DR. KEATING: The number of opportunistic infections depends a little bit on the stage of the patient. The patient with Rai Stage III and IV would have a very similar incidence of opportunistic infections that we see on this trial. For example, we would find that probably 10-15 percent of patients will have Herpes zoster either while they are on treatment or within the next 3 months after coming off treatment. A number of patients will have fungal infections if they start off with advanced stage disease, and a decrease in the ANC as well.

So, this sort of spectrum of infections and the deaths on study, this is not a surprising outcome for patients at this stage of disease on any treatment protocol that they would go on.

DR. NERENSTONE: Dr. Miller?

DR. SCHECHTER: I also think with regard to the deaths that we did provide you with the stage because so many of these patients did not have advanced Stage III/IV disease.

DR. MILLER: I just want to make a comment about the comparison between the third-line and the second-line. I don't really think it is a very valid comparison because they are completely different studies, and it is not like people had one cycle of prednisone and then went to fludarabine and then went to Campath. It is not clear to me

at all that Campath patients, the third-line Campath patients were any more heavily pretreated than the fludarabine patients in the initial Phase II trial that led to the licensing of fludarabine. Since we don't really have clear evidence in the data that it is fludarabine exposure as compared to alkylating exposure that led to the increase in toxicity. The fludarabine group of patients clearly got a lot of alkylating agents because that is all there was and we don't know which is worse, alkylating agents or fludarabine, especially when you are talking about a prolonged neutropenia. So, I do think that you have to be very careful when you say this is a worse group of patients because we consider this a third-line treatment as compared to second-line. I want to make that very clear.

With all due respect about the issue of being able to compare and, you know, do we need a comparison arm, I think you don't need a comparison arm when you are not looking at very much toxicity but I do agree it would be very nice to have a good comparison arm when we are trying to wrestle with is this toxicity disease related, which I personally believe it probably is, or is it treatment related. While it is hard to disconnect those two, it is clinically important when you are talking about a drug that is going to get approved and then be used not just in patients who may be this heavily treated but, once it gets

out there, people could use if first line. So, that is what I would like to know, and it would be nice if we knew a little bit more about any comparison or any data on how safe this is in other treatment groups. Somebody mentioned a purging study, and I know there are other studies out there. What is the risk of opportunistic infections in those patients? Is it the drug or is it the disease? I personally believe it is the disease but I wish I had more data, and if anybody has that from the sponsor, I would love to see it.

DR. NERENSTONE: Dr. Keegan?

DR. KEEGAN: I don't know at how much of a disadvantage the sponsor is. As you noted from the history, this drug was initially developed by Burroughs Wellcome and then when Glaxo acquired Burroughs, through Glaxo Wellcome. So, most of that data that you would be interested in was actually acquired by the first sponsor. I can tell you that there was a large number of patients treated for non-Hodgkin's lymphoma and there was also a series of studies done in rheumatoid arthritis. Opportunistic infections were seen in both those populations. In particular, the degree of opportunistic infections which included PCP, viral and fungal infections in rheumatoid arthritis was such that it led to the cessation of that development program. So, I think we feel fairly comfortable in saying that there are, in fact, immunosuppressive effects of this that one can see

in a population that has a less noisy background but we can't seem to come to grips with how much contribution it adds in this background.

DR. NERENSTONE: I have a question for FDA. In terms of accelerated approval, one of the considerations is that a Phase III trial has to be under way. Is there a trial that is either promised or under way at this time?

DR. SIEGEL: First, just to correct the premise, the regulation says something to the effect that normally the trial will be under way. So, it is not exactly a requirement but it is an expectation. As Dr. Schechter noted in her presentation, it was an expectation here. Having attempted to work with the company to get a controlled trial done, foreseeing the difficulties we are facing in interpreting uncontrolled data and having heard repeatedly that that couldn't be done, the plan as developed three years ago was, in fact, to do a controlled trial. The recommended trial was randomization with fludarabine in patients who were not yet refractory to fludarabine, and those data would then be supportive and confirmatory, with a clear understanding that that trial should be under way and with encouragement to get that trial under way. I do not believe, unless I am mistaken, that that trial is under way. I don't believe that that trial has been begun.

Coming back to the earlier issue as to how many of

these opportunistic infections are disease related versus drug related, it may well be, as Dr. Miller hopes -- and, it is very hard to know without a control that many of them are disease related. I would just comment on two things. One is that the CD4 count with this therapy does drop to a median of 3, I believe, or we know that risks increase when you get under a few hundred. So, it would be pretty hard to assume that that isn't a strongly contributory factor.

The other thing I would point out is that we talked about viral infections and we talked about fungal infections. Amongst viral and fungal infections are those that you see more commonly with neutropenia and those you see more commonly with dysfunction of CD4 lymphocytes and other cellular immune responses and, clearly, some subset of these infections fall into the latter group, perhaps more so than one would normally see in this disease population but, again, it is very hard to be definitive about that.

Questions from the Committee

DR. NERENSTONE: Are there further questions for the FDA presentation? If not, then I would like to turn our attention to the questions for the committee. They should have been distributed.

Actually, first of all I would like to open it for general comments for ODAC. Dr. Berman and Dr. Miller, if you would like to start us. Yesterday morning we started

alphabetically so, Dr. Berman?

DR. BERMAN: The first question addresses whether for patients with fludarabine refractory CLL, although the duration of response and clinical outcomes are reasonably likely to predict clinical benefit, I would say unequivocally yes. In the past, all of those have been used as very reasonable and successful surrogates to predict response. So my answer to that would be yes.

DR. MILLER: And I agree that the response rates and duration of response and clinical outcomes in this study are very consistent, and appear appropriate for a heavily pretreated patient population with CLL. So, I do feel that the efficacy endpoint is valid. Initial discussion was whether response rate should be and I think they are valid in this group of patients.

DR. NERENSTONE: Other comments from other members of ODAC? Dr. Blayney?

DR. BLAYNEY: I would also like to say that for several of these rare diseases, particularly the T-cell CLL and T-PLL, this is a very rare disease, very difficult to study but this is one of the few compounds that has efficacy in this setting, and I think it would be a valuable, although seldom used, addition to our armamentarium.

DR. NERENSTONE: Other comments? Looking at the questions, the first part just goes over all the data that

we have seen. The FDA has stated in guidance for refractory malignancies that the reduction in tumor volume can serve as a surrogate for clinical benefit.

Then, I would like to take a vote. For patients with fludarabine refractory CLL the response rate, duration of response and clinical outcomes observed in these studies, are these reasonably likely to predict clinical benefit? So, the first question is just whether we think that using those endpoints, that those endpoints are reasonably likely to predict clinical benefit in this patient subgroup.

May I see a show of hands of people who say yes, it is likely to show a clinical benefit?

[Show of hands]

And those who say no?

[No show of hands]

Abstentions?

[One abstention]

The vote is 14 yes, 0 no and 1 abstention.

The next question discusses that all of these three studies are uncontrolled and single arm. In any study it is difficult to determine the causal relationship of an adverse experience to the study drug, other interventions and the underlying disease. However, in an uncontrolled single-arm study one also loses the ability to assess the relative difference in toxicity between treatment groups. In

the primary efficacy study we discussed the toxicity profile. In particular, 90 percent of patients had infusional toxicity; 13 percent grade 3-4; 47 required interruption of therapy; 24 percent of patients discontinued treatment for adverse effects; 4 percent refused to continue; and 67 percent of patients experienced serious adverse experiences. Fifteen percent of the patients died possibly or probably from toxicity related to the therapy. In the absence of a well-controlled trial, the impact of Campath on the overall survival cannot be determined.

Then it goes on and talks about the hematologic toxicity which we have discussed, and the immunosuppressive and infections toxicities. The question to the committee is, is this toxicity profile of Campath acceptable in light of the benefit that may be conferred? Discussion? Dr. Przepiorka?

DR. PRZEPIORKA: I would like to start out by answering that question with an unequivocal maybe.

[Laughter]

And, the reason I say that is I am not concerned with the infusional toxicities. We see this with amphotericin every day and have for the last 15, 20 years. I am not concerned with the infectious complications seen. We know it is an immunosuppressive drug. We know that patients are immunocompromised just from their disease. This is a

problem that we have been fighting with CLL patients for a long time, independent of the drug used. I am not concerned with the hematologic toxicity. I would expect to see that in patients with compromised marrow receiving a drug like this, with immune reactions occurring in the marrow.

What I am concerned about is the 13 percent treatment-related mortality in a population with a very vague definition of eligibility. With fludarabine refractoriness went from anything from a partial response, which Dr. Keating indicated would have a median survival of two years, meaning that half those patients would survive longer than two years without therapy or with other therapy, versus those with progressive disease and an expected survival of six months. For those with a potentially short survival, I would think that for palliative therapy this type of a treatment might be worthwhile. For those with good duration of survival, I would be concerned about giving a treatment like this just for palliative care. Consequently, I am not sure, based on some of the response data that we saw by either by status at time of treatment or stage at the time of treatment, that the response data is actually going to hold up in the patients that would actually use a treatment like this and risk those toxicities.

DR. NERENSTONE: Dr. Berman?

DR. BERMAN: I would disagree. I think that within

the context of treating patients who have had a median of 3, range 1-10, prior treatments the fact that the response rate was what it was and, in fact, higher than the 20 percent which is what the FDA required, I think suggests that there is some real activity. There is no question that this is a potentially toxic regimen to be used. However, the benefits in my mind, especially in terms of patients whose response to this agent really, in fact, in some proportion of patients was even longer than the response to prior treatments.

I think that in the hands of responsible oncologists, who presumably are the oncologists out there practicing, and providing that the risks are well delineated in the package insert, I think that this is a drug that is acceptable.

DR. NERENSTONE: Dr. Blayney?

