regards to the neurotoxicity. I was wondering if those had been observed, the ones with greater severity had been observed in patients who had central nervous system involvement.

I didn't see any information regarding to that. Could you please comment on that?

DR. HO: Can I just clarify your question first. When you say central nervous involvement, you meant CNS leukemia?

DR. RODRIGUEZ: By the leukemia.

DR. HO: Yes. Okay. I can ask Dr. Blaney to comment from the COG trial.

DR. BLANEY: In the COG trial, there were 4 stratum of patients. Stratum 3 involved 22 patients with CNS involvement. The numbers are very small, but we didn't see any evidence of increased neurologic toxicity in that stratum of patients.

DR. RODRIGUEZ: So, the patient who had status epilepticus was not a patient with CNS leukemia, is that correct?

DR. BLANEY: There was one patient with

CNS leukemia that did develop seizures, but the patient with status epilepticus was not a stratum 3 patient.

DR. MARTINO: Dr. Cheson.

DR. CHESON: I have two questions. One is along the line of Dr. Perry. Sometimes it is a little subjective as to who goes to transplant or not. Maybe you showed it, but maybe it went by quickly. Do you have the data for the long-term outcome for the patients who underwent transplant? You can get a transplant, but whether it is successful or not is probably more important. That is the first question.

The second will be for Dr. Larson.

DR. HO: Okay. Very good. Let's have slide 212. Thank you.

[Slide.]

To address your first question in terms of outcomes, first, in adults and then in pediatrics. This is looking at survival of the patients who had a response, again, CR or CR*. In this case, of the adults in the CALGB study, we can see that of the

responders, out of 6 responders, there were 2 patients who did have a transplant, and the time of their transplant is shown here.

As Dr. Larson mentioned, we can see that there were patients who also had a prolonged survival without a transplant. So, in terms of trying to differentiate in this setting, and the same caveats that I mentioned before apply here since these studies were not prospectively designed to just contribute from transplant, we can just make gross comparisons to see if transplant, in and of itself, was the overriding factor in terms of longer durations of survival in these patients. At least in this limited set of patients, it is not.

If I can show the pediatric comparison.

DR. CHESON: Before you leave that, what did the transplantation die from? The second one down, isn't that X that they died?

DR. HO: I am sorry. That means censored, so they were alive. So, the patients with the plus signs were censored at the time that we closed the dataset in October of last year.

[Slide.]

In pediatrics, then, we can see that there were more patients who transplanted. Again, this is looking at the patients who did have a response, the 9 patients who had a CR or CR* response to nelarabine, there were 4 out of the patients shown here, here, here, and here, who had a transplant, and these are the times that they transplant occurred, and once again, we can see that, in and of itself, transplant does not appear to be the overriding factor for all of the patients who had a longer duration of survival.

But again, the caveat is these studies weren't designed with transplant in mind.

DR. CHESON: The second question. Prior to my taking over as Chairman of the Lymphoma Committee of CALGB, they had conducted another trial with nelarabine in non-Hodgkin's lymphomas, and the trial was shut down in large part because of concerns of neurotoxicity, and at the time Dr. Larson participated in those discussions.

Do you have any thoughts as to why, in

your study, the neurotoxicity was rather modest, and yet, in the other study, it appeared to be somewhat more prominent?

DR. LARSON: The short answer is no. I think there is a learning curve to using this drug. I think with greater experience, the neurotoxicity rate has declined, certainly, the severe neurotoxicity, but from our experience in the leukemia community, using this drug for this indication, we did not see concerning neurotoxicity. Whether it is related to the age of the lymphoma patients or prior therapies, those are possible reasons for the difference, but in the young adults with relapsed, refractory T-cell ALL, we did not see worrisome neurotoxicity in our Phase II trial.

DR. MARTINO: Dr. Ho, the patients who had a response, and who were not transplanted, can you review for me their outcome, the ones who went into a response, were not transplanted?

DR. HO: Yes, and were not transplanted, sure. May I have Slide E-27, please.

[Slide.]

We agree with the FDA that in terms of the treatment of the treatment of this disease, that transplant can be a confounding issue, so we have tried to do an analysis as shown here to try to separate out what is the duration of a response for these patients in the absence of transplant and in the absence of other systemic chemotherapy that can be confounders.

This is focusing on the 15 patients, adult and pediatric combined together, who achieved a response CR, CR*, and the duration for this slide, the response duration is from the time of an initial response, which for patients with ALL could be marrow complete response, clearing of leukemic blasts from their marrow. For the lymphoblastic lymphoma patients, that would be from the time of a complete remission until the time of a next event, with that next event being transplant, relapse, coming off therapy because of toxicities or other events, so any other event.

We can see, we can group patients into

three groupings. The first, shown here in blue, are patients who indeed do have a short duration of response. That short duration is because transplant was the intended next step for these patients.

So, although we believe that patients have their best chance from transplant, indeed, had they not had a transplant, one might have a better assessment of the duration of response to nelarabine, but clearly, it wouldn't have been shorter, it could only have been longer.

In this middle set, a grouping of patients in green, these are patients who again did not have transplant. Now, there is one exception here. This patient did have a transplant, but only after relapse.

So, for these patients, their next events are shown here. Most of them are relapsed. In one case, this is the one patient who is censored, still alive at the time of database closure, and this patient came off of therapy for toxicity reasons.

