relapse treatment is with stem cell transplantation.

[Slide.]

I am showing here a representation of a large population of over 1,200 children with acute lymphoblastic leukemia, and the results will show you that globally in the disease, we see today a 75 percent or more cure rate.

The heavy line is B lineage leukemia, the dotted line, T lineage leukemia , and the principal differences I would like to call to your attention are that there is more constitutively resistant disease de novo resulting in lower complete

remission rates, a statistically significant difference, and there is also a higher incidence of induction deaths in treating T-cell patients based on the intensity of required treatment, and again a statistically significant difference, but once they are in remission, the relapse rates are essentially the same.

The time to relapse in T-cell disease comes much sooner, at a median of 1.2 years compared to 2.4 years for B lineage disease, and there is more extramedullary disease seen in T-cell malignancy.

If we were to look at the pediatric lymphoblastic lymphoma cohort here, this curve would be at approximately 90 percent, and if we were to look at the adult T-cell ALL and T-cell lymphoblastic lymphoma, we would find them at about the 60 to 65 percent event-free survival.

So, today, we are left with about 1 child in 4, and 1 adult in 3 or 2, for whom first line conventional treatment if insufficient.

[Slide.]

What happens at the time of first relapse? Here, the population narrows. It's about 500 patients a year. Again, treatment is with curative intent, to induce the second remission followed by a transplant, and the post-transplant outcome for T-cell ALL patients transplanted in second remission is approximately 40 percent at two years for both children and adults. There is not a very large difference in outcome at this stage.

Treatment-related mortality clearly can increase at this stage to as high as 5 to 10 percent.

[Slide.]

Turning now to the proposed indication for drug use, and that is treatment after second relapse. Here, the data are a little more sparse. These are pediatric patients from the Children's Oncology Group, treated with what is available, a small n you will see, and you will see that the responses are brief, and the overall proportion alive is zero with none of them surviving as long as a year. This is the dilemma.

[Slide.]

My last slide indicates what that population has been treated with prior to their second relapse, and the answer is virtually all of the children have received virtually all of these drugs by the time of their second relapse, their disease is refractory.

They have frequently seen many of these drugs on two or more occasions, and interestingly, when one reviews the literature for single-agent activity in T-cell ALL, none of these drugs, as best one can compare, have the same activity against T-ALL as does nelarabine.

So, what our patients clearly need are new drugs for relapsed T-cell ALL to give them both complete remissions and meaningful durations or remission, which I would define as long enough to get a transplant after the first relapse, 2 to 8 weeks, and certainly longer than zero for those after the second relapse.

Thank you very much. I would now like to turn the podium over to Dr. Richard Larson, who

will discuss the efficacy of the pivotal clinical trials.

Efficacy Summary

DR. LARSON: Good afternoon. I am Richard Larson from the University of Chicago. I chair the Leukemia Committee for the Cancer and Leukemia Group B.

[Slide.]

There are two cooperative group studies that provide the basis for the nelarabine application. The Cancer and Leukemia Group B led a trial in adults called 19801 that was joined by the Southwest Oncology Group to accrue sufficient patients for this Phase II study.

We evaluated nelarabine in adults with refractory or relapsed T-lineage acute lymphoblastic leukemia or lymphoblastic lymphoma. Preliminary data were presented by Dr. Daniel DeAngelo at the American Society of Hematology meeting in 2002, and an abstract was published in Blood on those data. Dr. DeAngelo is here today if questions arise.

The second trial was conducted in pediatric patients by the Pediatric Oncology Group, now the Children's Oncology Group. This, too, was a Phase II study of nelarabine in patients with refractory T-cell malignancies. A complete report on the outcome of this trial was published in the Journal of Clinical Oncology earlier this year by Dr. Stacy Berg and her colleagues. Dr. Berg could not be here today, but Dr. Susan Blaney, one of her co-investigators, is with us today.

[Slide.]

Both of these Phase II trials used the efficacy endpoints shown on this slide. In the middle column is the conventionally defined complete remission of less than 5 percent blasts remaining in the bone marrow after treatment with no blasts in the bloodstream, with recovery of platelets to greater than 100,000, and recovery of neutrophils to greater than 1,500.

In addition, there could be no evidence of extramedullary disease or organomegaly.

A second response criteria of CR* was also

used in these trials, together with complete remission, again less than 5 percent lymphoblasts in the bone marrow was required, and no circulating blasts. The difference in this category, however, is that it did not require recovery of platelets to 100,000/microliter or neutrophils to greater than 1,500.

[Slide.]

This slide reviews the rationale for the CR* endpoint. This is similar to the CRi or CRp category for patients with acute myeloid leukemia. CRi means complete remission with incomplete recovery of hematopoiesis, and CRp is complete remission with incomplete recovery of platelets to greater than 100,000.

It seems true that in these heavily pretreated patients, many of these patients after successful anti-leukemic treatment may never have full hematologic recovery generally because of bone marrow injury from prior therapy, and yet they seem to benefit considerably from the absence of their leukemic disease.

In addition, many of these patients, soon after induction therapy, will proceed directly to allogeneic stem cell transplantation and thus never have full hematopoietic recovery.

This category of CR* was agreed upon between the sponsor and the FDA in June 1997, prior to the beginning of these studies.

[Slide.]

Now, all of the patients on these studies had received prior therapy for T-cell ALL or T-lymphoblastic lymphoma. Some had received one prior multi-agent regimen and proved either to have primary refractory disease or had a remission and later relapsed.

A larger number of patients had received two or more prior induction regimens and proven to be refractory or to again have relapsed disease.

Refractory disease here means less than a complete response following the most recent induction attempt.

[Slide.]

Now, the adult trial CALGP 19801 was an

open-label, multi-center Phase II study. The median age for the subjects enrolled was 34 years with a range of 16 to 66 years. All of these patients had refractory or relapsed T-cell ALL or lymphoblastic lymphoma.

The dose was 1,500 mg/m2 given on days 1, 3, and 5, to be repeated every 21 days. Two cycles of nelarabine were permitted for remission induction plus two additional cycles for post-remission consolidation therapy for those patients not proceeding to transplantation.

Thirty-nine patients were treated. Eleven of these had received 1 prior multi-agent induction regimen and 28 patients had received 2 or more prior multi-agent induction regimens.

Between the Cancer and Leukemia Group B and the Southwest Oncology Group together, these 39 patients were enrolled over 37 months.

[Slide.]

Shown here are the data on response rate and duration for the 28 patients who had received 2 or more prior induction regimens. The complete

remission rate was 18 percent. When the CR* category is included, the overall response rate was 21 percent. The median duration of remission was 29 weeks for the CR patients and 24 weeks for the overall response patients.

The duration of these responses extended from 15 to greater than 195 weeks, and continuing in remission.

[Slide.]

This bar graph demonstrates the response rates, shown first for the 28 patients with 2 or more prior induction regimens in the dark red bar, the complete remission rate of 18 percent, and in the stippled band, the additional CR* response, for an overall response rate of 21 percent, and the 95 percent confidence interval.

[Slide.]

Within these 28 patients, there were 17 patients who were refractory to their immediately prior chemotherapy program, and yet their overall response rate was 24 percent.

And there were 11 patients who had

received only one prior multi-agent induction regiment, and their complete response rate was 27 percent.