DR. BLAYNEY: I also speak in favor of the drug. I think that when this trial was designed our experiences with monoclonal antibodies and biologic therapy in the wide practice community was limited. Subsequently, there are a lot of monoclonals that we have become experienced with treating both the acute and the long-term toxicities, and this drug is likely to be relatively safe although it is not for surgeons, fortunately.

Finally, the sponsor recognized that it does

produce the AIDS phenotype and when they recognized that they put in PCP prophylaxis and dropped the number of pneumocystis infections. Now that they see fungal infections, I suspect they will want to add some anti-fungal prophylaxis. And, I think the dose and scheduling will probably be tweaked as well so that the toxicities can be managed.

I respect Dr. Simon's view, as always, and I would advocate that we do approve this Phase III trial. That was the rule that was set. We should get that done, and also it will help us to understand how to use this drug in our armamentarium. Thank you.

DR. NERENSTONE: Dr. Lippman?

DR. LIPPMAN: In regard to Dr. Przepiorka's comment, I had the same sort of concern and that is why I asked the question about the response in patients who had a prior response to fludarabine or who were resistant. I was pretty impressed that the response was very high relatively in the group that was resistant to fludarabine. So, in the risk/benefit equation it seems as though those patients derived quite a bit of benefit. So, again, that is why I am in support of this.

DR. NERENSTONE: Ms. Lackritz?

MS. LACKRITZ: Again, I am talking from a different point of view. I think that we tend to get too

caught up in the numbers and the figures and we forget that this really is a two-arm trial. The other arm is death because patients who are refractory to fludarabine and refractory to the alkylating agents don't have a lot of choice out there and we cannot lose sight of the fact that something needs to be there for those patients. Is this a perfect drug? No, not at all. Is this the silver bullet? Oh, don't I wish! But this appears to offer hope in a situation where there isn't a great deal of hope and researchers out there, would you please go looking for something that will give us what we need?

DR. NERENSTONE: Dr. Albain?

DR. ALBAIN: I would be in favor of having this drug on the market but I would also like to echo a previous comment that labeling needs to be very bold, in large letters and underlined, and whatever else you can do to caution the first time user of this compound about some of these. I mean, we have heard from the world's experts on CLL today who have experience with this compound and this their toxicity data. I am just worried -- not worried but concerned and want to encourage that the labeling be incredibly specific about this.

Secondly, what Dr. Blayney said is so important. We know that there is a commitment from the sponsor to do a Phase III trial. I haven't quite heard that yet and I

realize there is another question yet to go on that. And, we ought to look into this pharmacokinetic issue, in particular, can the dose duration be decreased; the frequency per week be decreased as the tumor burden decreases?

DR. NERENSTONE: Dr. Miller?

DR. MILLER: Yes, I agree that the toxicity for Campath is acceptable in this group of patients and I echo the fact that we don't know if the toxicity profile will be acceptable in other groups of patients. I would think a good confirmatory study looking at the infectious complications needs to be done.

DR. NERENSTONE: Does the FDA need us to vote on the requirement to link this to a Phase III, or is the sentiment of the committee, as you are hearing it, enough for you?

DR. SIEGEL: I think we are comfortable with the sentiment as experienced. I mean, most of this discussion has been along the line that if there is an approval it be an accelerated approval, and that would be linked to such a commitment and we will, under question three, get some discussion about the nature of that I think. I don't know that I need an additional vote in that regard.

DR. NERENSTONE: Other comments? Then, the second question, is the toxicity profile of Campath acceptable in

light of the benefit that may be conferred?

All those who say yes, please raise your hand.

[Show of hands]

All those who say no?

[No show of hands]

Abstentions?

[One abstention]

The vote is 14 yes, zero no and one abstention.

A third question which has actually been inserted for the FDA is, is this enough data to qualify Campath for accelerated approval? Would you like to just again reiterate for us what accelerated approval means rather than full approval, and what are the requirements?

DR. SIEGEL: Right. Well, accelerated approval is full approval; the product is approved. It is different from, I guess, what we probably most appropriately would call conventional approval in the sense that it is based on a regulation which permits us to make approvals based not on direct evidence of clinical benefit but on either surrogate endpoints such as tumor response, which are believed to be reasonably likely to predict clinical benefit or, in some cases although not highly relevant here, certain clinical endpoints that might be surrogates for the more important and more necessary clinical endpoints. With approvals under that regulation there needs to be a request from the

sponsor, which I believe there is here.

The FDA may, and generally does as per the regulation, impose a requirement to conduct a trial which is, as noted, usually ongoing at the time of the accelerated approval. In fact, it is often the same trial and the early endpoints lead to accelerated approval and later endpoints might be the confirmatory data, although in oncology it is often a different trial. That trial the company must commit to do prior to the approval -- must make the commitment prior to the approval. It is usually, as I said, ongoing and the agency has authority to withdraw the drug if the trial either fails to confirm the efficacy of the drug or fails to be conducted.

DR. NERENSTONE: Dr. Sledge?

DR. SLEDGE: If I could ask a question, has the FDA ever withdrawn approval for a drug based --

DR. SIEGEL: I think we believe that that is not the right remedy. If a trial doesn't get done, it is generally our thought -- we still think it might be a valid surrogate and we think ought to be taken against the sponsor, not against the patients if you still believe that the drug probably works. The problem is we don't have such a remedy. We don't have, for example, simple money penalties or other remedies, other than withdrawal.

The answer is though that, in fact, what we have

done in a number of cases is revised indications based on such studies, or failure to do such studies. So, a drug has gotten an indication that is more restrictive about its use as first-line therapy or its use in certain combinations based on a failure of a study to confirm that. In this case, this is already likely to be approved for third-line so I don't know the extent to which that would be relevant. But the answer is that failed studies and failed commitments have led to substantial relabeling of drugs but I don't believe to a withdrawal of a drug.

DR. NERENSTONE: Other questions? Dr. Simon?

DR. SIMON: Well, it is not a question but you invited some comments on that question, and I guess my comment is I hate to see accelerated approval used as a way of making it more different to do the clinical trial that really should have been done. I can see the rationale for accelerated approval when you have the trials ongoing and you think that you have a surrogate endpoint that is going to predict the results of those adequate trials that are ongoing, and you want to make the drug available to patients a little earlier. But to use it and then make the drug available and then have that availability essentially make it impossible or more different to actually do the trials that you don't even have ongoing at that time I think is a misuse of the mechanism.

Here, if you don't do the trial -- I guess we will get into a discussion of which trials you do -- I really feel that this drug was not available up till now. I don't understand why the sponsor could not have gone to centers who did not have access to this drug and say, look, for third-line therapy, would you like to either continue not having access to this drug or would you prefer to participate in a randomized trial where half of your patients would get this drug? I don't understand why it would not have been possible, in which the competing arm of the trial would have been physician's choice rather than any placebo agent. I don't understand why you can't use placebos or no treatment control arms. But I don't understand why that trial would not have been possible, and I think that that trial was actually the preferable trial than a comparison to fludarabine as second-line treatment. And, I think by accelerated approval you really make that trial impossible.

DR. SIEGEL: Just to comment on how accelerated approval is used within the agency and what this means, in many disease areas the typical approach has been that surrogates are generated from a trial; accelerated approval occurs and the same trial is carried out longer to get clinical benefit. This has been typical, for example, in treatment of people with HIV where surrogates such as viral

load and CD4 cell counts have been used. They are confirmed usually from the same trial and almost invariably from a trial that has been fully enrolled and well on its way toward completion at the time of the accelerated approval.

The agency has, in fact, determined in a number of disease areas that if a confirmatory trial is necessary, if there is a lot of uncertainty about the drug and if accelerated approval would make such a trial impossible, that accelerated approval may, on that basis, not be appropriate.

As applied in oncology, however, a somewhat different paradigm has often been in use and has been, I believe, acknowledged in some FDA guidance documents, which is that traditionally many drugs have been introduced through trials in patients refractory to all other therapies. In those cases, where there is an adequate response rate, where response is seen particularly more common or more durable than responses to prior therapy, where responders do well with all these types of things which, I agree with Dr. Simon, are different to draw inference from lacking control, and where notably toxicities are limited, let us say, the oncological community has generally felt in many such cases that that is adequate evidence for use in a Phase III trial and for use in a refractory patient. In the early days of accelerated

approval we talked a lot about confirming in that population with a control arm which, as I think you correctly pointed out, is sort of a backward way to do it and perhaps impossible.

But the other thing that was determined in many such cases was that that study is perhaps interesting from a scientific point of view but perhaps not the most important study to be done in terms of understanding how best to use a new agent and how it best will benefit people with the disease and where it fits into the overall armamentarium.

So, in fact, what has evolved over the years and, again, it is dependent upon the nature of the disease, available treatments and the amount of toxicity with it is appropriate, but what has evolved and been used in a number of prior paradigms where the original trial is based on response rates in a refractory patient population is that it receives accelerated approval, followed by -- although as we discussed earlier, hopefully accompanied rather than followed by a randomized trial at an earlier stage of the disease. Once you have done the open-label refractory trial, such a trial is considered often to be more informative.

I guess I will just leave it at that, but that is sort of the history of how our approach has evolved in this area.

DR. NERENSTONE: Dr. Lippman?

DR. LIPPMAN: Yes, just to follow up on that, if the confirmatory trial is done in an earlier stage or, let's say, second line, which seems highly likely and we will get into that, then the results of that, no matter what the comparator -- could do much worse than fludarabine in that trial, wouldn't change what we have seen here, having another drug to give people who failed fludarabine. So, in this sense I don't understand the accelerated mechanism.