But in any event, all of these patients, as shown here, had a duration of remission of 10 weeks or longer, and the ranges are shown there.

There also is a third set of patients shown at the bottom here in orange, who do have a short duration of remission, and in most of these patients, relapse occurred quickly, consistent with what we know about the aggressiveness of their disease.

So, this is the best that we can do to try to isolate the effect of Arranon for these patients in the absence of other confounding factors.

DR. MARTINO: Can you redescribe for me how these patients were treated? In other words, they were given several cycles. You then decided that they did or did not respond, and if they did respond, you then consolidated.

Can you just review your consolidation for me?

DR. HO: Right. Certainly, in upfront treatment, as was described by Dr. Sallan, the treatment schema for these patients is multi-drug

induction followed by varying lengths of therapy, which have consolidation intensification, maintenance, and so forth.

Can I have the slide back up again.

[Slide.]

So, in this case, for these patients, other than intrathecal therapy which may have been given, which we do not capture here, in these cases, there was no other additional therapy given in transplant.

In these cases, yes, you see here in this last column, some patients did have systemic chemotherapy, but this occurred after the time that these events occurred, censoring relapse, et cetera, et cetera.

In this case, on the bottom, you see here most, well, 3 out of the 4 patients who had a short duration of remission before relapse, did to on to other therapies, but again, that wasn't a complicating--we tried to isolate out that effect in terms of the duration.

In this case, transplant for the top

group, transplant was, in our view, the overriding factor there, so we did not feel that looking at systemic chemotherapy given after a transplant, if any, was contributory.

DR. CHESON: Were any of the subsequent therapies, your Y's up there, effective in any patients?

DR. HO: It is difficult to assess very clearly, because by the time these subsequent therapies occurred, in fact, even for most of the patients at the time of transplant, they were off study, so we have tried to collect that data, but it again wasn't prospectively done as part of the study.

So, the data collection on that are probably spotty at best. The best that we can do is to look at from the time of, let's say, a transplant, or a time of systemic chemotherapy, what was the patient's survival when we have that information. So, we can look at that, but that is very complicated by many factors, and it won't give you a very clear idea of whether the patient

actually responded to therapy or not.

Where we do have the information, no patient had a response to chemotherapy. In many cases, we just don't have the information.

DR. MARTINO: Dr. Fleming.

DR. FLEMING: This is really getting at an issue that I have really been focusing on. I think it is very important to understand as best possible the course of these 9 patients in the pediatric trial who are responders, and the 6 patients who are CR, CR*, and the 6 patients in the adult.

I think a lot of the questions we are asking now, at least in the pediatric setting, appear in the FDA briefing document on page 38 and 39. I think it is worth looking at that quite closely, because it lays out in parallel, for these 9 pediatric patients, their duration of CR, CR*, their corresponding survival, and also it can be categorized by whether or not they received transplantation, intrathecal therapy, and systemic therapy.

What we see looking at the bottom 6

patients on page 38, and the top 3 patients on page 39, these are the 9 responders that, if you focus on those 4 patients who were bridged, so to speak, to transplant, the duration of CR, CR* was, in one patient, 36, and the survival was 57, so there was an additional 21 week post-CR, CR*, but for the other 3, 4.7 weeks and survival was 16.6. 36.7, survival was 39.6, only 3 weeks longer, and 14.1, survival was 22.4.

So, when we look at the totality of these 9 patients, the overall, as was reported, the median duration of response is only 9 weeks. The duration of survival is only 5 months in these patients, the median duration of survival.

None of these patients survived passed 57 weeks, so none of them survived much past 1 year whether or not they had received additional transplants or intrathecal therapy or systemic therapy. So, all of these patients had a fairly short course even though they were the responders.

I don't have the parallel. The FDA didn't provide us the parallel table for the 6, but you

have, on slide, could you give your sponsor Slide 25, because in that slide, you present to us the response data.

[Slide.]

So, this is now in the adults where the situation appears to be somewhat more favorable. So, this is the duration of response and there are 2 long-term responders at the top who are censored, and I presume therefore, their survival is censored, and I think that is what you showed us.

DR. HO: That's correct.

DR. FLEMING: Could you remind us, for the bottom 4 patients who had response durations of 4, 15, 19, and 30 weeks, what is their survival again for those 4 patients, the survival duration?

DR. HO: Can we have slide T-12, the survival of this cohort of patients.

[Slide.]

DR. FLEMING: So, that's it for the bottom 4 patients, so the survivals were about 58, 45, 62, and 21?

DR. HO: Right. Could I just comment on

your question?

DR. FLEMING: Just one other quick reminder, those that were transplanted in this group are the two that showed the orange triangle?

DR. HO: Right. As it turns out, these two patients were the transplanted patients. I would say that you have to note that compared to the prior slide, this patient here, this transplant occurred after relapse, whereas, most of the transplants, both adults and pediatrics, occurred while the patient was in a continuous complete remission.

In this particular case, the patient had relapsed first and then gone on to the transplant. That is why it is shown here.

Dr. Fleming, are you finished with your question?

DR. FLEMING: Yes.

DR. HO: One of the issues, in fact, it is shown in the FDA briefing document, is the date that these patients had undergone transplant, and certainly, transplantation has evolved very rapidly

from the time that some of the patients were first transplanted up to now.