[Slide.]

Shown here is the duration of best response for individual patients. Here are the 6 patients who had received nelarabine after 2 or more prior multi-agent induction regimens. In this and in subsequent slides, the dark blue bar indicates those patients treated at a time of refractory disease, and the light blue bar, those treated with relapsed disease.

The red arrowhead indicates the time of allogeneic transplantation in this long-term survivor although this patient has survived without transplantation having received just 3 cycles of nelarabine and no further therapy.

The median duration of response for these 6 patients was 24 weeks.

[Slide.]

In this slide is shown the duration of best response for 3 patients, 3 complete responders

after 1 prior multi-agent regimen. Again, the time scale goes out to 4 years. There was one of these patients who received a transplant.

[Slide.]

This slide shows the overall survival for the 28 patients with greater than or equal to 2 prior multi-agent induction regimens. The median survival for this group was 21 weeks. The 1-year survival, as indicated by the vertical dashed line, was 29 percent with a 95 percent confidence interval of 12 to 45 percent, and you can see several long-term survivors.

[Slide.]

Superimposed on the previous curve is the survival of the 11 patients with 1 prior induction shown in the dashed line, and again several long-term survivors.

[Slide.]

The pediatric trial was also an open-label, multi-center, Phase II study for children with refractory or relapsed T-cell ALL or T-cell lymphoma. The dose was 650 mg/m2 given

daily on days 1 through 5 and repeated every 21 days.

The median age for these children was 11 years and the range was 3 to 20 years. 151 children were enrolled on this study and treated across 4 different strata. At the recommended dose of 650 mg/m2, there were 31 patients with 1 prior multi-agent induction regimen, and 39 patients with 2 or more prior multi-agent regimens.

The Children's Oncology Group accrued these patients over 61 months time.

[Slide.]

Shown here are the response rates and duration for the 39 children with 2 or more prior induction regimens. The complete remission was 13 percent. The overall response rate was 23 percent.

The median duration of response was 9 weeks in each category, which is a clinically meaningful difference and allowed many of these children to proceed on to stem cell transplantation, which is the curative therapy in this subset of patients.

The overall duration of response extended from 5 to 36 weeks in this group, and 3 to 42 weeks in the overall response group.

[Slide.]

Shown in this bar graph are the CR and CR* rates. First, for the 39 children with 2 or more prior induction regimens for an overall response rate of 23 percent.

[Slide.]

Among those 39 patients were 22 children who were refractory to their immediately prior chemotherapy, and yet their response rate was still 27 percent after nelarabine.

[Slide.]

There were also 31 children who had received 1 prior induction therapy before receiving nelarabine. Their overall response rate was 48 percent. Within this cohort of 31 patients were 9 patients with primary refractory T-cell disease who had never achieved a remission, and their response rate to nelarabine was 56 percent.

[Slide.]

Shown here for individual patients are the 9 patients who entered complete remission after 2 or more prior multi-agent induction regimens and receiving nelarabine.

Unlike the previous slide, the time scale here extends only to 45 weeks. There were 4 patients within this group of 9 who were able to proceed to a transplant after nelarabine therapy.

[Slide.]

This slide illustrates the duration of best response for 15 patients who had received 1 prior multi-agent induction and then entered complete remission after nelarabine therapy. A larger number of these patients were eligible and able to proceed to an allogeneic transplant.

Here, the time scale again extends to 5 years time, and there have been a number of long-term survivors both in patients with relapsed disease and the patients with refractory T-cell ALL.

[Slide.]

Shown here is the overall survival for the

39 children who had received 2 or more prior multi-agent inductions prior to nelarabine therapy. The median survival for this cohort was 13 weeks. After 1 year, 14 percent of these patients were alive. The 95 percent confidence interval was 3 percent to 26 percent.

[Slide.]

Overlaying on the previous slide is the survival of the 31 patients who had received 1 prior induction regimen with a higher 1-year survival and a number of long-term survivors extending out to 4 and 5 years.

[Slide.]

Additional efficacy data are shown on this slide for a group of 90 patients with relapsed refractory T-cell ALL. Some of these were adult patients treated on the NCI Treatment Referral Center protocol or the Special Exception Program through the University of Frankfurt.

You can see their complete response rate in the right-hand column. In addition, both adults and pediatric patients were enrolled on 1 of the 3,

Phase I trials, and you see here the patients with relapsed or refractory T-cell ALL and their response rates.

[Slide.]

The FDA had asked the sponsor to retrospectively collect data on the outcome of transplantation in these patients who had received nelarabine, and the CALGB and the Children's Oncology Group have provided these data on 6 adults who underwent transplant after nelarabine therapy and 21 children.

You can see the majority of there patients did achieve myeloid engraftment as indicated by more than 500 neutrophils for 3 consecutive days after allogeneic transplantation.

[Slide.]

There is an additional dataset from the University of Frankfurt in Germany where Dr. Dieter Holtzer treated 18 patients with relapsed refractory T-cell ALL with nelarabine with the intent of proceeding directly to transplantation, and 94 percent of those adults had myeloid

engraftment following transplantation.

[Slide.]

Shown here is a summary of the efficacy data for those patients who had previously received 2 or more prior multi-agent inductions. In the adult trial, the overall response rate was 21 percent, and in the pediatric trial, 23 percent.

The duration of the response was 4 to 155-plus weeks for the adults and 3 to 42 weeks in the pediatric series.

The median overall survival was 21 weeks for the adult trial and 13 weeks for the pediatric study, and the 1-year survival was 29 percent in the adult series and 14 percent in the pediatric series.

[Slide.]

In conclusion, nelarabine has shown a meaningful clinical benefit as demonstrated by the induction of complete remission in these heavily pretreated patients with relapsed and refractory T-cell ALL of lymphoblastic lymphoma.

There have been consistent rates of

remission for both adult and pediatric patients, for patients with both relapsed and refractory disease, and across the Phase I and Phase II studies.

In addition, these responses have been durable and have allowed many patients to proceed to a successful transplant procedure, and finally, the 1-year survival has been quite encouraging.

Thank you very much. Dr. Russo will now present the safety data.

Safety Summary

DR. RUSSO: Thank you, Dr. Larson.

[Slide.]

This presentation is safety results derived from the full Arranon Development Program. We will cover the safety populations and the Phase I experience, then, focusing on the experience at the proposed doses, the hematologic adverse events, and the non-hematologic adverse events will be presented, followed by some additional detail of the neurologic events, and the finish with mortality due to the adverse events.

[Slide.]

At the time of data cutoff, over 980 patients with various malignancies had been exposed to Arranon. Any SAEs that might have occurred in these 980 patients are available and are presented in the NDA. Additional data are available for a substantial subset of these.

Full adverse event data are available for all GSK IND studies, as well as for the 2 pivotal trials. Together, this represents 459 patients with full adverse event data.

Safety data specific for the proposed adult and pediatric dose regimens are derived from several sources. For the adults treated at 1,500 mg/m2 on days 1, 3, 5, we have 36 patients from the CALGB study that you have just heard of.

In addition, we have patients treated at the same dose and same schedule on PGAA2003. This is a study of patients with chronic lymphocytic leukemia refractory to fludarabine and alkylator therapy.