DR. SIEGEL: Actually, you heard at the end of my comment that I had lost my train of thought because that is the last thing that I wanted to add, I think that is a correct perception. In this particular case, one might argue that it is somewhat different because what a controlled trial will tell you, although at a different stage of the disease it will not speak directly to the amount of benefit that the surrogate predicts, it will potentially help weed out how much of the toxicities of the agent are treatment versus disease related, although, obviously, in comparing to an active treatment that has its own toxicity that won't be clear. But, such a controlled trial, as also Dr. Simon has pointed out, is not the ideal trial. In a sense, the ideal trial would have been, and might still be a controlled trial in this population with alternate treatment if that were feasible. But you are right, a failure of a trial second line with fludarabine would not automatically lead to a

withdrawal of this, although were it to confirm and increase some of the safety concerns it might lead to further discussion about whether withdrawal is appropriate.

DR. NERENSTONE: Other comments? If not, we need to vote on the actual question. So, is the information that we have been given enough to qualify Campath for accelerated approval?

All those in favor, please raise their hand.

[Show of hands]

All opposed?

[One person raises his hand]

Any abstentions?

[No show of hands]

So, the accelerated approval is recommended, 14 for, one against.

The last question, if Campath receives the accelerated approval, please discuss the types of confirmatory studies that should be conducted. Comment on the following study designs:

The sponsor proposes a Phase IV study, multi-center, randomized study of Campath versus no additional therapy in patients who have received a CR or PR to fludarabine. FDA recommends a Phase IV study, multi-center, randomized study of fludarabine versus Campath in patients with CLL who have not yet received fludarabine; multi-

center, randomized study of Campath versus supportive care or no additional therapy in patients who have failed fludarabine.

Then we need to comment on the preferred primary study endpoint -- survival or progression-free survival. Please comment on the acceptability of the criteria for progression proposed by the sponsor versus the NCI Working Group criteria. Dr. Berman?

DR. BERMAN: I think the first two studies ask different questions and I think the second study should be addressed first, and that is the randomized study of fludarabine versus Campath in patients with CLL who have not yet received fludarabine.

This is a little bit complicated by the recent publication in this week's New England Journal by Dr. Rai, who is the first author, stating that, in fact, fludarabine is the generally preferred treatment of choice in patients with CLL. So, it may be that this is a study that, in fact, may not be able to be done as I think fludarabine will replace chlorambucil for the majority of patients with this disease.

DR. NERENSTONE: Other comments? Dr. Kelsen?

DR. KELSEN: The first two suggestions do ask different questions. One is can you prolong maintenance in a patient who is already in remission. It is a very

interesting question. It doesn't directly address the accelerated approval. Certainly, I would be very interested in that.

The last one, I wonder if we couldn't modify that to accept Dr. Simon's suggestion because I don't think it is going to fly if you give accelerated approval to the drug because we think it has benefit, and then randomize people to no treatment when the drug is available. I am skeptical that you would have an awful lot of accrual. I wonder, if that is pursued, whether it wouldn't be wise to accept the physician's choice as the control arm, which may include supportive care or no treatment.

I am also concerned that whenever you have the drug available and you are offering it to patients as a treatment that we think works versus not that treatment, accrual will be difficult.

DR. NERENSTONE: I guess I would have a lot of reservations about the first Phase IV study in a drug that may have a 15-30 percent mortality rate, to take patients who are in a CR in a disease that is not curable and subject them to that kind of toxicity, and I think our whole debate is really about toxicity, not about activity. I think before we have further delineation of exactly what is the toxicity, I think that that first trial, from my perspective, is really inappropriate at this point in drug development. Dr.

Berman?

DR. BERMAN: The current trial that we were shown today -- I would be in favor actually of the first trial because I think it is a very interesting one, as Dr. Kelsen pointed out. And, this is not a curable disease and we know that CRs with fludarabine have a very short response even for those patients who do achieve a complete remission.

But the group of people who were treated here, again to emphasize the extensive disease these patients had, there was a high proportion of patients who had over 98 percent bone marrow involvement and presumably people who achieve a PR or CR -- obviously, these criteria will not have anywhere near that degree of involvement so it is likely, in fact, to be a safer compound in patients who have less disease. So, I do think that the proposed Phase IV study is an interesting one.

Just lastly, a word about the last suggestion which was versus supportive care, I would echo Dr. Kelsen's statement that I think that the accrual would be so slow as to make this a meaningless trial.

DR. NERENSTONE: Dr. Lippman?

DR. LIPPMAN: I was going to make that same point but in a different way. I don't think based on the data we have seen today that you could do this last trial. I mean, again we are coming back to the fact that the activity in

the fludarabine-resistant population was 28 percent. It was very active. So, I think the only real option of the three that we have potentially would be the first one.

DR. NERENSTONE: Dr. Miller?

DR. MILLER: Well, Dr. Berman brings up that fludarabine is moving closer up into the front line, and so I guess the question whether or not a second-line therapy versus alkylating agents may be a trial that could be done. If patients aren't getting alkylating agents for first line but alkylating agents are clearly adequate treatment for patients with CLL, the option of Campath versus second-line alkylating agent therapy could clearly be done. You could pick an alkylating agent therapy and truly define the toxicity. So, I think as you move up to fludarabine the alkylating agents go out with all the concerns we have about alkylating agents, but it may be reasonable to do that type of trial.

I also am concerned about that first trial, adding the Campath on right after fludarabine in patients who are already in a CR or PR. Maybe if they are already in a PR you could measure additional response but I do have a little bit of a concern about how valuable that study is going to be and with or not there is going to be potential excess toxicity in that group of patients.

DR. NERENSTONE: Dr. Kelsen and then Dr. Lippman.

DR. KELSEN: This is sort of a question to the FDA. It seems to me that only option three, with or without modifications, addresses confirmation of the accelerated approval. The other options, which are valid ones -- you know, I defer to the experts on the safety, etc., etc. -- don't really confirm what we are recommending today but they sort of indirectly would say this is really an active drug and what we did was right. So, I am asking not specifically about this but sort of in a more procedural sense, any trial after accelerated approval, a Phase IV study that shows that it is a good drug; that it is useful is acceptable in confirming the decision for accelerated approval?

DR. SIEGEL: This is what I was trying to get at when I went through that brief history of this regulation. That is, in fact, the current way this regulation is being used and that is acknowledged in our guidance document. De facto, what that means is that response rates are simply accepted as adequate in refractory patients and don't get directly confirmed. The reason, as I said, and a lot of it evolved over discussions over the last decade with this advisory committee, was that in many diseases having proven good response rates in refractory patients, to then wind up investing the company's money, the investigators' time and efforts, the patients' dedication and contributions to research on controlled trials in refractory disease has

often seemed not the wise way to proceed with development of a drug when, knowing that it is active; knowing that it causes tumor shrinkage, there are often far more important questions to be answered about how, when and where to use it.

So, I think one can, and often does look at the regulation and look at that approach and see a little bit of a disconnect, but the answer is, yes, this is in fact an accepted approach that is acknowledged and supported in our guidance documents as a way to use accelerated approval.

DR. NERENSTONE: Dr. Lippman?

DR. LIPPMAN: Coming back to the specific questions that you have asked us, having heard Dr. Berman and Dr. Miller, I would like to come back to Dr. Miller's design because that actually is the most attractive to me. Hearing just now that there is a paper, which I haven't seen yet, that Dr. Rai is recommending fludarabine up front, then that does set up the possibility of a randomized trial -- not exactly what Dr. Simon wanted but a randomized trial of Campath versus alkylator therapy. So, I would like to ask the experts, since we have the world's experts here with Dr. Keating and Dr. Rai, whether that would be acceptable among the people that treat this disease.

DR. RAI: My name is Rai, from New York, and I have been very fascinated by this discussion going on. What

you are considering and hoping to achieve is to come up with a front line, randomized trial which will do two things, one is to demonstrate that ODAC and FDA were right in going Campath approval in the accelerated phase and, number two, to demonstrate more clearly the toxicity profile as well as efficacy of Campath in a different population of CLL patients.

Dr. Berman and Dr. Miller, who I know have more experience with hematological malignancies, have made some very important proposals. I still believe with due humbleness that this is probably not the right forum to come up with a proposal for a disease for which, for the last 40 years, no one has come up with a really exciting, interesting, effective treatment. And, if you would charge the company, if I may presume to suggest, to convene a panel of CLL people who are not entirely full of themselves --

[Laughter]

-- but are interested in coming up with some better treatment, and propose a randomized trial which will satisfy the ODAC's concerns, which are very real and very palpable, as well as the patients' needs, I think that can be done. My own suggestion at this time would be to bring Campath to front line and, even though Dr. Kelsen has not seen today's New England Journal of Medicine, it does not give any brand-new information. It is information that you

have known, that fludarabine is being used in the front line, and this paper merely confirms in a randomized fashion that it seems to be better than the standard, so-called, gold standard.

You are not aware that redaximab, an anti-CD20 antibody, is entering the front line of treatment of CLL. It surprised me when it was approved for lymphoma but I did not expect its activity in CLL. If you would ask the company to convene a panel of CLL experts to review such new entities, such as Reduxan, fludarabine Campath, and come up with an algorithm of a trial which will be acceptable by all, including the patients, you will be doing a great service.

DR. NERENSTONE: Dr. Sledge?

DR. SLEDGE: After hearing those wise comments, I hesitate to make any further remarks --

[Laughter]

-- that would reveal my great ignorance of this disease though I will, as a fool, go where angels fear to tread. I guess if the question is, is Campath a better or worse drug or an equivalent drug to fludarabine, the question I might ask is whether or not one might design a trial in which one would allow patients to receive it as first-line or second-line therapy versus fludarabine and just simply stratify. It would take a larger number of patients but, if that is an important question to answer, I

think that would be a reasonable approach to doing so.

DR. NERENSTONE: Dr. Simon?

DR. SIMON: I guess just to respond to Dr. Siegel, whereas I think I understand what you are saying in terms of the way that accelerated approval has been used, and I think you are right in what you are saying, I think it is basically an illogical strategy and may be based on practical considerations. But to approve a drug accelerated because you think it is likely to be effective, and then be in a situation where you can't really evaluate whether it really is effective for the indication for which you are approving it is not a logical way to go about reviewing new drugs.