I wonder if I could ask Dr. Kurtzberg to comment on transplantation and what was being done 5 and 10 years ago versus what is being done now.

DR. KURTZBERG: I am Joanne Kurtzberg and I direct the Pediatric Blood and Marrow Transplant Program at Duke University, and also ran the Phase I trial of nelarabine.

I would also like to comment that I have personally treated over 100 patients, mostly on the Phase I trial, although some on Phase II, and some who come to us for transplant, but relapse enroute and need to be put back in remission before they can have a transplant.

This drug has been in trials almost 20 years, and the reasons for that are that it was a grass-roots effort. It went through three companies, and it was really spirit and push that got it survived through that time, as well as the remarkable disease activity that it had.

In fact, the Phase I trial was kept open

for a longer period of time because of the disease activity. Now, during that time, transplantation medicine changed a lot, as well. In the '80s and early '90s, there were not good sources of unrelated donors, and most patients who didn't have a matched sibling did not go to transplant.

In the '90s and now certainly in this last five years, both with the advent of bigger donor registries, better understanding of unrelated transplant and cord blood transplantation, most patients can find a donor quickly if they don't have a donor in their family.

So, it is typical practice now for a patient in first relapse to be put back in remission and go to transplant within 6 to 10 weeks, and that wasn't possible n 1990 or 1985, or even probably 1995.

So, the practice was changed and the rapidity with which people can get a donor and get to transplant has changed, so I think some of what you are seeing is a reflection of practice of transplantation medicine.

Also, outcomes are much better. GVH therapy and supportive care is better, so that if you look at the most recent cord blood transplant study of unrelated transplant in children with malignancies, the overall event-free survival is at 40 or 55 percent for children, all comers, and there are about 65 to 70 percent for children transplanted in second CR, and that includes T-cell patients.

So, you can make a huge difference with a drug that can get a very resistant patient back into remission, so that they have access to transplantation therapy.

DR. MARTINO: Dr. Fleming, are you done, or do you have something else you need?

DR. FLEMING: Not on this issue.

DR. MARTINO: Can you review for me where you are taking this drug at this point? You gave us a little bit of an understanding earlier, but I would like to rehear it, please.

DR. HO: Based on the clinical trials' experience thus far, it is very clear that Arranon

has activity, clinically significant activity in patient with T-cell ALL, T-call LBL. You have seen the data.

Right now the focus for the development with the COG and with the trial that Dr. Carroll described, the Phase III randomized trial. We can show that slide, the schema, just to refresh your memory.

[Slide.]

This is a large trial, 640 patients to be randomized with a 2 by 2 factorial design, two questions being asked, one of which is an Arranon question in the front line setting. At this stage, this is the focus for development for GSK.

DR. MARTINO: Are there other questions? Yes, Dr. Fleming.

DR. FLEMING: So, on this issue, are we going to come back later to the question as to whether the goal here is full approval or accelerated approval?

DR. PAZDUR: Let me comment on that. We have, over the past applications, looked at

complete responses that have adequate durations in acute leukemia as evidence of clinical benefit.

In situations where we have a complete response rate, we are uncertain as far as the duration of the response because of the confounding effect of transplant, i.e., our previous discussions on clofarabine. We have given those products accelerated approval.

So, as far as agreements that we have made with other companies, we have generally given these agents where we have a complete response rate, that demonstrates activity, we are uncertain of the duration, accelerated approval, and that is why the questions are written in the fashion that they are.

In discussion with the sponsor, they made some arguments that perhaps these response rates are higher than we have seen in other leukemia applications. I think that is fraught with danger here to compare Phase II studies in different diseases and try to claim some superiority. I think that we are dealing in all of these situations with relatively meager databases.

The trial that has been presented here that the COG is doing is one that we would consider to be probably of benefit to convert the product to full approval if the trial is positive.

I am more than happy, by the way, to entertain any discussion if people feel that this something that would deem it should give full approval.

DR. MARTINO: Dr. Fleming, are you done with your question?

DR. FLEMING: I have a related question to the last thing that Dr. Pazdur said. The COG trial that has been put forward, which is a 640-person, randomized trial in first line. First of all, am I correct in recollecting that the anticipated duration for enrollment is 7 years? I thought I read that somewhere.

DR. HO: Can I speak to that?

DR. FLEMING: Yes.

DR. HO: Dr. Carroll, could you please address this question?

DR. CARROLL: Given the fact that the

trial will include a safety phase, and that patients with standard risk T-cell ALL, those with low white counts will be excluded from the Arranon randomization, it is anticipated that the total duration of accrual may approach about 6 years.

DR. FLEMING: Secondly, you define the primary endpoint to be 4-year event-free survival. Can you clarify that characterize the events other than death?

DR. CARROLL: If I understand the question, event-free survival includes any event whether it's relapse or death due to toxicity. Of course, most of the events in this population will be relapse.

As you might anticipate, the T-cell patients tend to relapse early, so you get an answer a lot quicker than you would ordinarily on your average childhood ALL protocol.

DR. FLEMING: So, in essence, it's a relapse-free survival endpoint although you are saying if someone has toxicity, that counts as an event? So, it is really mixing efficacy and safety

into an efficacy endpoint, did I understand that?