Together, this yields a total of 103 adult

patients treated at the adult dosing schedule. The experience of both populations are combined to improve our ability to characterize for you both the nature and the frequency of adverse events at this dose.

For the pediatric population, there were 84 patients treated at the 650 mg/m2 daily for 5 day schedule, all of them from the Children's Oncology Group study. Given the low incidence of the disease under study, we feel that this represents a substantial database upon which to characterize the clinical safety profile of Arranon.

Before discussing the Phase II experience at the proposed doses, I will present a brief overview of the Phase I safety experience.

[Slide.]

181 patients were treated in Phase I across a broad range of doses. Three schedules were examined with most experience gained at the daily X 5 schedule. In each schedule, the dose-limiting toxicity was neurologic. At the

higher doses in Phase I and especially above the maximally tolerated dose, severe neurologic events occurred, such as ascending polyneuropathy, uncontrolled seizures, and severe somnolence.

However, based on the significant anti-tumor activity seen, it was deemed appropriate to proceed into Phase II with recommended doses initially of 2,200 mg/m2 on days 1, 3, 5 for adults and 1,200 mg/m2 X 5 for pediatrics.

In Phase II, the doses were reduced following the occurrence of significant neurologic adverse events now to the proposed adult dose of 1,500 mg/m2 on days 1, 3, 5, and in pediatrics, 650 mg/m2 daily X 5.

The dose reductions, together with heightened clinical awareness, allowed for the continued successful development of Arranon at the proposed doses. The safety data presented here then are from the experiences of the proposed doses in the proposed indications.

[Slide.]

Beginning with the hematologic toxicity,

there was frequent hematologic adverse events observed. Grade 4 hematologic adverse events for both populations regardless of relationship are shown here.

This profile is expected with nucleoside analogues when used in induction therapy for patients who have been heavily pretreated and who have bone marrow compromise related to their disease. These events were considered manageable and of limited clinical significance by our investigators.

[Slide.]

So, what are the most common non-hematologic adverse events? Here are the most frequent Grade 3 or 4 non-hematologic adverse events occurring in the adult population treated at the proposed dose. Events determined by the investigator to be possibly related to treatment with Arranon are shown in red, while any Grade 3/4 events regardless of drug relationship are shown in blue. Not shown are the Grade 3/4 events that occurred in fewer than 3 patients.

From this bar graph, one can see that most Grade 3/4 non-hematologic adverse events occurred in less than 10 percent of patients.

Many of the events, such as febrile neutropenia, pneumonia, and other infections would be expected to occur in such a heavily pretreated population of patients with leukemia.

[Slide.]

Similarly, for the pediatric population treated at the proposed dose, the most frequent Grade 3/4 events occurred in less than 10 percent of patients.

As seen here and in the previous slide, the Grade 3/4 non-hematologic events are ones that are generally not of great clinical concern with the exception of the neurologic events, for example, peripheral sensory neuropathy shown here, convulsions shown here.

The neurologic dose-limiting toxicity seen in Phase I and early Phase II have already been presented. The important question at hand, then, is what was the safety profile of Arranon observed

in the Phase II trials at the proposed doses and schedules.

[Slide.]

Presented here are the drug-related neurologic adverse events observed at the adult dose. Shown in orange bars is the frequency of a given event occurring at any grade. Recall that the previous 2 slides displayed only Grade 3/4 events. Here, the green bars represent the drug-related Grade 3/4 events.

The high grade neurologic events were infrequent, 2 percent or less, while the lower grade events were more frequent, for example, the 17 percent hypoaesthesia represented by the top orange bar.

This population of patients may be expected to experience some additional neurologic events regardless of the treatment, because they have been heavily pretreated and because of their underlying disease.

The next slide shows all events regardless of drug relationship.

[Slide.]

When events are shown regardless of drug relationship, Grade 3/4 events remain under 3 percent frequency as just shown. The only change is that the frequent and typically unrelated events, such as headache, now appear.

[Slide.]

Moving to the pediatric neurologic-related events, presented here at the pediatric dose. As before, orange bars represent the frequency of the given event occurring at any grade, while the green bars represent the related Grade 3/4 events.

Note that the high-grade neurologic events occurred in a frequency of 6 percent or less, and overall, the frequency of the neurologic events at any grade appear less frequent in the pediatric population.

[Slide.]

For completeness, I would like to show you the neurologic events regardless of drug relationship in the pediatric population.

Similarly, several event terms become more

prominent when presented regardless of drug relationship. For example, the previous slide had related Grade 3/4 headache in only 1 percent of patients, and at any grade at 5 percent. But here, regardless of relationship, 6 percent have Grade 3/4 headache and 17 percent had any grade headache.

Similarly, for convulsions, 2 percent of patients had related convulsions, while 4 percent had convulsions regardless.

[Slide.]

Now, from a patient's perspective how often would a patient be anticipated to experience a Grade 3/4 neurologic event when treated with Arranon at the proposed dosing schedule?

When considered without regard for drug relationship, 10 percent of the adult population treated at the proposed dose had a Grade 3 neurologic event, and 3 percent had a Grade 4 neurologic event, for a total of 13 percent Grade 3/4 neurologic events in adults at the proposed dose.

Eleven percent of the pediatric population

had a Grade 3 neurologic event, and 8 percent had a Grade 4 neurologic event, for a total of 19 percent Grade 3/4 neurologic adverse event rate.

[Slide.]

Some data are available on the resolution of these events. Resolution of events was documented in 47 percent of the neurologic events occurring in the adults and in 63 percent of the neurologic events occurring in pediatric patients, but resolution data were not available in all cases.

Where information is available, at least two-thirds of cases are known to have resolved. So, what do these events look like at the bedside?

[Slide.]

Investigators have described for us the neurologic events in detail. Somnolence occurring in 20 percent of adult patients and 7 percent of pediatric patients is on this slide. For the typical patient, they would be drowsy or sleepy on the day of administration, and the somnolence would resolve in the days immediately following the last

dose.

Most cases of somnolence were not considered clinically significant by our investigators.

[Slide.]

Moving to the typical patient with peripheral neuropathy, they might present several days following the completion of therapy with a complaint of tingling, pain, or numbness in their lower extremities in a stocking-like distribution, perhaps with a complaint "I can't feel my feet when I walk."

Investigators tell us that the neuropathy resembles that seen with vincristine or taxanes, and was mostly sensory. The typical patient might also have some degree of weakness, and the resolution of the neuropathy may take a number of days to a number of months to resolve.

Fourteen out of the 980 patients treated across the entire course of the Arranon development have developed an ascending polyneuropathy that has been referred to by some as a Guillain-Barre-like

syndrome.

The observed rate of 1.5 percent should be placed into the context of a desperate need of these heavily pretreated patients who have exhausted their treatment options.

Treatment-related mortality is a reality for some patients being treated for relapsed, refractory disease. For prospective historical data for this and similar patient populations include toxic death rates as high as 20 percent although today's practitioners suggest that a 5 to 10 percent treatment-related mortality rate in this heavily pretreated population may be more common.

[Slide.]

Death due to adverse events during treatment with Arranon in the pivotal trials is shown here. Nine out of 187 patients, the 187 coming from the 84 plus 103, 5 percent then had adverse events ending in death.

Only 2 of these were assessed as related to Arranon therapy, for a 1 percent treatment-related mortality rate.