First of all, I didn't understand that Dr. Lippman was suggesting a first-line treatment. I thought he was saying if fludarabine is going to be used first line, then chlorambucil will probably be used second line and, therefore, design two that was listed here, which would actually potentially be a trial as Dr. Miller said, of the antibody versus chlorambucil. I guess I think that, as has been said, the best design that we could have had would have been the antibody against physician's choice. I voted against accelerated approval because I think accelerated approval probably makes that trial impossible to accrue to.

I think that design one that was listed here is

the kind of design that appeals to investigators but it provides practically no information in terms of the issues that we have been struggling with in terms of relative toxicity -- what is toxicity and what is disease effect, and what is benefit and what is physiological reduction in counts.

I think design two, possibly with fludarabine replaced by chlorambucil as second-line treatment is probably the closest we would get to it.

DR. NERENSTONE: Dr. Pelusi?

DR. PELUSI: Within this discussion, I think that we need to, again, remember the patient's perspective in terms of symptom management. I would hope that whatever type of trial is done we look very closely at symptom management and have that built into the trial because I think a lot of times as we are worried about toxicities, once this goes on the market the question is how do we manage it. That is one of the things we never really see built into trials. So now with this toxicity profile that we are seeing, if we could just be mindful of that as the new trial goes forward.

DR. NERENSTONE: Dr. Lippman?

DR. LIPPMAN: Just to clarify, that is exactly what I meant, as second line. Again, if fludarabine is being accepted, as Dr. Miller said, as first-line therapy, then one could, at that point, randomize to chlorambucil or

alkylator therapy of choice versus Campath with the same definitions of fludarabine resistance as were used in the current trial.

DR. SIEGEL: Or presumably you could use it in a randomized trial compared to either second-line therapy and stratify as to whether that second-line therapy was fludarabine or not.

DR. NERENSTONE: Dr. Albain, and then we are going to have to break for lunch.

DR. ALBAIN: Except that if what Dr. Rai said is, indeed, correct -- and I am also not a liquid tumor specialist, but if Reduxan is going to be used also now by many up front -- I think the suggestion for a scientific panel to convene and to debate the design of this trial, with perhaps FDA collaboration -- we talked about such novel ways of moving new designs forward, let's throw that out there also.

DR. NERENSTONE: There is no question here so we don't need a vote. I would like to break now for lunch. Please, everyone, be back at one o'clock. We have a long afternoon. Thank you.

[Whereupon, at 12:10 p.m., the proceedings were recessed, to resume at 1:10 p.m.]

AFTERNOON PROCEEDINGS

DR. NERENSTONE: If the committee members could please take their seats, we would like to get started. We have somewhat of a tight schedule today and many people have planes to catch so I would like to start.

I would like to start first with going around the table and everyone introducing themselves. Dr. Pazdur, if you would like to begin?

Introductions

DR. PAZDUR: Dr. Richard Pazdur, Division Director, Oncology, FDA.

DR. WILLIAMS: Grant Williams, Medical Team Leader, Drugs, FDA.

DR. WEISS: Karen Weiss, Director of Division of Clinical Trials in the Center for Biologics.

DR. KEEGAN: Patricia Keegan, Division of Clinical Trials, Center for Biologics, FDA.

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

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

DR. PRZEPIORKA: Donna Przepiorka, Baylor College of Medicine, Center for Cell and Gene Therapy.

DR. KELSEN: Dave Kelsen, medical oncologist, Memorial Sloan-Kettering.

DR. SUGARMAN: Jeremy Sugarman, Director of the Center for the Study of Medical Ethics and Humanities at Duke, in the Department of Medicine.

DR. TAYLOR: Sarah Taylor, University of Kansas Medical Center, medical oncologist and Director of Palliative Care.

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

DR. NERENSTONE: Stacy Nerenstone, medical oncology, Hartford, Connecticut.

DR. SLEDGE: George Sledge, medical oncology, Indiana University.

DR. PELUSI: Jody Pelusi, oncology nurse practitioner, Phoenix Indian Medical Center and consumer representative.

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

DR. ALBAIN: Kathy Albain, medical oncologist, Loyola University Chicago Medical Center.

DR. PELLEGRINO: Edmund Pellegrino, Professor of Medicine and Medical Ethics at Georgetown University.

DR. LINDEN: Ruth Linden, Director of Curricular Reformats, School of Medicine, Stanford and Department of Family and Community Medicine at UC, San Francisco.

MS. PLATNER: Jan Platner, Director of

Administration and Programs, The National Breast Cancer Coalition.

MR. ERWIN: Robert Erwin, Marti Nelson Cancer Research Foundation.

MR. DIXON: Carl Dixon, President and Executive Director of the Kidney Cancer Association.

DR. SPIEGEL: Dr. Robert Spiegel, Senior Vice President of Medical Affairs and Chief Medical Officer at Schering-Plough.

DR. KENNEALEY: Gerard Kennealey, Chief Medical Oncologist, AstraZeneca Pharmaceuticals.

Conflict of Interest Statement

DR. TEMPLETON-SOMERS: The following announcement addresses the issue of conflict of interest with regard to this meeting, and is made a part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda and information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting, with the following exceptions. In accordance with 18 USC Section 208(b)(3), waivers of general applicability have been granted to all participating committee members and consultants. A copy of these waiver statements may be obtained by submitting a written request

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

With respect to FDA's invited guests, there are reported interests that we believe should be made public to allow the participants to objectively evaluate their comments. Robert Erwin is the Director of the Marti Nelson Cancer Research Foundation. He is founder of a large-scale biology corporation and owns stock in the company. The company conducts biotechnology research, including work that is relevant to oncologist.

Carl Dixon is the President and Executive Director of the Kidney Cancer Association. Jan Platner is the Director of Administration and Programs of the National Breast Cancer Coalition. Dr. Robert Spiegel is the Senior Vice President of Medical Affairs at the Schering-Plough Research Institute and, lastly, Dr. Gerard Kennealey is Vice President, Clinical Research, Oncology at AstraZeneca Pharmaceuticals.

In the event that the discussions involve any other products or firms not already in 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 product they may wish to comment upon. Thank you.

DR. NERENSTONE: We are going to begin, and we are going to try and stick to the schedule that I think everyone has, with the open public hearing part of this afternoon.

Open Public Hearing

DR. TEMPLETON-SOMERS: Due to the weather, people have had changes in plans so I am going to be making a few changes and be reading a couple of letters from my seat. The first change will be that Bonnie Kroll will be the first speaker, and she will be followed by James Roberto, and then we will go on to Natalie Brainerd. Thank you.

MS. KROLL: Hello there. My name is Bonnie Kroll, I am a patient. I am here today -- the purpose of being here is to expose the misleading news and press releases by the drug companies concerning their trial drugs.

I am 59 years old. I was diagnosed four years ago with conjunctival melanoma, skin cancer of the surrounding skin of the eye. Fourteen months ago it metastasized to the liver and the bone. Three weeks ago it metastasized to the brain. I began radiation treatment of the brain on Monday, December 11 in hopes that in 30 days I will be able to be put on a new drug for the metastasis to the liver.

I will be leaving these things here. These will be

the news releases -- and, by the way, I am speaking of the Genta Corporation which has the new trial drug Genta-G31-39 out there, with some great news releases about how wonderful it is. Attaches as part of my presentation are two news articles, entitled, "Late-Breaking Research Results" from the 91st annual meeting in San Francisco, April 1-5, 2000, from the American Association for Cancer Research.

How excited I was to find out that there was a new treatment for me since I had failed all others to date. This new treatment was having amazing results for people with my condition. According to the researchers, patients with advanced melanoma received both G31-39 and anti-melanoma drug dacarbazine. Most of the patients had failed to respond to other treatment. The combination regimen produced responses. Six of the 14 people got a 43 percent, evaluable patients, some lasting more than a year. Of the responses, one was complete, two were partial and three were minor. Two other patients had evidence of antitumor activity. Antitumor activity was even seen in some patients after failure of DETEC.

How surprised I was to learn that actually the response rate was only 20 percent because unless there is at least a 50 percent response, it is my understanding, it doesn't count as a truly effective response. The cancer news hoopla in April of 2000 was extremely misleading when one

considers an actual response of 20 percent versus the research claimed 43 percent. In any event, despite these facts I still wanted to learn more about this new therapy since my time was running out.

Also an article from MSMBC, attached here as a press release, claimed that each of the 14 patients had exhausted standard chemotherapy treatment for their disease prior to taking G31-39. The average survival of the 14 patients in the study, all of whom had exhausted standard chemotherapy treatment to control disease, is 9 months, said the clinical investigator from Vienna, Dr. Janssen. Typically, the advanced patient would be expected to die in less than 6 months. This is a very exciting development, said Dr. Peter Jones, Director of USC Cancer Center.

Last month additional information was released on the 14 patients within the study, which revealed to my doctor that only 5 of the patients had Stage IV melanoma. The other patients had cancer of the skin. Two of the patients had not received any prior chemo. The news releases showed that all had exhausted standard chemo efforts. This latest information is contradictory to the original release information that is misleading as to the patients having been treated prior to G31-39 with chemo or no chemo.

As a result of these studies, even though the results were distorted, I began immediately to attempt to

obtain the drug through various means, including compassionate use which will be addressed by my cousin, James Roberto, who will follow me. My doctor, at Thomas Jefferson University Hospital in Philadelphia, who has handed my case since the initial diagnosis joined with me in attempting to deal with the Genta Corporations miscommunications, falsehood, etc. that culminated in him writing a letter explaining to me what Dr. Finger of Genta Corporation thought of his own trial.