DR. CARROLL: Not being a statistician, I want to make sure I understand this correctly. It is just than relapse, but in actuality, it turns out that most of the patients relapse from their disease. It constitutes the overwhelming majority of events.

DR. FLEMING: So, in essence, it is relapse-free survival, nearly all the events would be relapse or death?

DR. CARROLL: Yes.

DR. MARTINO: Dr. Eckhardt.

DR. ECKHARDT: I just wanted to clarify. I think the numbers are relatively small to probably--you know, and the duration is of question to think about full approval, but my only concern here is that it looks as if the only feasible way to conduct a randomized study will be in front line, and my only concern there would be whether people in this field have any concerns whether or not that will be positive.

I mean it sounds like you would assume,

but we have been burned before certainly in colorectal cancer when we moved things into adjuvant therapy, so I think if that is the case, you know, what the risk is with regards to ever getting a full approval in their refractory setting, whether there is thoughts about how to think about that, because certainly, this also is a long-term randomized trial.

DR. PAZDUR: In may disease situations, we have looked at the confirmatory studies in an earlier phase of the disease than the approved indication, for example, if we have something for a third line setting in colorectal carcinoma, we might look at a trial in a first line setting.

The reason why we do that, we feel that this moves the field forward and really places the drug in a more appropriate context rather than simply studying it in a very, very refractory disease setting. I think we are willing to take that risk.

DR. MARTINO: Dr. Perry.

DR. PERRY: The question was answered.

DR. MARTINO: Okay. Are there any other questions? Dr. Fleming.

DR. FLEMING: You mean for the sponsor or in just general discussion?

DR. MARTINO: Do you have any questions for the sponsor or for the FDA? Is that a no, or are you thinking?

DR. FLEMING: I have a lot of discussion issues. I think we have gotten from them what I was needing to get.

DR. MARTINO: Dr. Mortimer?

DR. MORTIMER: I just want to ask the sponsors, in the adult population, the use of high-dose ara-C, was there a relationship between neurotoxicity and high-dose ara-C, or was high-dose ara-C not used in those patients?

DR. HO: Dr. Russo, would you like to address that?

DR. RUSSO: I am going to start with a short answer, and I can give more if you wish.

The short answer is in our exploratory analysis where we looked at risk factors, we were

not able to identify any particular prior therapies that were associated with increased incidence of neurologic toxicity.

The data that we had available to us were somewhat limited, and so that does not exclude the possibility that there is a relationship, but our data did not support that relationship.

DR. HO: Can I also ask Dr. Blaney perhaps to comment on the COG experience in terms of prior therapies in ara-C that might have been given to these patients?

DR. BLANEY: Again, the COG experience, our numbers are small, 150 patients total, but we did not see any correlation between prior therapies and any neurologic or other toxicities associated with Arranon.

DR. MARTINO: Anything else for the sponsors or the FDA?

Seeing no other questions for them, we will now turn to the discussion portion of this, and, Dr. Fleming, if you want to restart, you may.

Committee Discussion

DR. FLEMING: I am pleased that the FDA, in posing the questions that we will eventually discuss have separated the pediatric and adult settings, because I am struggling with trying to interpret the efficacy data particularly in the pediatric setting where we have evidence of 9 responders, but the duration of response is relatively short, it is 9 weeks, and the overall duration of survival even in these responders is only 5 months, and while the survival of the entire cohort of 39 patients is 13 weeks, it's about 3 months.

That means that the aggregation of the effect that you would have from the induction of the response, together with any contributions that would have come from intrathecal therapy and systemic therapy and transplant would translate into a totality of 2 months. Even that is an overestimate because when responders live longer than non-responders, we can't say that the reason and the duration of that longer response was entirely due to the induction of the response.

It could largely be due to selection factors for who was intrinsically different. So, I will come back to some of these numbers a little bit later, but in the bottom line, it seems as though the response is giving you at very best 2 extra months in one quarter of the patients, and that translates to 2 weeks for average patient, and that is almost certainly a overestimate, because responders living longer than non-responders is likely as much due to intrinsic differences in patients than the intervention.

One of the things I am trying to do is put this into context. There are limited data available for other interventions, and I would like to get a sense about the relevance of these other data as we are interpreting this.

Vincristine, for example, is referenced in relapsed pediatric patients for 103 of these patients where there was a 57 percent CR rate. The sponsor said, but only a 9-week duration of response. Well, that is all their duration of response is, as well, but only in 23 percent.

Then, the clofarabine is 32 percent response rate as I understand, and in the CR is the duration of response was 6 weeks to 23 weeks, and then there is a limited amount of data on tonoposide of 3 CR in 9 patients, but from that information, it is limited, but it looks as though those interventions yield higher response rates and higher durations than we are seeing in the pediatric group here.

Dr. Pazdur correctly pointed out it is always treacherous to compare agents, but nevertheless, I am struggling to try to understand what is evidence of something that is really meaningful in the context of benefit to risk, and in the pediatric setting, the overall duration of effect here seems to be so short because of the short duration of responses and the short survival in those responders even when they are transplanted. It is less impressive than the other agents in the literature.

Am I misinterpreting anything?

DR. COHEN: I think one of the problems is

most of the studies that you are referring to included both T- and B-cell patients, and probably more B's than T's, and here, you are dealing exclusively with T's.