[Slide.]

So, in summary, Arranon therapy is associated with frequent expected and manageable hematologic toxicity. Neurologic events are the adverse events of greatest clinical significance. These were common, predominantly of low grade, and reaching the Grade 3 or 4 level in the minority of patients.

Many of the neurologic events resolved. One percent of patients had fatal related adverse events. At the recommended doses, Arranon treatment demonstrates an acceptable risk profile for these desperately ill patients.

At this point, I would like to turn it over to Dr. Bill Carroll, Chairperson, Children's Oncology Group ALL Committee.

Role in Treatment

DR. CARROLL: Thanks, Mark.

I am Bill Carroll and I have the good fortune of running the Children's Oncology Group ALL Committee, and I will summarize for you COG's approach to the development of Arranon and our

ongoing commitment to the evaluation of this promising agent.

[Slide.]

Like most cancers, the evaluation of new agents for T-ALL and acute lymphoblastic lymphoma takes place in the refractory or relapsed setting. These are heavily pretreated patients and as you have already heard, most of these patients have adverse risk factors at initial diagnosis and have already received the most intense treatment arm on our upfront trials.

Historically, treatment for relapse is usually individualized based on response to prior therapy, and I will point out that stem cell transplantation is often the goal of therapy with chemotherapy used to induce remission and lead to subsequent BMT.

Our approach to clinical trials in the circumstance is to evaluate a new agent's ability to induce complete remission in these heavily pretreated patient. Randomized trials are not possible in the relapsed or refractory setting due

to small patient numbers, the inability for investigators to reach agreement on a uniform retrieval strategy, the lack of good results using recycled chemotherapy agents, and finally, the urgency that the doctors have in getting these patients to subsequent bone marrow transplantation.

Instead, our overarching goal has been to integrate the most promising new agents, compounds to provide clinical benefit into the front-line therapy.

[Slide.]

Arranon, in our estimation, provides clinical benefit, data you have already seen in patients with 2 or more prior inductions, with notable CR rates, especially for patients in this treatment setting.

Moreover, Arranon has significant activity in patients at first relapse where single-agent activity is at a minimum, at least equal to that provided by aggressive multi-agent regimens.

Moreover, the safety profile in patients with relapsed or refractory disease is acceptable,

and this led us to initiate a feasibility trial in 2001 whereby we are integrating sequential nelarabine into a backbone of chemotherapy. It's our currently open AALL00P2 protocol for patients with new diagnosis, high-risk T-cell disease.

[Slide.]

This trial, in turn, formed the foundation for our newly, soon to be initiated Phase III randomized trial, AALL0434, currently being negotiated with CTEP, which is a large randomized, multi-center study that seeks to enroll 640 patients with T-cell ALL between the ages of 1 and 30 years.

The study design is such that the chemotherapy platform is a modified BFM regimen, which is essentially the best arm of our recently completed therapy for high-risk ALL. It is identical to the currently open study for higher risk B precursor disease.

Patients will be randomized in a 2 by 2 factorial design to either receive or not receive Arranon. It will also be randomized to two

different formulations of methotrexate during interim maintenance.

I might point out that only high-risk and intermediate-risk T-cell patients will be eligible for the Arranon randomization. The primary endpoint is event-free survival at 4 years, and the first 20 patients with very high-risk disease defined by an MRD level greater than 1 percent will receive Arranon in order for us to complete a safety phase, and there are five interim evaluation points during the course of this study.

[Slide.]

This is basically the outline of the study, where after a 4-drug induction, patients are randomized to either receive Arranon or 2 different formulations of methotrexate.

Six courses of Arranon will be received in consolidation, delayed intensification, and during the first 3 cycle of maintenance.

The dose of Arranon will be 650 mg/m2 based on the Phase I and Phase II studies for 5 consecutive days during the periods I have showed

you on the last slide.

The assessment will be event-free survival and we are building in a surrogate endpoint, a minimal residual disease endpoint at post-consolidation where half of the patients will receive 2 courses of Arranon.

[Slide.]

So, in conclusion, Arranon provides clinical benefit with an acceptable risk-to-benefit profile. It is an effective treatment for patients with relapsed or refractory T-cell ALL, most of whom have exhausted all other forms of effective therapy, and lastly, it has shown clinical benefit for patients with first, second, subsequent relapse, and those with refractory disease.

At this point, I will turn it over to Peter Ho to provide concluding remarks.

Conclusions

DR. HO: Thank you, Dr. Carroll.

[Slide.]

This afternoon, we have described that patients who have T-cell ALL and T-cell LBL in

second or greater relapse or in the refractory setting have a rare and lethal disease.

We have shown that Arranon has an acceptable safety profile. As with other nucleoside analogues, Arranon exhibits myelosuppression and has associated with it neurological events.

As Dr. Russo has described, the hematologic adverse event profile is expected and can be well managed in this setting. The early experience with Arranon at higher doses is particularly concerning for neurological adverse events, but following reductions in the recommended doses, these events are now mostly of low grade.

We do fully acknowledge that Grade 3 and 4 neurological events may occur with treatment, however, this must be viewed within the context of these patients who have exhausted standard treatment options.

[Slide.]

As Dr. Larson has described, Arranon has shown us clinically meaningful benefit as a single

agent in patients with relapsed and refractory T-cell ALL and T-cell LBL.

As a targeted agent, it shows consistent rates of complete remission in second line and in third line treatment, in patients who have been refractory to their most recent induction attempt, and in children and adults.

These complete remissions are durable and allowed time for transplantation. Complete remissions are clinically significant in the treatment of patients with leukemias and lymphomas, and are historically accepted as an endpoint for the approval of novel agents in these diseases.

Moreover, we have demonstrated in our pivotal trials survival at one year for patients, the first such demonstration of this endpoint for this patient population.

So, we agree with Dr. Carroll that Arranon exhibits an overall favorable benefit-risk profile for our proposed population of children and adults with T-cell acute lymphoblastic leukemia and lymphoblastic lymphoma, and that is why we are here

seeking regular approval for Arranon in this indication this afternoon.

Thank you very much.

DR. MARTINO: Thank you, Dr. Ho.

Next, I would like the FDA to present their review of these studies.

FDA Presentation

Arranon (nelarabine) FDA Review

DR. COHEN: Good afternoon. I am Dr. Martin Cohen and the NDA being presented today is No. 21-877.

[Slide.]

The study drug is nelarabine, which is a pro-drug to Ara-G. The sponsor, as you know, is GlaxoSmithKline. Nelarabine, as we have heard, is a purine nucleoside analogue that is metabolized to its triphosphate conjugate by deoxycytidine kinase within tumor cells.

The relative sensitivity of T-cells to Ara-GDP is due to a higher initial intracellular Ara-GDP concentrations in T-lymphocytes versus B-lymphocytes.

[Slide.]

The proposed indication for this NDA is that nelarabine is indicated for the treatment of patients with T-cell acute lymphoblastic leukemia, subsequently designated as T-ALL, and T-cell lymphoblastic lymphoma, subsequently designated as T-LBL, whose disease has not responded or who have relapsed following treatment with at least two chemotherapy regimens.

[Slide.]