Here is where I will take a moment to read this letter: Dear Miss Kroll -- this is from my doctor to the second person in command at Genta. I did talk to Dr. Finger. He told me that in their clinical trials there had been no response in patients who already failed the standard chemotherapy -- zero response rate. This means that this medicine will not work for the multi-drug resistant tumors. He said he does not think it is ethical -- this is Dr. Finger telling this to my doctor -- he does not think it is ethical to give the medication to patients who already failed the standard treatment. However, he admitted that the number of their cases is not sufficient enough to publish this fact. I did not say -- my doctor is saying that I did not say that I agreed with him but I did not discuss any further. Although it would be their excuse for not giving you this medication, I felt that they probably know that

their medicine has only marginal effect on chemoresistant tumors. I would blame them if they start a clinical trial for the patients like you. In that case they are lying. Based on a zero response rate, if that is what they are saying, I do not think you should pursue further.

I am sorry to say, everyone, that I called Dr. Finger the next day. I managed to get through to him on a cell phone in a meeting. And, the sad ending of this story is that when I personally confronted Dr. Finger, Dr. Finger told me that Dr. Tikami Sato misinterpreted his information, and I think he called it a breakdown of communications. This has all been part of the lying and the media hoopla.

One more paragraph and I am done. As a result of all this information, my family and I began to wonder if all the efforts were really worth continuing since the Genta information was so greatly distorted.

My condition continued to get worse and my doctor advised me that I must go on some type of salvage drug as soon as possible. The promise of this drug had greatly heightened my desire to try something new that appeared to be effective in fighting my melanoma and further prolonging my life. In reality, it appears the published information was more smoke screen. The reality -- maybe it is too late for me at this point but I want to appear before you today in hope that other people who might have some condition

where you would hold out false hope from misleading published data, with their efforts directed in a more effective direction. Please do something about the media hype with these drug companies. Thank you for your time.

DR. NERENSTONE: Thank you very much. Mr. Roberto?

MR. ROBERTO: Thank you. My name is Jim Roberto. I am, at least occupationally, the Chief Executive Officer of Dow Systems which is a health care information and technology company that serves the hospital and integrated health care delivery network as part of our industry. It is one of many positions of that nature that I have held on the early stage developing side of health care, including biotechnology.

I am a businessman in this area so I probably fall under the heading of a little knowledge being more dangerous than none at all, but because of my experience and background, going all the way back to Pfizer in the '60's, my cousin asked me if I would do the negotiating and dealing with Genta Pharmaceutical in an effort to get her onto a compassionate use program with G31-39, back when we were just interpreting the success of this drug on the basis of the statistics that we were seeing in the media.

I am here today to bring to this committee's attention -- because I think what Genta did, although it looks like we are picking them out and beating on them

today, is representative of what a lot of the emerging biotechnology and pharmaceutical companies do to keep patients from access to their drugs on compassionate use while, meanwhile the FDA, which they use continually as the whipping boy, has gone so far beyond them in listening to the American public at large, and I think it is time for them to get the message that the world has changed; technology has changed the world; and it is time to look at your old policies and procedures.

I made one of the first calls to Genta and I spoke with their manager of clinical operations. I said, gee, can't you get my cousin onto this program on a compassionate use basis? And, she said, oh no, no, you just don't understand. You say you have been in the business, you know what the FDA is like; you know what the logistics of getting this approval are like. So, I hang up the phone and I say, hey, I do know what the FDA is like and I do know what the logistics are. They are not as difficult as they are being made out to be. So, there is hope for my cousin and I tell her that. And then, I am fortunate enough to meet, via the telephone, Terry Martin of the FDA who, after listening to the background on it, says, look, you get the necessary forms down here; we will get them processed. Thank you, I said. And, back I go to Genta, saying, I've got great news. The FDA is going to take care of this. I have

never seen such personal direct concern in my life for one, single patient from a government organization. Oh, I was told, you just don't understand. Do you know what the cost would be to give your cousin compassionate use of this drug? We are not exactly mass producing this you know. In addition, the logistics of administering it to her are something that we just cannot afford right now.

So, I hung up the phone again because I just didn't quite understand, and I talked it over with her. She is one of the most successful business women in the Delaware Valley. She can afford it. She told them, whatever it costs I will pay for. As a follow up, the hospital said we will make our staff -- and, by the way, the hospital was a clinical trial site for G31-39 -- we will make our hospital facilities available to administer this drug.

So, once again I told her, just wait a while. I think this is going to work out for you, and I called them back and I said, I have great news. We can cover all those costs and the hospital will take care of the administration. To which the reply was, oh no, you just don't understand. If we start giving this drug out on a compassionate use basis we won't be able to draw anybody into our clinical trials; they are all going to want to go onto a compassionate use program because then they don't run a 50-50 chance of getting a placebo.

For a minute there I thought this was the end of the line until I came back and I talked to my cousin and she said, wait a minute, I'm Stage IV. Stage IV patients aren't eligible for this clinical trial.

So, back I went to Genta and I explained that to them and they said, no, you just don't understand. There is no evidence whatsoever that this drug will help a Stage IV sufferer of metastasized melanoma.

That, ladies and gentlemen, is like telling me that the reason that the reason that black people had trouble in the South during the '50's was that they didn't get out to vote. How can there be any examples of people having succeeded on the drug when they are systematically eliminated from the clinical trial? And, if my cousin is willing to take the risks -- we talk so often about patient empowerment -- if my cousin is willing to sign every release document that is put in front of her that she will take the safety risks, at her stage of the game why isn't that acceptable?

The fact of the matter is I do understand. I understand that the drug companies are behind the FDA in terms of the rate of progress here. They still have this mentality that every failure is a black mark against getting their drug approved, even if it is a compassionate use that is outside the context of a clinical trial. So they

systematically refuse, and what is unforgivable about that is that it is their right to refuse. That drug is their property but they do not have the right to systematically give one story after another except for the real story because every one of those times that I went back and I told my cousin to wait two more weeks, her doctor was telling her that she had to get on some treatment. So I don't know what that did to her life. All I know is I made a very, very bad judgment that I could reason with a pharmaceutical company, when it was a PR move all along and they just don't want unfavorable publicity so they won't accede to participation in a compassionate use program with a late stage victim of melanoma or a lot of the other potentially fatal diseases.

Last but not least, hopefully ending on a note that doesn't sound like we are just beating up on Genta, I think this committee ought to carefully consider recommending to the FDA that we get rid of these double-blind studies when we are dealing with potentially fatal diseases. To want to measure for a placebo effect in a situation like that -- I mean, if somebody is going to have a placebo effect and it is going to save them their lives we don't need to screen for it; let's just have it. There are plenty of other examples where placebos are very, very important for really measuring the true impact of a new drug. With fatal illnesses that is just not an area where it

needs to be done. Then maybe we could get the "Gentas" of the world to come around a little bit. Thanks for listening.

DR. NERENSTONE: Thank you. You have touched on some very important issues. Natalie Brainerd?

MS. BRAINERD: Hello. Thank you. Good afternoon. My name is Natalie Brainerd, and I am Director of Patient Programs at the Angiogenesis Foundation, a global non-profit organization dedicated to advancing research and medicine in the angiogenesis field.

The Foundation is concerned with addressing single-use IND access to antiangiogenic third-lines because they are representative of a new class of cancer drugs called cytostatic agents. Cytostatic third-line, unlike standard cytotoxic chemotherapy, does not kill all proliferating cells. Instead, most antiangiogenic third-lines attack tumors indirectly by selectively targeting the vascular endothelial cell, thus inhibiting new blood vessel growth to cut off the tumor's blood supply.

Although neither safety nor efficacy has been fully established for investigational drugs in our field, cancer patients are increasingly motivated, as we just saw, to seek antiangiogenic medicines that offer hope of benefit, driven in part by media coverage, the internet and patient advocacy groups.

As a rule, the Angiogenesis Foundation believes

that all cancer patients should benefit first from the best available approved third-lines. When standard therapies are ineffective for an individual cancer patient, we believe he or she should seek a suitable clinical trial. Clinical trials are the most effective tool we have to scientifically validate new drugs, to advance the standard of care, and to make safe and effective new pharmaceuticals broadly available to the public. More than 50 trials are currently in progress for antiangiogenic agents, and the Angiogenesis Foundation has guided more than 2000 patients towards them.

When no trial protocols are suitable, Singe Use IND access may be a reasonable last resort. We have two recommendations for FDA review of single use applications with antiangiogenic agents: First, we believe the FDA should limit single use access to drugs that have some clinical evidence supporting benefit and, second, we believe the FDA should consider the cytostatic paradigm in making the risk/benefit assessment.

What do I mean by the cytostatic paradigm? In terms of risk, Phase I clinical trials of more than 40 antiangiogenesis inhibitors have demonstrated that these cytostatic agents are generally well tolerated and are much less toxic than conventional chemotherapy. Thus, when compared to a cytotoxic agent, antiangiogenic agents, in general, appear less likely to cause harm to a cancer

patient even when their efficacy has not yet been fully demonstrated.

With respect to patient benefit, antiangiogenic agents are not designed to have the usual sought after antitumor activity, i.e., reduction in tumor size. Instead, antiangiogenic therapy is most likely to cause disease stabilization. Phase II clinical trials of antiangiogenic drugs provide ample evidence for this with few cases of complete responders, but many patients experience stable disease. Consequently, the benefits of an antiangiogenic agent may be improved quality of life and lengthened progression-free survival. These benefits may not be captured by standard serial imaging.

So, in summary, when the FDA reviews single use IND applications for cytostatic agents, such as angiogenesis inhibitors, we reel it is critical for evaluators to consider the unique features of these biological agents. First, their cellular selectivity positions them to be safer and better tolerated than cytotoxic agents and, second, their benefits may include improved quality of life due to stable disease and, thus, may be challenging to measure using current standard instruments. Thank you.