DR. FLEMING: Can we do any better, is there anything out there, or is it just going to be incredibly limited?

DR. MARTINO: Dr. Rodriguez, do you want to answer the question?

DR. RODRIGUEZ: From my experience, T-cell disorders of any grade, indolent, well, there is some promising things in very indolent disorders, but for very aggressive T-cell disorders, there is nothing that looks exciting or miraculous right at the moment.

DR. MARTINO: So, what would you offer someone who has had at least two therapies and failed? What do you view as the natural behavior of the oncologist at that point?

DR. RODRIGUEZ: In adults, it is probably hospice. I mean if they are in very, very good shape and they can go in a Phase I/Phase II study,

maybe, but otherwise it's hospice.

DR. MARTINO: And in children?

DR. RODRIGUEZ: Well, I don't treat children, but my experience with our colleagues, I mean at M.D. Anderson, frankly, what we are exploring is lysosomal vincristine, back to a very ancient drug, and it happens to work in some people, but it is very experimental, and then you do try to get them to transplant. I mean that is the reality today, that is what one wants to do.

DR. MARTINO: Dr. Cheson, do you want to shed some light on this?

DR. CHESON: Yes. I agree with my colleague from Houston that these are exceptionally difficult patients with virtually no options, and hospice, clinical trial is pretty much it. In fact, a while ago, on a number of occasions, we would just call the NCI and ask for compound 506U, because that was considered perhaps the most active drug out there, which is the one we are dealing with right now.

There is nothing for these patients.

Transplant is the best option if you can get them there, and I know of nothing out there for T-cell leukemias and lymphoblastic lymphomas that has as much promise as what we are looking at now, albeit very small numbers of patients.

DR. MARTINO: And so the fact that even when these patients are transplanted, that their survival is not great. I am assuming that is not a surprise to anybody, that is the natural sort of outcome here.

DR. CHESON: Yes. The goal would be to identify patients earlier in the course of the disease through a variety of prognostic markers that might require earlier, more aggressive, or earlier different intervention, and that is where at least we are going in adults, and I trust the pediatricians are going there also, so you would know which patient not to wait until they are in third relapse to transplant, that they might require a consult, whether it be cytogenetic or molecular or microarray signatures, that you can say this patient is not going to do well, and this

patient might even do well with transplant, and this patient's signature might suggest that a drug like nelarabine or whatever else comes down the pike is the appropriate therapy.

So, we need to do better in identifying patients who benefit from different treatments, but we are not quite at that point yet, but transplanting in third relapse is just doomed to a bad result.

DR. MARTINO: Go ahead, Doctor.

DR. FLEMING: I am still then struggling with trying to get a sense of how low is this bar for declaring that there is something that truly is of meaningful benefit.

What we are looking at in the pediatric population is 23 percent response rate with a duration of 9 weeks, where even though it is highly flawed, because it overestimates effect, the responders live two months longer than the non-responders, so you have one-quarter of the patients that are living two months longer than others, and I am only using that paradigm because

that's the primary endpoint is CR, CR*. We don't have for reasons I understand direct survival data.

So, essentially, what we are looking at here is an intervention that would provide, on average, at best, a two-week improvement in survival if the surrogate is fully valid, and that is, in fact, confounded with intrathecal and systemic therapy, and what the effect of transplantation is.

It seems like an incredibly low bar when one also says, but it is not accounted for by having some people surviving a long time. The longest pediatric survival in the responders was 57 weeks, so none of these patients, in fact, had a really long course.

How low is the bar for us to say this is something that patients really need to have access to, is a one-week difference or a two-week difference on average of interest?

DR. MARTINO: Dr. Bukowski.

DR. BUKOWSKI: I guess I am looking at from the perspective of saying that it is very

difficult to evaluate the data because it is small, you are right, they are small numbers, but clearly, patients do get to transplant, and that seems to be the order of the way, at least currently.

I mean these studies were done 3, 4, and 5 years ago, so now if we have this agent, it is clearly going to move the bar, view it differently, because these people do get to transplant, and transplantation procedures are an order of magnitude better than they were 5 years go.

So, I mean I think my view of it is yes, you are right, that it's a very low level of activity that we see here if you exclude the transplanted patients, but I think we have to include somehow that notion that these individuals are taken to transplant, and some of them do have long survival.

DR. FLEMING: None of them survive past 57 weeks.

DR. CHESON: But that is remarkable.

DR. BUKOWSKI: But that is remarkable. I mean given this disease is fatal to everybody, it

is fatal, so it's a remarkable effect to see that happen.

DR. FLEMING: But there are non-transplanted people who survive longer than that.

DR. MARTINO: Dr. Ho, you want to shed some light?

DR. HO: To some of Dr. Fleming's points regarding what is the status of therapy against some of the literature that is cited is old, very old in terms of patients from the past who received much less intensive therapy than they do now, I would actually like Sallan to comment on this in terms of where nelarabine is and what you are seeing Arranon do compared with the historic experience here.

DR. SALLAN: Yes, I need to be very clear that that long list of drugs that these patients have been intensively treated with before they see nelarabine are drugs to which they really are refractory.

Nelarabine in this setting is giving

responses that are the same as those old drugs like vincristine and 6-MP and methotrexate gave as single agents to previously untreated patients. This is that sort of 20 percent single agent complete response rate.