As you have heard, two, Phase II clinical trials to demonstrate the safety and efficacy of nelarabine were submitted, one in pediatric patients conducted by the Children's Oncology Group, the other in adult patients conducted by Cancer and Leukemia Group G as an intergroup trial in cooperation with the Southwest Oncology Group.

The pediatric study included 145 patients, 21 years of age and younger, who had relapsed or refractory T-ALL or T-LBL.

Several different nelarabine doses were studied. The relevant pediatric efficacy population

included 70 patients, 30 of whom had received two or more prior induction regimens, and 31 who had received one prior induction regimen.

The CALGB adult study included 39 treated patients, 28 of whom had received two or more prior induction regimens, and 11 who had received one prior induction regimen.

[Slide.]

The dose and schedule of nelarabine in the pediatric study was 650 mg/m2/day administered intravenously over 1 hour daily for 5 consecutive days repeated every 21 days. The dose and schedule of nelarabine in the adult study was 1,500 mg/m2 administered intravenously over 2 hours on days 1, 3, and 5 every 21 days.

[Slide.]

Response definitions are listed on this slide. A complete response required no circulating blasts, no extramedullary disease, and an M1 bone marrow defined as having less than 5 percent lymphoblasts. There also had to be recovery of peripheral blood cell counts to a level of an

absolute neutrophil count greater than or equal to 1,500/microliter, platelets greater than or equal to 100,000/microliter, and hemoglobin greater than or equal to 10 g/dL for subjects less than 2 years of age, and greater than or equal to 11 g/dL for patients greater than or equal to 2 years of age.

A complete response starred or CR* meets all the criteria of a CR except that one or more elements of the peripheral blood count had not reached levels specified above or that the bone marrow remained hypocellular.

There was an independent review of bone marrow aspirates and/or biopsies for responders whose marrow slides were available.

[Slide.]

For both of the Phase II studies, the primary efficacy objective was to determine the complete response rate and the CR* rate. One secondary objective was to document response duration. This evaluation was frequently confounded by the fact that patients in nelarabine-induced complete remission may have

received additional therapy including stem cell transplantation prior to disease progression or recovery of peripheral blood cell counts.

This additional therapy, as we have heard, is considered standard of care.

[Slide.]

Turning now to the pediatric study.

[Slide.]

Study inclusion criteria included an age less than or equal to 21, and the diagnosis of refractory or recurrent T-ALL or T-LBL. Eligible patients were in their first or subsequent relapse and/or they were refractory having failed to achieve a remission following one or more different regimens.

Patients had a Karnofsky performance status greater than or equal to 50, and had adequate bone marrow, liver, and renal function, and no severe infection. Exclusions included pregnant or lactating women and patients with baseline greater than or equal to Grade 2 neuropathy.

[Slide.]

A total of 78 United States and Canadian sites participated in the pediatric Phase II study. There were 109 investigators. As I mentioned previously, there was independent pathology review to confirm response to therapy for patients whose marrow slides were available, and approximately 90 percent of responders were, in fact, reviewed.

[Slide.]

Efficacy study patients who received nelarabine, 600 mg/m2 daily X 5 are listed on this slide. The 39 Group 2 patients, the patients relevant to the proposed indication, had T-ALL or T-LBL that had relapsed or had been refractory to two or more prior induction regimens.

The 31 patients in Group 1 had relapsed or had been refractory to one prior regimen.

[Slide.]

Demographics and Karnofsky performance status of study patients are shown on this slide. A total of 70 patients, 39 Group 2, and 32 Group 1 were enrolled and treated. As indicated, the mean

age was approximately 11.5 years. The major of study patients were male and caucasian. The majority of patients had a Karnofsky performance status of 80 or better.

[Slide.]

Disease characteristics of study patients are shown on this slide. As seen, a large major of patients in both groups had T-cell ALL, 79 percent in Group 2, and 90 percent in Group 1. Nearly all patients had bone marrow involvement, 3 percent of each group had CNS involvement, and 44 percent of patients in Group 2 and 32 percent in Group 1 had extramedullary involvement including lymph nodes, spleen, liver, and kidneys.

[Slide.]

Number of induction regimens administered to Group 2 patients prior to entry into the nelarabine study are listed on this slide. As indicated, the majority of patients have received two prior induction regimens, 18 percent of treated patients have three prior induction regimens, and 5 percent each had four or five prior regimens.

[Slide.]

As previously indicated, rate of complete response and complete response without hematologic and/or bone marrow recovery were the primary nelarabine efficacy endpoints. All responses were confirmed by the FDA.

For Group 2 patients whose disease had relapsed or was refractory to two or more induction attempts, the CR rate was 13 percent and the CR plus CR* rate was 23 percent.

Additional evidence for nelarabine activity against T-cell ALL and LBL is evident from the 31 Group 1 patients who had failed only one prior induction. In this group of patients, the CR rate was 42 percent and the CR plus CR* rate was 48 percent.

[Slide.]

This slide summarizes response rates by disease type, namely, T-ALL versus T-LBL. As indicated, there were relatively small numbers of LBL patients, 8 in Group 2, and 3 in Group 1.

For Group 2 patients, CR plus CR* rates

were roughly comparable for the two histologic cell types, 22 percent and 25 percent. None of the three Group 1 LBL patients responded.

[Slide.]

This slide shows pediatric T-ALL/LBL patients who received a transplant after initial nelarabine treatment. Because stem cell or marrow transplants may be associated with durable remissions, there is pressure to proceed with transplant if a suitable donor is available.

In the present study, 4 of 9 CR or CR* Group 2 patients underwent transplant. For Group 1 patients, 10 of 15 CR or CR* patients, or 67 percent, received a transplant.

[Slide.]

This slide summarizes remission duration in weeks for Group 2 and Group 1 CR and CR* patients who received nelarabine 650 mg/m2 and who did not undergo a transplant. There were 5 Group 2 patients and 5 Group 1 patients.

While in remission, these patients may have received additional intrathecal therapy

denoted by IT on the slide, and additional systemic chemotherapy denoted by SYS on the slide.

The longest remission duration for Group 2 non-transplanted patients without additional therapy was approximately 14 weeks, the first Group 2 patient listed who had an overall remission duration of 42.1 weeks, and the longest remission duration for Group 1 patients without additional systemic therapy was approximately 9 weeks.

[Slide.]

Turning now to the adult study.

[Slide.]

Demographics and Karnofsky performance status of study patients are shown in this slide. A total of 39 patients, 28 Group 2, and 11 Group 1 were enrolled and treated. As indicated, the mean age was approximately 30 years. The majority of study patients were male and caucasian. The majority of patients had a performance status of zero or 1.

[Slide.]

The disease characteristics of study

patients are shown in this slide. As seen, a large majority of patients in both groups had T-ALL, 61 percent in Group 2 and 82 percent in Group 1. Extramedullary disease was present in 71 percent of Group 2 patients including CNS leukemia in 14 percent. Fourteen percent of Group 2 patients had had a prior transplant.

[Slide.]

This slide indicates the percent of patients with a CR and the percent of patients attaining either a CR or a CR*, and again, all responses have been confirmed by FDA.

For Group 2 patients whose disease had relapsed or was refractory to two or more induction attempts, the CR rate was 18 percent and the CR plus CR* rate was 21 percent. For Group 1 patients who had relapsed or were refractory to one prior regimen, corresponding response rates were 18 percent and 27 percent.