DR. TEMPLETON-SOMERS: Next we have a letter from Ann Fonfa, founder of the Annie Appleseed Project which educates and informs cancer patients, health care providers

and others on issues of interest, especially complementary alternative therapies.

This is an extremely difficult question to address but I want to share with you some of my thoughts on the issue of compassionate use of unapproved therapies. As a woman who has had neither chemotherapy nor radiation, I am not eligible for most trials. While I understand why there are study entry criteria, I wonder if they are directed to ease the approval of a particular drug and not so much toward the benefits of the trial participants or the patient population in general.

For patients who have been heavily pretreated, and there are so many of these with metastatic breast cancer, I wonder if the entry criteria have to be set up they way they often are. If someone like myself, and I am not alone in this category, wanted to enter a trial we could not. We would have to have compassionate use approval. So, with those most needing a new therapy, women who have tried just about everything else first, in order to benefit these women a drug may actually have to work in that patient population. So, perhaps testing it on them is a good idea.

I recently read an article that stated drug companies can increase the likelihood of a drug success by using exclusion criteria, as one investigator told the Inspector General's office, to enrich trials with patients

who are most likely to benefit. Yet, having attended two meetings devoting to discussing how to promote clinical trials, I understand that we need completed studies to better aid us in discovering good treatment. Should performance status be a standard for entry?

On the other hand, when I look at the actual survival of most approved therapies I often fail to understand their benefit to patients. At another ODAC meeting I referred to continued approval of drugs with so little better benefits to patients in existing drugs by comparing the process to crawling on our hands and knees through a field of broken glass.

Patients want to leap forward, yet we are continually presented with tiny steps. Yes, they add up to moderate gains, as has been stated at various medical conferences I attend, but must we continue to crawl inch by inch or is that simply an artifact of the current system?

So, part of my problem is continuing to doubt whether we are using the best possible methods of finding, testing and approving drugs at all. As a cancer patient myself, I cannot imagine denying women with advanced disease the opportunity to try one more conventional therapy even when the end results will be two more months of survival laden with the negative effects of the therapy.

I will end by urging everyone in this room to

consider the benefits of complementary natural therapies. Studies in animals and cell cultures indicate benefits may include better tolerance to cytotoxic regimens, support to the host -- that is us, human beings -- and possibly enhancement of therapy.

Please consider starting trials immediately that will look at chemotherapy with the use of antioxidants. Thank you for your attention. As you may imagine, no pharmaceutical company has ever sponsored the Annie Appleseed project. Ann Fonfa.

[Laughter]

DR. NERENSTONE: Our next speaker is going to be Susan Weiner. Is Susan here?

DR. TEMPLETON-SOMERS: I haven't seen her.

DR. NERENSTONE: Then we will move on to Diane Dorman.

MS. DORMAN: Good afternoon. I am Diane Dorman, the Senior Director for Public Policy for the National Organization for Rare Disorders. NORD is the unique federation of voluntary health organizations dedicated to helping people with rare orphan diseases and assisting organizations that serve them. We are committed to the identification, treatment and cure of rare disorders through programs of education, efficacy, research and service.

I appreciate the opportunity to address publicly

the important topic of single-patient use of investigational drugs in oncology. We applaud FDA's willingness to consider providing promising treatments to patients living with the unusual forms of cancer who have no other therapeutic options.

I am happy to note that the rare disease patient community insisted that access to investigational drugs be included in the text of the Orphan Drug Act, which was drafted between 1980 and '81 and was enacted in 1983. Subpart (e), entitled, open protocols for investigations, allows for an investigational orphan drug to be provided to a patient outside a clinical protocol for the purpose of treatment, not research. We are proud of this legacy, grateful for your willingness to consider its implications in oncology, and programs like these should be available to all patients with life-threatening illnesses, including rare disorders.

Why was the open protocol stipulation included in the Orphan Drug Act? Historically, pharmaceutical companies did not want to develop drugs and biologics for small populations of people with rare diseases. The sponsor of an investigational drug for breast cancer, for example, would often not permit a doctor to obtain the compound under an compassionate IND produced in a single-patient with bladder cancer.

NORD knew then and knows now that the compound would never be tested in bladder cancer because bladder cancer is a rare and, thus, potentially unprofitable disease. An NDA for bladder cancer would never be filled at the FDA and use in bladder cancer would forever remain investigational. We also knew that manufacturers chose not to conduct pediatric studies. I would like to say that today, however, I am happy to say that the new regulations governing pediatric exclusivity are promoting trials in this area.

The open protocol section of the Orphan Drug Act removes these excuses and encourages sponsors to provide investigational compounds to physicians who want to use it with single patients outside of an existing protocol. It also encouraged the FDA to quickly approve compassionate use requests. In fact, the open protocol section was so important to the rare disease community and so successful in providing access to investigational drugs that former FDA Commissioner, Dr. Frank Young, cited its success when he proposed the treatment IND for all drugs, not just those for orphan diseases. Institution of the treatment IND marked a major turning point in the agency's recognition that patient access to investigational drugs cannot be ignored.

We applaud the FDA, manufacturers and the advocacy community which, together, have taken a next step in

building the single-patient IND program and expanded access to protocols that ensure that promising compounds are available to our constituents.

NORD administers several treatment IND programs to provide a finite supply of experimental drugs to many patients who are eager, if not desperate, to receive experimental therapies. For example, we ran a computerized, random selection program for Ralutec, a drug manufactured by Aventis for Lou Gehrig's disease, and we are currently administering a program for AstraZeneca's Iressa, a novel agent for the treatment of non-small cell lung cancer. The expanded access program we have instituted and will continue to institute at NORD may very well serve as a model for the distribution of limited supplies of drugs to a larger population who want it, and that program takes an important step forward in this search for appropriate access.

For many rare diseases, including some cancers, small in numbers as they are, access to an investigational drug outside of a controlled clinical trial can be the only treatment option. For some cancer patients there are no other therapeutic possibilities. Unfortunately, however, we often hear from patients or families who have been trying for weeks or months to obtain an investigational compound through a single patient IND but are unable to do so. Most of the time they blame the FDA simply because the agency

will not provide any valid reason for inaccessibility to a compound.

We firmly believe that FDA does not serve the public well when it refuses to respond honestly and openly to inquiries about single-patient INDs. We believe that FDA must remove its own gag rule and truthfully communicate with patients and physicians so that they will know the specific obstacles to access.

When a parent calls the FDA and asks why her child cannot obtain a compound through a single-patient IND, the FDA should be able to say, we have not received a request from your child's physician, or, the pharmaceutical has denied the physician's request, or, the physician's paperwork cannot be processed until his or her institutional review board grants permission for the doctor to use the drug on your child. Doctors and patients need and deserve these answers when their lives or the lives of their loved ones hang in the balance.

NORD continues to get phone calls from cancer patients as well as their mothers and fathers, friends, cousins and spouses, which tell us that the FDA provides no detail on their search for treatments. The agency's code of silence does an injustice to these patients and their families and even to the agency. Too often the blame for inaccessible therapies falls back on the FDA even when it is

willing and eager to allow an experimental compound to be given to a patient who is not in a controlled clinical trial.

In closing, we applaud your willingness to consider new means of ensuring access to promising cancer therapies where no other adequate therapies exist. We also ask that you keep ensuring that patients, their loved ones and their doctors have all the information they need to guarantee the access we want them to have. Thank you.

DR. NERENSTONE: Thank you. The next letter will be read.

DR. TEMPLETON-SOMERS: This time I am reading this for Lorelei Rosenthall. Thank you for giving me the opportunity to address you today. I am not an activist, just a wife, mother and working woman. I am also trying to survive, as is my husband and our family, a devastating illness, renal cell carcinoma because when an individual is stricken it affects everyone.

My husband's illness was stable until a year ago when conventional therapies failed him. We were advised to look into experimental drugs or a clinical trial. With the help of our physician, the Kidney Cancer Association, or which we are active members, and the internet, we were able to narrow down our options to a couple of experimental therapies. We were not sure if my husband would be eligible

for a clinical trial so it was suggested that we try for single-patient use of an investigational drug.

I was somewhat familiar with the process because several years before our family was successful in obtaining a protocol exception for a drug for my father who had suffered a severe brain trauma. While the drug was of marginal value, it did give some relief and hope to both my father and our family. Our experience with the pharmaceutical company was a positive one so I was unprepared for the resistance that I met from the company I was currently dealing with.

I had been told it would be difficult to find anyone willing to talk and they would be less than understand and, indeed, I met with resistance immediately from the young woman who initially took my call, to the researcher who told me in no uncertain terms that they would not allow compassionate use of the drug. They went on to say that they were not even sure that they would continue with the production of this drug because they were not sure there was a large enough population for this drug.

I was treated as though I wanted something that was of a high priority and top secret, and I guess I did, a drug to save my husband's life. I met people who had lost loved ones because they could not access the drug and had no other options. It became clear that this was the company's

attitude. It was the same attitude they had displayed with the now well-known drug, successful in treating another form of cancer.

Throughout all this I did not become embittered or angered, I just became empowered. That is why we have traveled here today at our own expense. Ultimately, my husband entered a clinical trial and was stable for a year. Now his disease is progressing and he is out of the trial. The rules of clinical trials are black and white, I understand. However, when one has a partial response when you are dealing with a disease with a high mortality rate there should be some latitude where compassionate use of the drug comes into play.

The search is on again. This time we are traveling to Europe. We have been encouraged to do so by a number of U.S. oncologists. Ironically, the procedures was developed here but is not yet available. Just imagine what it is like if you do not have the resources, a support system or the wherewithal. I understand that with some drugs there is a risk but then just living is not without its dangers. I also realize companies need profits to survive, that they must protect their patents and have a fear of litigation, but they must also show compassion and be helpful.