So, you really can't at all compare the likelihood of a response to single-agent vincristine. I know we are avoiding these comparisons in this very intensively, 21st century treated patient to a de novo leukemia treated 40 years ago.

DR. FLEMING: The issue, though, that I am pressing isn't so much the response rate, it's the duration of response and the duration of survival in those responders. In the pediatric setting, those are extremely unimpressive results, so it is not what is the rate of response, it's what are the clinical consequences associated with that.

DR. SALLAN: Well, the duration of remissions, I mean the post-transplant outcome data that I presented in the overview shows that 40 percent of patients treated for relapsed ALL,

adults and children, there is really no difference by those age, have long-term, event-free survival that are clearly not reflected in those small numbers that you are citing.

DR. MORTIMER: Could I just ask, what is the median time to finding a donor?

DR. KURTZBERG: Nowadays, you can activate a cord blood donor from the NMDP and have the donor in your center in 11 days. An unrelated living adult donor, they have an expedited process that takes 4 weeks, and a matched sibling can be activated within days.

So, the practice of transplantation medicine is completely different now than it was in most of these patients, and if you look back over the duration of these trials, they literally started in the '80s, went through the '90s, and now are, you know, in 2000, and most of these patients were not given access to standard transplantation medicine as we practice it today.

The other is to say that a third remission, a T-cell patient is a very high risk,

very sick, very poor performance status patient, and that patient will not do as well with transplant as a second remission patient especially in the context of intensive therapy as we give it today.

Thirdly, in response to your question, to have any response of any duration is remarkable in a patient perhaps for first release in T-cell ALL, any response, a month, 9 weeks, 12 weeks. If you work with these families, you realize that a response of 9 weeks actually has a lot of significance, and it prolongs that child's life for that much more time with the obvious intent of getting them to a therapy that is curative, and the ability to do that now is very different in 2005 than it was in 1995 or 2000.

DR. FLEMING: When was the pediatric trial, cay you remind us, the interval over which the enrollment occurred?

DR. KURTZBERG: It was '96 to about 2001.

DR. FLEMING: So, essentially, what you are saying is we have 39 patients upon which to

base our assessment, and the results are quite unimpressive in terms of the consequences in the 20 percent that respond, but that these data really probably aren't relevant to what could occur today, so we would be approving an agent on speculation for what actually the consequences could be today?

DR. KURTZBERG: I mean I think that you are underestimating the changes in transplantation medicine and the ability of transplant to rescue a patient today compared to 5 years ago, as compared to 10 years ago, and that you shouldn't penalize the drug because of transplant practices 10 years ago when the unrelated donor pool was very different and the time to get to transplant was very different.

DR. MARTINO: Now, I am getting confused. So, are we now saying that if we were to treat these patients today, that we would have an easier time finding a transplant, number one, and that that transplant would be more effective? Is that what I am hearing as opposed to when the study started?

DR. KURTZBERG: Yes, that is absolutely true, and these survival rates for children transplanted with ALL and CR2 are now in the 60 to 70 percent range today.

DR. MARTINO: So, that means that the data that we are seeing is, at best, difficult to interpret.

DR. HO: Could I just clarify? Remember, CR2 is first relapse, and that was the data that Dr. Kurtzberg cited. What we are showing you primarily is essentially CR3, worst prognosis.

DR. MARTINO: Dr. Hussain, do you have some comments to make?

DR. HUSSAIN: I am not a hematologist, but you look at this data. These patients or adults are facing death. You have better technology, better supportive care now. You have to put these patients, as I understood, into a CR in order to get them into a transplant, and this drug gives you the opportunity to put a certain person into a CR long enough to get a transplant.

The way I see it, this is a drug that is

worth approving.

DR. PAZDUR: Let me comment because I want to support Maha on that point, and I think we have to take a look at kind of a general principle here. This is not the first drug that we have talked about in a very refractory disease setting where we could talk about minor response rates, whether one wants to consider 10 percent, 20 percent with 3 or 4 months duration, and one could argue back and forth about the value of that.

Some instances have been winners. We have approved capecitabine on a 10 percent response--or CPT-11 and irinotecan on a 15 percent response rate, and it showed curative advantages--not curative--but prolonged survival in a first-line setting. Capecitabine was approved on a small response rate.

I think the philosophy that we have had here is--when we study drugs in a very refractory disease setting, perhaps we are picking up new mechanisms for action, for example. These patients have been refractory to multiple agents here. The

likelihood, when we see a response, is perhaps that does reflect a new drug which is worth taking a chance on in a sense.

That is kind of my philosophy on this. I know we have argued back and forth here the benefits of how low do we go. This case is probably not the same situation, if we were talking about breast cancer with the large numbers of patients that are available to study it, I think we would all be having a very much different discussion, but here again we are dealing with a relatively rare disease that has been studied over a long period of time, does the drug have activity, does the drug look like it may have some activity when one puts it in a first-line setting, and I think that is yet to be looked at, but I think most rational people would say that it perhaps deserves a chance at showing that.

DR. MARTINO: I also think we have a little additional supporting evidence which is that in patients that have only had one prior therapy, you again see responses, and the responses are

actually better, which is in keeping with our usual understanding of disease.