[Slide.]

This slide summarizes response rates by disease type, namely, T-ALL versus T-LBL. As

indicated, there were relatively small numbers of LBL patients, 11 in Group 2 and 2 in Group 1. For Group 2 patients, CR plus CR*, rates were roughly comparable for the two histologic cell types, 24 percent and 22 percent respectively.

In Group 1, CRs were seen in both ALL and LBL phenotypes.

[Slide.]

This slide shows adult T-cell ALL/LBL patients who received a transplant after initial nelarabine treatment. In the present study, 1 of 6 CR or CR* Group 2 patients underwent a transplant. For Group 1 patients, 1 of 3 CR or CR* patients, or 33 percent, underwent the transplant.

[Slide.]

This slide summarizes remission duration for Group 2 and Group 1 CR and CR* patients who did not undergo a transplant. There were 5 Group 2 patients and 2 Group 1 patients. None of these patients received additional therapy while in remission.

The longest remission duration for Group 2

non-transplanted patients was 195-plus weeks, and the longest remission duration for Group 1 non-transplanted patients was 217 weeks.

[Slide.]

Supportive evidence for nelarabine efficacy in pediatric and adult T-cell ALL/LBL patients comes from response rates observed in three, Phase I trials that included pediatric and adult patients.

There were a total of 25 pediatric patients in the three studies. The nelarabine scheduled study included daily X 5, daily X 3, and days 1, 3, and 5. For each schedule, treatments were to be repeated if indicated at 3-week intervals. Nine pediatric patients, or 36 percent, achieved a CR. Four adult patients, or 16 percent, also achieved a CR.

[Slide.]

Turning now to safety, Grade 3/4 in non-neurologic adverse events regardless of causality occurring in 84 pediatric patients receiving nelarabine 600 mg/m2 daily X 5 are

summarized on this slide.

As expected, hematologic toxicity manifested by decreased hemoglobin, decreased white blood cell and neutrophil counts, and decreased platelets were most frequent. Approximately, 90 percent of study population had Grade 3/4 hematologic toxicity.

Grade 3 neutrophil toxicity was observed in 10 percent and Grade 4 neutrophil decrease in 28 percent of patients. Febrile neutropenia was reported, as was infection complicating neutropenia.

A variety of laboratory toxicities was also observed including Grade 3/4 increased transaminases and bilirubin in 4 and 9 percent of patients, and decreased albumin and potassium in 6 percent of patients. Constitutional symptoms included asthenia and of note, Grade 3/4 gastrointestinal toxicity was not observed.

[Slide.]

This slide lists neurologic adverse events observed in the COG study. As mentioned,

neurologic toxicity was dose limiting. For pediatric patients, at 650 mg/m2 daily X 5 days, 38 percent of patients had neurologic events, 14 percent Grade 3, and 8 percent Grade 4.

These numbers, though, are likely an underestimate as patients were often removed from study if they developed Grade 2 neurologic toxicity. The most frequent neurologic adverse event irrespective of causality was headache. Six percent of patients had Grade 3/4 headache and 17 percent of patients had any grade of headache.

Other toxicities included somnolence or lowered consciousness, hypoesthesia, and neuropathy, and neuropathies as we have heard might be either sensory or motor or both. Seizures, paresthesias, tremor, and ataxia also occurred, and 1 patient had status epilepticus.

[Slide.]

Grade 3/4 non-neurologic adverse events regardless of causality occurring in 103 adult patients receiving nelarabine 1,500 mg/m2 days 1, 3, 5, every 21 days, are summarized on this slide.

As expected, again hematologic toxicity was most frequent and occurred in about 70 percent of study patients. Grade 3 neutrophil toxicity was observed in 4 percent, and Grade 4 neutrophil decrease in 12 percent of patients. Again, febrile neutropenia was reported, as was infection complicating neutropenia.

Grade 3/4 gastrointestinal disorders included nausea, diarrhea, vomiting, constipation, and stomatitis. Each of these Grade 3/4 toxicities occurred in about 1 percent of treated patients.

Constitutional symptoms included fatigue and asthenia. Respiratory disorders included cough and dyspnea, and Grade 3/4 AST increase was noted in 2 percent of treated patients.

DR. MARTINO: Dr. Cohen, I am sorry, I need to stop you. You confused me a bit. The 103 N comes from?

DR. COHEN: Comes from Phase I.

DR. MARTINO: So, it's all of the data combined. Thank you. I assumed as much, but I need to be sure.

[Slide.]

DR. COHEN: Again, in adults, neurologic toxicity was dose limiting. Four adult patients at 1,500/m2 on days 1, 3, and 5, 72 percent of patients had neurologic events, 10 percent Grade 3, and 3 percent Grade 4.

As previously indicated, this is likely an underestimate as patients were often removed from study with greater than or equal to Grade 2 neurologic events. Frequent neurologic adverse events irrespective of causality included headache, somnolence, hypoesthesia, and neuropathy.

Dizziness, paresthesia, tremor, and ataxia also occurred. Additional Grade 3 events were aphasia, convulsions, hemiparesis, and loss of consciousness, each reported in 1 patient or about 1 percent.

Additional Grade 4-plus events were cerebral hemorrhage, coma, intracranial hemorrhage, leukoencephalopathy, and metabolic encephalopathy, each reported in 1 patient. Blurred version was also reported in 4 percent of adult patients.

There was a single report of biopsy-confirmed progressive multifocal leukoencephalopathy in the adult population. There have also been reports of events associated with demyelinization and ascending peripheral neuropathies similar in appearance to the Guillain-Barre syndrome.

[Slide.]

In conclusion, this slide summarizes CR and CR* rates in pediatric and adult patients with T-cell ALL/LBL who had relapsed or were refractory to 2 or more prior treatment regimens, the patient population corresponding to the proposed indication.

The CR rates were 13 percent and 18 percent in pediatric and adult populations respectively. The CR plus CR* rates were 23 percent and 21 percent respectively.

[Slide.]

Additional evidence for nelarabine activity against T-cell ALL or LBL is evident from patients who had only 1 prior induction. In this

group of patients, the CR rates were 42 percent and 18 percent in pediatric and adult populations respectively, and the CR plus CR* rates were 48 percent and 27 percent respectively.

[Slide.]

This slide indicates that CRs and CR*s occurred in both disease types, that is, T-cell ALL and T-cell LBL. Included in this tabulation are both pediatric and adult patients. The pediatric patients were treated with nelarabine doses of 650 mg/m2 or 900 mg/m2. The CR rates were 13 percent and 21 percent in T-cell ALL and T-cell LBL populations respectively.

The CR plus CR* rates were 23 percent and 25 percent respectively.

[Slide.]

As to the safety conclusions, toxicity was as expected for a pretreated relapsed, refractory, acute leukemia population. Principal toxicities in pediatric patients were primarily laboratory abnormalities and included hematologic toxicity occasionally accompanied by febrile neutropenia and

infection.

Other laboratory abnormalities included increased transaminases and bilirubin and decreased potassium and albumin. Principal toxicities in adults were hematologic, gastrointestinal including nausea, vomiting, diarrhea, and constipation, and respiratory disorders including cough and dyspnea.