I also know that it is not just industry. Industry and regulators must have a better mechanism with which to

deal with cancer drugs outside clinical trials. Lorelei Rosenthall.

DR. NERENSTONE: Our next speaker Melissa Yazman.

MS. YAZMAN: Good afternoon. My name is Melissa Yazman. I was diagnosed in May of 1997 with Stage IV pancreatic cancer. I am here today, three and a half years later, as a survivor who has battled to survive the odds. I am a veteran of both standard treatment and clinical trials.

I have been blessed because I am here to fight another day. Most people with pancreatic cancer are not so fortunate. I am also here today as a representative of the Pancreatic Cancer Action Network, called PANCAN. PANCAN was founded in 1999 as the first and only national advocacy organization for pancreatic cancer. Within a few short months the ranks of our grassroots volunteers have swelled to thousands, and today we work to increase awareness and bring attention to the urgent need for well-designed, medical research with positive outcomes.

Pancreatic cancer is the fourth leading cause of cancer death for men and women in this country. The American Cancer Society tells us that at the beginning of the year 2000 we will see 28,300 Americans diagnosed with pancreatic cancer. One year later we will find that 28,200 people will have died from pancreatic cancer. These are not good numbers, folks. A typical pancreatic cancer patient is

diagnosed at Stage IV with metastatic disease, and has the life expectancy of three to six months. There are no early detection models out there. No PAP smears; no scans; nothing to help us.

Our treatment options are severely limited. There are only two FDA approved drugs for treatment of pancreatic cancer. One of these drugs was only recently approved, in the last three years, and the other drug, 5-FU, is a standard oncological drug. Both are considered palliative. No expectation of cure, merely palliative.

We want to thank FDA for initiating these discussions on compassionate use. This is an issue that is vitally important to the pancreatic cancer community because we are desperate. We need access to as many options for treatment as possible, and we are here today to listen and to share our views in the hopes that this meeting is the beginning of the process that will be productive for all us. We believe that our starting point is to clearly define the roles of all the agents, all the parties -- the patients, the advocates, the FDA and the drug companies. I can assure you that, as part of the advocate community, we want to be part of your process.

The issues are clearly complicated and there are more questions than can ever be answered in an afternoon's hearing, but the Pancreatic Cancer Action Network feels that

this issue is important enough that the FDA should convene a full-day meeting or a series of meetings with patients, advocates, health and industry professionals to tackle these questions head on. We strongly urge that a Part 15 hearing take place. We believe that by working together and by talking to each other we can all be an active part of the solution for a situation that is clearly bigger than all of us. We have no hidden agendas at PANCAN. Our bottom line is simple. We must find a way to provide patients with access to the best treatments, the most options and the greatest hope without undermining the safety and efficacy of new drug development. In today's age of discovery and application, anything else is simply unacceptable. Thank you.

DR. NERENSTONE: Thank you. Chelsea Kidd?

MS. KIDD: Good afternoon. I am Chelsea Kidd, Legislative Liaison for the National Patient Advocate Foundation, and a breast cancer survivor. On behalf of NPAF, I would like to thank you, all, for allowing us to share our views with you on patient use investigational drugs.

NPAF is an organization that seeks, through policy and legislative reform, to ensure individuals access to health care. Our advocacy activities are influenced by the information that we receive through the counseling and case management activities of our companion organization, the Patient Advocate Foundation.

The Patient Advocate Foundation is a national, non-profit organization that serves as an active liaison between the patients and their insurers, employers, and health care providers to resolve matters related to access to health care. PAF uses the services of professional case managers and attorneys to guarantee that those with serious and life-threatening illnesses, including cancer, receive the care they need. The need for our services is great. In 1999, PAF handled over 29,000 patient calls, and we have on more than one occasion been called upon to assist patients in securing access to investigational drugs.

We strongly support the expanded access provision that was included in the Food and Drug Administration Modernization Act of 1997, and recommend that implementation of that provision be made as simple and straightforward as possible.

We would like to comment on the basic requirements that must be met before a patient may receive an investigational drug. FDAMA specifies that the patient's physician has to determine that there is no comparable or satisfactory alternative therapy to the investigational drug the patient seeks. In the case of those who are seeking access to an unapproved drug, decisions about the availability of an alternative therapy should be made by a specialist who is properly trained to offer such an opinion.

Under the statute, the FDA is required to determine that there is sufficient evidence of safety and efficacy to support the use of the investigational drug. We recommend that this determination should include a consideration of the professional qualifications of the individual's physician, including his or her training to assess the availability of alternatives to the investigational drug.

Under FDAMA, the agency is also charged with determining that provision of the investigational drug does not undermine the ongoing clinical investigation. We agree that efforts must be made to ensure that clinical trials are not disrupted and that clinical research enterprise is not hindered in any way. On occasion, our clients need individual access to investigational drugs, however, all of our clients benefit from the clinical research that leads to improvements in medical care. NPAF believes that the agency, relying upon the expert advice of medical specialists, can balance the sometimes competing needs of the individual patient and the need to ensure clinical research is not interrupted.

We would like to thank you again for providing this forum for consideration of an issue of great importance to our organization and many others representing those with cancer and other serious and life-threatening diseases.

Thank you for the opportunity to address the committee.

DR. NERENSTONE: Thank you. Martha Solonche?

MS. SOLONCHE: Good afternoon. I am Martha Solonche and I serve on the Board of Directors of SHARE, and I am here this afternoon to read a statement on behalf of that organization. Please note that the opinions set forth in this statement are those of SHARE and do not necessarily reflect my personal sentiments, or the sentiments of any organization or client I may serve.

SHARE, a non-profit organization located in New York City and serving the tri-state area, offers survival groups for women with breast or ovarian cancer and their families and friends. SHARE also offers health and wellness programs, educational programs, outreach training, alternative and advocacy programs and three specialized hotlines.

SHARE's participants continue to want to be able to exercise all their options, including the use of experimental drugs and treatments that may not ordinarily be available to them, often because they have already been treated with more than one chemotherapy regimen. At this time, SHARE supports the proposition that non-approved oncology drugs and biologics should be made available to individual patients if, one, the patient's condition is life-threatening and a request is made by the patient; two,

the patient is monitored in a structured, consistent manner; three, there is sufficient drug safety information available either from a completed Phase II trial of the drug or other data that provide some basis for determining that the drug may be efficacious; and, four, there is a set procedure and record-keeping structure whereby all patients who receive a non-approved oncology drug or biologic must provide a specific set of information which may be similar to data collected in existing trials, and such information must be made available to specified researchers, and the clinician treating the patient with the drug agrees to follow the patient and provide data to the trial sponsors.

SHARE is aware of the problems that exist regarding resources, allocation of supplies and the possibility that such drug access may possibly undermine existing trials and delay scientific conclusions. However, we believe that a review can and should be made of the current guidelines, and further recommendations can be made to address some of these concerns.

SHARE is at the FDA today to hear all of the dialogue that will be presented today regarding single-patient use of investigational anti-cancer agents. We see this as the beginning of an information gathering process.

On a personal note, as a survivor of two concurrent primary cancers, Stage IIIc ovarian cancer and

Stage Ib uterine cancer, I am not eligible for any clinical trial. Thank you.

DR. NERENSTONE: Thank you. Jennifer Bryson?

MS. BRYSON: Good afternoon. I am Jennifer Bryson, an employee of Genentech, where I head up our efforts with advocacy groups, which means that I work with advocates on issues such as expanded access, clinical trial enrollment and protocol design. By way of disclosure, Genentech pays me a salary and also paid my travel expenses to be here today. But I am glad to be here to share Genentech's perspective on expanded access.

We have had experience with pre-approval access to Herceptin, and we have adopted several key principles that apply to our considerations of expanded access. Although we believe strongly in these principles, we do not believe that they are the only answer to this complex issue.

Our highest priority is to pursue high quality research that advances our understanding of disease and our ability to provide improved therapies. In order to preserve this priority, we base the decision-making process about access programs on specific factors related to each product's development, such as safety data, efficacy data and available drug supply.

Specifically, the decision about whether to create an access program for a particular drug is based upon

impartial factors related to the suitability of that drug for a specific patient population, as opposed to criteria related to any individual patient such as who they know, how much money they have, or how much media attention they can achieve.

In fact, when an access program is appropriate, Genentech is completely committed to providing that access in a fair manner. Therefore, we cannot support or allow individual patient exceptions or single-patient INDs. Because drug supply is usually very limited during development, the size of access programs may necessarily be small and, therefore, we may not be able to meet the tremendous and urgent demand by individual patients, and we recognize that is very real. But we use the system that randomly selects eligible patients without regard to any subjective factor that could influence the selection process.

We will only consider an access program when an investigational agent has shown adequate safety and efficacy data at the completion of Phase II. We believe these criteria must be met in order to justify the risks of administering an unapproved agent into a very ill patient.

We will provide access in a way that does not interfere with the accrual or retention of patients into controlled clinical trials that will determine an agent's

potential benefit and safety. Therefore, eligibility criteria for access programs must not compete with the eligibility criteria for controlled clinical trials, which I think is a point that has been made here before. Patients must also have immediately life-threatening disease for which no other appropriate treatments are available.

In addition, we have learned a lot from our Herceptin experience and we believe strongly in working with the affected community to work out a specific program that addresses the needs of that population. So, we are committed to going forward and working with advocates in any future access programs that we design, to work with the affected community to make sure that we meet their needs. Thanks.

DR. NERENSTONE: Thank you. Gayle Tibbett?

DR. TEMPLETON-SOMERS: Gayle Tibbett is another victim of the bad weather. This letter is from Gayle Tibbett. I am appreciative of the invitation to write to you regarding the experience my husband has had since he was diagnosed with colorectal cancer in 1997. His experience is very common. Thus, as I write to you of our personal situation, I know that I speak for a much larger population of cancer patients and their families.