So, even though I think we can all agree that the number of patients that fit the circumstance for discussion are few, but there is some supporting evidence, and the other problem is the fact that the rarity of the disease doesn't lend itself to being able to say, you know, you have got 3, 4 years to answer all kinds of questions.

There are certain practical limits that I think we also have to appreciate.

DR. PAZDUR: With the classical chemotherapy drugs, generally, we have seen that response rates go up as you go backwards from third line to second line to first line. Some classes of drugs, such as the tyrosine kinases, Arissa, Tarceva, their response rates were uniformly 10 percent across the board whether one takes a look at first, second, or third line therapy.

So, there is some variation, but with the classical chemotherapy drugs, we have generally

been supportive of that approach. Although we will see relatively meager response rates, these will be bolstered as one studies the drug in a less heavily pretreated population.

DR. MARTINO: Dr. Fleming.

DR. FLEMING: It does appears that, as you were saying, the response rates are better in first relapse, although that is not true, interestingly, in the adult setting.

Rick, could you go beyond, and I think you were already doing it before, you were referring to the importance of CR rate, but I am assuming duration is extremely important, as well, because it is a surrogate, it is, in fact, representing the ability or likelihood that the intervention is delivering tangible benefit, I presume duration of response should be given considerably heavy weight, is that correct?

DR. PAZDUR: We do consider duration obviously, but here, and that's why we elected to go toward an accelerated approval strategy, we believe that a lot of this data is confounded by

subsequent transplantation.

So, I think we have what we have, and we have to make a decision as we pointed out with other applications.

DR. MARTINO: I think the word "confounded" is confounding in the sense that it implies that something erroneously was done here, where, in fact, taking them to transplant is really kind of the clinical goal. So, we have to understand why it happens that way.

DR. PAZDUR: Confounding the interpretation it should be.

DR. FLEMING: But ironically, what we are hearing, usually, we think of the confounding as something that could lead to an overestimate of what is due to treatment, because there is systemic, intrathecal, and transplantation, but what we are being asked to believe is that when those results, even with the confounding, are very unimpressive, to believe that if it were actually today's world, we would actually see a better result, and that makes it very difficult to

interpret these data because they were generated and they are the best evidence that we have at this point.

How are you to adjust, so to speak, for what is speculated as the benefit that you would see, when, in reality, the duration is very short in these patients.

I guess the last issue that is somewhat related to what you were saying, Rick, if this goes accelerated approval, obviously, there has been a whole lot of controversy about how the accelerated approval process has worked, and, in particular, because unfortunately, there has been a very long lag between the accelerated approval and the completion of the validation trial, and we have seen that I think with Ontak in T-cell lymphoma, and we have obviously seen it with many other agents, and there are congressional reviews now to look into the inappropriate response in the majority of cases for the length of time that it is taking from accelerated approval to the validation trial.

Aren't we setting ourselves up here for that type of situation? We are projecting a 6-plus year enrollment period, and this could go on for a decade.

DR. PAZDUR: No, Tom, the answer to that question, we are demonstrating flexibility here by allowing a case-by-case analysis. This is a relatively rare disease that we are dealing with. Yeah, I would get relatively anxious again if we were talking about 10 years or 7 years to look at lung cancer or breast cancer or even melanoma, however, this is a relatively unusual disease here.

So, I would have a great deal of sensitivity that as long as the sponsor is approaching this with due diligence and the enrollment is progressing in an orderly fashion, that we see, you know, that we are approaching this with due diligence.

I think when we created the accelerated approval regulations, it was left to be somewhat nebulous with the quote, "due diligence" in quotations expressed in the regulations.

Here again, it is a disease-by-disease basis. This is a relatively rare disease that is hard to treat, and I think we have to be sympathetic that as long as progress is being made in the enrollment, that the sponsor is approaching this with due diligence.

DR. MARTINO: Dr. Cheson.

DR. CHESON: Just to add onto that, the less than wonderful success in completing the Phase IV commitments with all these other drugs that have had accelerated approval, have been primarily in the adult population where about 3 percent of patients enter onto clinical trials.

Here, we are dealing with the pediatric population where they get about 80 percent of patients onto clinical trials, so it is more likely that this trial will get completed than a similar trial in adults.

DR. PAZDUR: We will be discussing, as many of you know, and I can't specify the date, but these accelerated approval Phase IV commitments, and there is a wide variety of reasons that people

have not fulfilled their accelerated approval conditions.

Sometimes disease change, for example, AIDS-related KS has changed dramatically with the introduction of hard therapy. Our chemotherapy regimens change, which make chemotherapy regimens sometimes impractical to use, because of the changing technology that evolves or changing regimens that evolve over time. So, there is a vast array of reasons here.

DR. MARTINO: One more and then we are going to get to the questions.

DR. FLEMING: Just a very brief follow-up. I think it is very appropriate to point out, as Bruce and Rick have pointed out, that what is achievable can definitely vary from one setting to another, and the issue of concern would be, as you appropriately indicate, less in a setting where it's intrinsically more difficult.

The reality, though, still remains the same in the sense that if accelerated approval is leading to an extended period of time before you

obtain validation of benefit to risk, it does influence one's sense about how persuasive the data need to be to achieve that first accelerated approval, because that will be the basis for, in fact, determining long-term treatment decisions.