Neurologic toxicity was dose limiting for pediatric and adult patients. The neurologic toxicity was similar to that seen with several other anti-cancer drugs including fludarabine and high-dose cytosine arabinoside. Most neurotoxicity resolved over time, but status epilepticus was fatal in 1 patient.

[Slide.]

To conclude, I would like to indicate a difficulty encountered in evaluating this operation. As listed on this slide, the traditional endpoints for evaluating acute leukemia studies include complete response rate, complete response duration, and overall survival.

A confounding factor in evaluating this

NDA were that some patients who were CRs or CR*s were transplanted early, before nelarabine response duration could be determined. While early transplantation is the standard of care, it makes it difficult to determine how much of the subsequent response duration can be attributed to nelarabine and how much to transplant-related treatment.

In present the study results, I chose not to discuss response duration in transplanted patients because of the previously mentioned uncertainty. I also did not present survival data because there was no comparator. Whether this was reasonable or not must be considered by ODAC, and thank you for your consideration.

DR. MARTINO: Thank you, Doctor.

At this point ladies and gentlemen, I would like to give you all a 10, not 15, 10-minute break. So, I would like you back here and ready to go at 25 after.

[Recess.]

Open Public Hearing

DR. MARTINO: The next portion of this meeting is the Open Public Hearing. There are two folks who have asked to be heard. Please, for those of you that are going to address us, there is a microphone at the end of the tables, and that is the one we would like you to use.

As you get ready, our first speaker is Michelle Pollak from the Wellness Community. Is Michelle available? Apparently, Michelle is not going to address us.

David and Kyle Naber, if you would approach the microphone, but before you speak, I need to read something to you, please.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decisionmaking. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning

of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its products, and, if known, its direct competitors.

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

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

Please.

MR. NABER: Thank you. Good afternoon. My name is David Naber and I am here with my 10-year-old son Kyle, who is a 5-year T-cell leukemia survivor.

I want to thank you for the opportunity to speak before you today, and for the record, as a way of disclaimer, GlaxoSmithKline has paid for our

travel here and is paying for our hotel and accommodations, meals, and such while we are here in the Washington, D.C. area. However, they have not compensated me in any other way to speak on behalf of either their company or, in particular, for Arranon.

One of Shakespeare's most famous quotes is "To be or not to be, that is the question," and that quote is really about making decisions. In this case, the decision that my wife and I were faced with was one that could result in my then 4-year-old son living or dying.

You know, we make thousands of decisions every day. Some are very easy, some are hard, and some are downright impossible. About five years ago, my wife and I were faced with a life or death question regarding Kyle. That basic question was should we use 506U78, which will always be known to me as that, Arranon to everybody else, but it's indelibly in my mind as that term, but do we use that or do we not.

Obviously, the answer to that question was

yes, which is why Kyle and I are here today. But in order to tell you the full story, I need to rewind about five years ago and tell you how we came to be faced with that actual decision, how did we get to that question, how did we get to that point in our life.

In January of 2000, my family and I were living in Cairo, Egypt, where I worked installing computerized medical systems into hospitals there. One night on coming home from work, my wife asked me if I could check Kyle as if I have some clinical background and could make a better judgment than she could, but she had noticed a lump in his stomach, just below his ribs, and asked me if I could check that, which I did, and I notice the same thing, so, okay, we both now realized there is a lump there, so what do we do about it.

The fortunate part of this is that in my workings on the projects that I was doing there in Cairo, I was fortunate enough to have an M.D./Ph.D. on my staff, who also actually happened to work for the National Cancer Institute in Cairo, so I had a

very well-qualified person to give me a hand.

I asked him to come over and check on Kyle, which he did. After examining him in my house, his conclusion was that it was probably his spleen and that in order to know that for sure, he would need an ultrasound.

Fortunately, we were able to arrange an ultrasound that evening, which was done and it confirmed that, in fact, it was his spleen that had grown out, up and below his ribs, and was now protruding.

Again, and you will find as I read this story, I think, that many miraculous things happened during this time, things that just fell right into place for us. As it happened, this particular doctor also had a colleague who owned a lab in the same town that we lived in, convinced him he would like him to open that lab and actually do some bloodwork on Kyle that night still, which he did.

So, we went to the lab, we had labwork done. I am going back home, I am riding with the

doctor and myself in our car, and I am going back to my house, and the phone rings for the doctor. I can still very well remember listening to that conversation, most of which was in Arabic. I do speak some Arabic, but not well enough to keep up with that particular conversation.

However, as we all know, medicine is practiced in English and all the disease names are in English, so amidst all this Arabic, the word leukemia came out. Now, honestly, I can't tell you how far my heart sank when I heard those words, and the reason I say that is for many people, finding out that your child might have leukemia is bad enough. When you are finding out that your child might have leukemia when you have had a brother who has died from leukemia, it is really devastating.

Not only do you know what the disease is, you know probably way more than you want to know about what the future could possibly hold for your son.

Our next stop after hearing that news was to head downtown to see an Egyptian pediatric

oncologist to confirm the lab's assessment, and in this case, by doing a bone marrow biopsy. However, in looking around his office, which was less than what I would consider my standards of cleanliness and therefore goes over into what you might expect his procedures to be, and those kinds of things, when looking around, I opted to decline at that point for those reasons, as well as the fact that I assumed that once he returned to the U.S., which it was obvious he would get treatment here, that no doctor in their right mind would just take that person's word for it, and they would just do it again, and I saw, having actually witnessed one of these, I saw no reason to put him through that twice in probably a 24-hour period.

At that point, then, we are still relatively unsure whether Kyle has leukemia or not. We know that the bloodwork would show that, but from my understanding, and I have no clinical background, so if I say something that is wrong, I apologize to all of you well-educated folks here, but I understand that the lab results for leukemia

can look very similar to mononucleosis, so I was hoping for a misdiagnosis from a lab guy. However, not knowing whether that was true or not, I had no choice but to send him home, which I did.

I sent my wife back along with Kyle where they immediately went to Children's Hospital of Wisconsin, which was located in Milwaukee. There, he was diagnosed with T-cell acute lymphocytic leukemia. Of course, knowing that this is the most common, highly treatable as we heard today, the cure rates are quite high, you sort of count your blessings and think, okay, if I have to have a leukemia, this is not a bad one to have, if you can actually put it that way.

So, we counted our blessings on that and said, okay, let's get started, so he was started in the standard induction protocols that were consistent with is findings, and things were looking pretty good.

I arrived back in the United States along with my daughter about a week after Kyle and his mother had left the country, where I went straight

to the hospital to meet with the oncology team to learn about Kyle's condition and what the plan was to treat him.

One of the things that surprised me the most during that meeting was that the drugs that were being used to treat him were the same drugs that were used to treat my brother 25 years before, and as they listed off several of the drugs names, and again here today I heard many of the same ones that bring my quite a few memories of my childhood, I couldn't help but sit there and think is it really possible that 25 years later, we really are still using the same drugs, have we not come up with something better.

Of course, I asked all the questions, you know, like that, and what I was told made sense, is that we are still using the same drugs, but we know how to use them better. That is where the gain has been over the last few years.

About six weeks into his treatment, we were told that the chemotherapy was not working, so he failed his induction. It had helped a little

bit, but his numbers were still out of range, he was still active in his leukemia.

At that point, we were told that the only other potential treatment was a bone marrow transplant, and, of course, like any parent, you ask all the same questions, are you sure it's not working as if they would lie to you, but you ask those questions are you sure it is not working, aren't there other protocols, aren't there other drugs, isn't there anything else, and the answer to those questions was no, there is not.

As I alluded to in the beginning, my brother subsequently succumbed to leukemia, and he was never really a candidate for bone marrow transplant, so now we were sort of getting into territory that was a little unfamiliar to me.

In discussing these things with our doctors, what I found out is three things, that in order to do a bone marrow transplant, first, you have to have a donor. Makes sense. Two, you have to be in remission, and, three, that was really the only other treatment option for Kyle at that time.

So, for the first one of whether or not we had a donor, that is where you hope and pray that you find somebody who is going to match. For the second one, I just assumed that our oncology team had a plan to get him into remission, and for number three, just try not to dwell on the fact that if this fails, there is no other option.

For our purposes, prayers were answered. We found out that Kyle's mom was almost a perfect match. I believe there are eight factors that are matched for donors, she was a seven out of eight, which is really a miracle, as Kyle, as we found out, has an unusual chromosomal allele not normally found in the general public. His mom, my wife, also has that same allele, so they matched on seven out of eight, so we had a viable donor.

So, then, we get into how do we get Kyle into remission. We were told that there was a promising new drug currently in clinical trials, as I alluded to before, 506U78, which it will be forever to me.

It was available for use and this was his

best option. I have to admit at this point that I am not sure there were other options. Again, looking at your oncology team, we implicitly trust the doctors that they know the best course of action and what they are doing is the right thing, and I assume at that time that Arranon was the best choice available inclusive of things that were already approved.

I remember reading through the information that you are provided, you know, about the drug when you are entering a clinical trial, and looking at the list of potential side effects and skipping all the other stuff that made no sense to me just to get to the point of what do I need to know in order to decide for my son if this is the right course of action.

I have to tell you, you know, from a layman's perspective, it's funny, because every time you look at any side effects listing for any drug, it always seems to go from runny nose to death. There is never like a drug that just has rash.

So, it is always seemingly this huge spectrum of choices to live with, but what you don't find out at the time of a clinical trial is you get the list of side effects, which you really have no idea how those fall out, did one person die, die half the people die, did one guy have a runny nose.

You don't know these things, so you sort of walk into it certainly with your eyes open, you know what the ramifications of your decisions are, but you don't have all the data that you may need in order to make the best possible decision.

So, Mary and I were faced with a decision to put him on Arranon and, of course, hoping that he wouldn't die as a result of that, but, of course, the opposite choice was do nothing and which is certain death, so you are basically faced with no choice, and that is one that I certainly hope that anybody here would never have to face, because one of those almost impossible decisions to make.

So, we opted to put him on Arranon and at

the time we were told that it was an outpatient treatment. You come in, you do your IV thing, you go home. I was way too nervous, so I asked the hospital to please keep him for the entire week, afraid of what the side effects might be and the fact that I wouldn't respond quick enough or do the right thing, or whatever, and somehow be responsible for the failure of this.

I can tell you that at the end of the week, as was discussed earlier, we were one of the five-day trials, and I can tell you at the end of the week, that he was in complete remission. To the best of my recollection, there were no side effects that I could see of, and to date, I don't think he has suffered any ill side effects as a result of that course of treatment, certainly nothing that I have noticed.

So, with Mary, my wife, as the donor, and Kyle in remission, his bone marrow transplant was done on April 28th of 2000, just four days before his fifth birthday. It has now just been a little bit over five years since his transplant, and as

you can see, he is doing great, and I am here today to tell you that he is in good health and he has really had no setbacks during that five-year period. He has really not relapsed at all, there has been no complications as a result of his original diagnosis that I am aware of.

Many things during the course of Kyle's diagnosis and treatment really have been miraculous, and when I was writing my comments for today, I was thinking is there not a miracle drug. You know what? I don't know, I really don't have an answer to that, but to the question of is there not a new drug that could become an effective weapon in the fight against leukemia, well, I really honestly believe that that is true.

While it may be specific as we saw today, it may have a very small cohort to which it belongs to and to which it can be applied to, I look at it and say that my cohort of one is the one that matters, is the one that was successful in this treatment, and have no doubt in my mind that Arranon played a very important role to that, and I

thank God that at the time that all these things were happening, everything came together, this drug is on the clinical trial, we are in the right place at the right time, and it's effective for us.

Now, whether or not that turns into something bigger than this, I don't know, but I know that if I am faced with that situation ever again, that I would want to know that whatever might be effective even for a small group is available if it can be.

Obviously, we wouldn't be here sharing our story if it wasn't effective. I can look, you know, in hindsight at the difficult decision we made five years ago and tell you that it was the right choice. Of course, hindsight is 20/20. At the time it was a very difficult decision to make, but obviously, looking back, it was really the only decision we could make and it turned out very well.

It is my hope that your decision as it regards Arranon will be positive, and it will not be as difficult as the decision to put Kyle on it was for my wife and I, and I can honestly tell you

that I think Arranon, probably not in and of itself, is certainly is a useful agent, saved his life, and there is really no other way to say it.

He has a good quality of life, he is as normal as a 10-year-old can be as a result of this treatment, and I think Arranon is a huge part of that.

I want to thank you again for the opportunity to speak before you today and for doing the work that you do for the families dealing with cancer, and it really does make a difference, and I know sometimes we all have jobs where it seems like we get on pat on the back, we get no strokes of confidence, no positives about what we do, but what you are doing here both in the research companies and the FDA, obviously, you make a huge difference, and for today, you have made a huge difference for my family, and I appreciate the opportunity.

Thank you.

DR. MARTINO: Thank you both.

Ladies and gentlemen, at this point, I would like to open the committee for questions to

either the sponsor or the FDA.

Dr. Perry, you may start.

Questions from the Committee

DR. PERRY: Thank you, Madam Chairman.

A question for the sponsor, please. This is obviously a useful drug, but not a wonder drug, and it seems to me that its niche is to get people who have relapsed into bone marrow transplant.

If that is the case, then, I would like to know what is the success rate of people who eventually got a bone marrow transplant.

DR. HO: From our pivotal trial experience, those trials were not designed prospectively to assess the contribution of transplant, so you have to look at the data that we are going to present to you with appropriate caveats. So, we can only present what is there.

DR. PERRY: I understand.

DR. HO: If we can have the slide, please.

[Slide.]

This slide shows patients according to whether they have had a response as defined as a

complete remission or the CR* that you heard about earlier versus any response less than the CR*. It shows of the indicated population of two or more prior therapies and also for reference one or more, the number of patients who were able to go on to a transplant, and you can see that for adults, it is 2 out of 6 patients were able to go on to a transplant versus only 2 out of 22 who did not have a response to Arranon.

In pediatrics, it is 4 out of 9 versus 4 out of 30, but even still, as you can see by the footnotes there, there was 1 patient in each of these groups that had a marrow complete remission, 1 here, 1 there.

So, these are patients who cleared leukemic blasts from their bone marrow, but didn't have the appropriate recovery to qualify for a CR*. So, one might certainly think of contribution that Arranon made for these patients in terms of getting to their transplant.

DR. MARTINO: Dr. Rodriguez.

DR. RODRIGUEZ: I had a question with