Questions for the Committee

DR. MARTINO: Ladies and gentlemen, I do want to turn to the questions.

The first question relates to the pediatric population, and I do want your vote and your thoughts on the two populations distinctively.

So, what pediatric population, are the results reasonably likely to predict clinical benefit in this setting? That is the question, in the pediatric population.

Is there any further important and brief discussion, or are you ready to vote? Okay. That being the case, I will take a vote starting on my left. Please state your name and your vote.

DR. FLEMING: Fleming. My vote is no with the interpretation that to predict clinical benefit, I am thinking of clinical benefit as more

than an average of a week improvement in survival or what would predict that at best, recognizing that what has been stated is the nature of the benefit that could be achieved from these CRs could be better hypothetically based on today's practice, but I find it very difficult to approve an agent based on a hypothetical.

So, based on the data that we have here in the pediatric setting, no, I can't justify a conclusion that the data make it reasonably likely to predict clinical benefit.

DR. HUSSAIN: Yes.

DR. DOROSHOW: Doroshow. Yes.

DR. BUKOWSKI: Bukowski. Yes.

DR. CHESON: The usual hard case here says yes.

DR. MARTINO: I would like to names from all of you, ladies and gentlemen, as you give your vote.

DR. CHESON: Cheson. I said "hard case." They should know who that is.

DR. ECKHARDT: Eckhardt. Yes.

DR. PERRY: Perry. Yes.

DR. RODRIGUEZ: Rodriguez. Yes.

DR. MARTINO: Martino. Yes.

DR. MORTIMER: Mortimer. Yes.

MS. HAYLOCK: Haylock. Yes.

MS. EICHNER: Marilyn. Yes.

DR. MARTINO: The vote is 11 to 1 yes.

The next question is the same question, but relates to the adult population. Are these results likely to predict clinical benefit?

Dr. Fleming, you may start with comment or vote.

DR. FLEMING: All right. I will keep it brief by saying I think the results here are certainly much more favorable, several times longer durations with evidence that the survival is considerably longer, as well.

So, in terms of making it reasonably likely, I would say yes in adults.

DR. HUSSAIN: Hussain. Yes.

DR. DOROSHOW: Doroshow. Yes.

DR. BUKOWSKI: Bukowski. Yes.

DR. CHESON: Cheson. Yes.

DR. ECKHARDT: Eckhardt. Yes.

DR. PERRY: Perry. Yes.

DR. RODRIGUEZ: Rodriguez. Yes.

DR. MARTINO: Martino. Yes.

DR. MORTIMER: Mortimer. Yes.

MS. HAYLOCK: Haylock. Yes.

MS. EICHNER: Eichner. Yes.

DR. MARTINO: The vote is amazingly unanimous with 12 yes's.

The next question is related. Is the benefit-risk ratio favorable?

DR. PAZDUR: Since that really is a form for us, why don't we just go to the approval question.

DR. MARTINO: You are happy for us to void that one, okay. I am so happy to do that, thank you, Doctor.

This is the approval question. Should this NDA be granted accelerated approval? Rick, do you want to deal with this as a combined question for both populations, or do you want to hear a

separate vote?

DR. PAZDUR: We probably should hear a separate vote.

DR. MARTINO: Okay. Fine. Let us take the first vote of approval for accelerated status in pediatric population first.

Dr. Fleming.

DR. FLEMING: My answers will be the same as in 1 and 2, so for pediatric, my answer is no.

DR. HUSSAIN: Hussain. Yes.

DR. DOROSHOW: Doroshow. Yes.

DR. BUKOWSKI: Bukowski. Yes.

DR. CHESON: Cheson. Yes.

DR. ECKHARDT: Eckhardt. Yes.

DR. PERRY: Perry. Yes.

DR. RODRIGUEZ: Rodriguez. Yes.

DR. MARTINO: Martino. Yes.

DR. MORTIMER: Mortimer. Yes.

MS. HAYLOCK: Haylock. Yes.

MS. EICHNER: Eichner. Yes.

DR. MARTINO: The vote is 11 to 2 yes--I am sorry, 11 to 1 yes.

The last question, and the final question is accelerated approval status for the adult population. Same order of voting, please.

DR. FLEMING: Fleming. Yes.

DR. HUSSAIN: Hussain. Yes.

DR. DOROSHOW: Doroshow. Yes.

DR. BUKOWSKI: Bukowski. Yes.

DR. CHESON: Cheson. Yes.

DR. ECKHARDT: Eckhardt. Yes.

DR. PERRY: Perry. Yes.

DR. RODRIGUEZ: Rodriguez. Yes.

DR. MARTINO: Martino. Yes.

DR. MORTIMER: Mortimer. Yes.

MS. HAYLOCK: Haylock. Yes.

MS. EICHNER: Eichner. Yes.

DR. MARTINO: On the adults, the vote is unanimous, and it is yes.

Dr. Pazdur, do you need anything else from the committee?

DR. PAZDUR: No. I would just like to thank everyone for providing to us the information, their time, and I think that this was really one of

the most productive ODAC meetings that we have had. It certainly was one of the most interesting ones that we have had regarding the applications that were quite varied.

DR. MARTINO: Thank you. The meeting is adjourned.

[Whereupon, at 3:50 p.m., the meeting was adjourned.]