After my husband's initial diagnosis in 1997, his oncologist recommended standard treatments. Two years later he experienced recurrence to the liver. All first-line

treatments failed. He began trial drugs. They failed. In spite of this, today he is healthy and works full time. Unfortunately, we find ourselves at a place where there are almost no options remaining for him. We discovered there are three drugs now in the process that are in his best interest, but he cannot qualify for these drug trials because he has too much pretreatment. Thus, the only option for us is really no option at all. Phase I drugs are out of the question. Remember, he is healthy; he works full time.

As I explained, this treatment cycle is very common. When the initial diagnosis is given the patient is encouraged by their oncologist to take first-line drugs. When they fail, the patient begins trial drugs. Then the trial drugs fail or are exhausted. At this point, if more trial drugs become available the patient is disqualified from participation in these trials because the protocols established by the pharmaceutical companies discriminate against individuals who have already participated in a standard treatment process. Essentially, the patient's earlier treatment prevents them from participation in additional drug trials. When they reach this point, most patients give up. Their only choice is the risky Phase I trial. The reason this is their only choice is because very few compassion trials are available.

The simple solution the this treatment dead-end is

to make more compassion trials available, especially for drugs that are showing potential. However, I know this solution is not simple for pharmaceutical companies or the drug approval process. Compassion trials stir up many fears. One of these fears is that the compassion trials will pull candidates from Phase II and III drug trials, creating a potential competition between compassion trials and other standard trials. Another fear associated with compassion trials is the creation of negative data that might be damaging to a drug's approval process. These fears are legitimate in that they are directly related to the process of drug approval. However, there is a way compassion trials could be established which would address these fears.

Guidelines could be created which we make compassion trials a real solution for cancer patients as well as manageable venture for the institutions that oversee them. First, open compassion trials only to individuals who have exhausted all other options, those patients who are unable to meet protocol and thus are disqualified from standard Phase II and III trials. In other words, create a protocol that requires all standard treatment to have failed before a patient could participate in a compassion trial. With this guideline compassion trials would be unable to detour qualified patients from participation in standard trials. Second, allow compassion trials to be controlled by

the same institutions that control the Phase II and III trials. Hold the compassion trials at the same location as the standard trials so the possible candidates for either trial could participate in the most scientifically appropriate trial, rather than selecting a trial based solely on geographic convenience. Third, consider the data received from the compassion trials as valid data. While this data would be of a different nature than Phase II and Phase III trial data, the distinctive qualities of this information could be a source of valuable information and helpful in reaching the goal of drug approval and possibly a cure.

A compassion trial is the only hope for my husband and many more like him. His local oncologist and physicians at NCI agree that the three drugs available would be in his best interest, but he cannot qualify for those drug trials. He has already contributed to scientific research and is ready to contribute to further studies. Please move quickly. My husband is not an isolated case; many people's lives are at stake.

Thank you again for the opportunity to communicate our experience. Gayle Tibbett.

DR. NERENSTONE: Karen Doran is our last speaker.

MS. DORAN: Good afternoon. I would like to take the time to thank the FDA for permitting me to be here today

to discuss four issues regarding my mom and gene therapy. First of all, mom had been approved for gene therapy through the University of Pennsylvania, in Philadelphia. It was the only source of hope in fighting her rare, deadly lung cancer, classified as mesothelioma. We know that gene therapy was a trial treatment with no guarantees, but the family agreed that it was the best option she had. We were told treatment could begin as early as January 2000, and we thought it was a great way to begin the New Year.

Secondly, after weeks of waiting with no word from Philadelphia, we contacted them and received no firm data for mom's therapy to begin. This was a very stressful time for everyone, especially since she was receiving no conventional medical therapies pending the start of gene therapy.

Third, it was only through the news media that we found out that the gene therapy was put on hold due to the death of one of the participants.

Finally, we believe all patients should be able to make their own decisions in regard to taking gene therapy after being fully informed of all the potential risks and benefits. Because of an incident that took the life of a young man who voluntarily underwent the treatment, fully knowing the risks, my mother and countless others were denied their best fighting chance against cancer. So, I am

here today to talk about decision, choice and being informed.

Here is a full account of our story. In October, 199, our lives changed drastically. That is when my mother was diagnosed with late-stage mesothelioma which us a rare, deadly form of lung cancer caused by exposure to asbestos. I want to emphasize that my mother was a non-smoker. Up until her diagnosis, mother was vibrant and energetic, very active in the community, home and church. We believe she was exposed to asbestos as a young adult from washing her father's clothing.

At the time of the diagnosis, we were told there were very limited treatment options. Our only hope for any cure was a gene therapy clinical trial being done in Philadelphia at the University of Pennsylvania. We learned of this gene therapy through a local pulmonologist, Dr. Michael Wei, who suggested we take mom for evaluation.

The appointment was scheduled for Friday, November the, 1999. Mom and I flew to Philadelphia on Thursday. This was mom's first flight and she was given a first-time flyer's certificate from the flight cres. We were both excited and hopeful.

Mom was evaluated by Dr. Daniel Sterman, Assistant Professor of Medicine, and Clinical Director of the Mesothelioma Gene Therapy Program. It was determine that she

was a candidate for gene therapy. Loaded with much information about gene therapy and possible side effects, we returned home to permit mom time to consider whether or not she wanted to do this as it was a non-proven therapy that could have serious consequences. Dr. Sterman stressed that this had to be mom's decision, no matter how much her family wanted her to try this gene therapy. After much thought, prayer and careful consideration with her family, mom decided to undergo gene therapy. Mom did not want to die and was willing to take this chance so that she might live.

Dr. Sterman was contacted and mom was in line to start the gene therapy in January, 2000. We received this news on December 20, 199 and thought what a Christmas present. Mom was very excited and, at the same time, was anxious to get started since she would have to spend several weeks in Philadelphia undergoing treatment. Many of mom's family and friends had already offered to go with her. She was told not to take any chemotherapy as it would interfere with the gene therapy.

We waited patiently to find out when she would be going to Philadelphia. She even had her bag packed. However, the FDA put a hold on the gene therapy trial when a participant passed away in September, 1999. When the FDA was contacted, I was told the reason for the gene therapy clinical trial being put on hold was confidential due to

pharmaceutical stock prices being affected. After a follow-up telephone call to the University of Pennsylvania we learned that mom would not be able to start gene therapy as planned. We were advised to seek other treatment options.

Mom's medical records were sent to cancer centers all across the United States but to no avail. Her cancer had rapidly progressed since her evaluation in November. We were told there was really nothing that could be done except some chemotherapy, which might make her more comfortable but have minimal impact on the disease.

Mom passed away on May 26, 2000 at the age of 72. She was denied a possible cure for her disease by a group of people who did not know her. They apparently did not understand that mom knew her options and was willing to take a chance. My mother knew she might die with this treatment but she also knew she was going to die without it.

My family and I strongly believe mom should have been given the opportunity to try gene therapy. She had full faith in Dr. Sterman and the gene therapy and should have been permitted to receive it. Her strong Christian beliefs would not permit her to be afraid of death, and her love for her family and friends would not permit her to give up either. Mom was surrounded by numerous devoted family members and friends. She was extremely active in the church and community and still had much to give. When a person is

told they are going to die from a devastating disease such as mesothelioma, and that the might die with an experimental treatment, then there should be a choice.

If my mother had undergone gene therapy in January 2000 as planned, and if she had died as a result of the treatment, what would she have missed in the last remaining months of her life? She would have missed seven hospital stays. She would have missed having a feeding tube inserted on three separate occasions because she could no longer swallow. She would have missed an extremely painful bed sore, loss of hair and sickness brought on by chemotherapy. She would not have had a Foley catheter or lost control of her bowels. She may not have suffered as much both mentally and physically. Mom was never one to depend on others for her personal needs. In fact, it was just the opposite as she was always caring for others. So, becoming increasingly dependent and less functional was a terrible hardship for her. If she had undergone gene therapy, I know she would have still experienced hospitalizations and pain and uncertainty, but at least she, and all of us, would know that we were fighting cancer with the best weapon available instead of being empty-handed with no weapons at all. And, if we had known in November that gene therapy had been cancelled we would have put mom on conventional therapies, possibly extending her life and making her final days more

comfortable.

It is felt there is a higher ethical need for the patient to understand why they have been denied access to treatment than the need for confidentiality due to pharmaceutical stock prices.

My family and I believed, and still believe, that mom should have been permitted to receive this gene therapy. We know that it is too late to save my mother but it may not be too late to save someone else's loved on. Thank you.

DR. NERENSTONE: On behalf of ODAC, I would like to thank all the speakers for taking their time in addressing this committee.

Dr. Williams is going to give us an introduction now on this topic.

Single-Patient Use of Non-Approved Oncology Drugs and Biologics

Introduction

DR. WILLIAMS: Madam Chairman, committee members, ladies and gentlemen, first of all, I would like to express my thanks to the many speakers that we have heard today, your stories, your issues. I think you have raised several issues that I really think we should look into. I really appreciate your input.

Today I will briefly provide the regulatory background for discussion of single-patient use of

investigational drugs and biologic products. When I speak today of drugs, please understand that I am referring to both drugs and biological products. I am from the Division of Oncology Drug Products for drugs at FDA, but our Division works closely with the Center for Biologics and oncologists there, and today we have Karen Weiss and Pat Keegan at the table with us. As you know, this committee commonly reviews applications from both drugs and biologics.

So, what are the objectives for our meeting today? One objective is to educate the public on the many issues surrounding the treatment use of experimental drugs. I think you have been educated already from the patients that have spoken today, and we will be hearing from many others.

A second objective is to get the advice and input on when it is appropriate to allow experimental drugs to be used for the treatment of individual cancer patients.

To accomplish these goals today, we plan to hear from a number of individuals who may have a variety of perspectives on this issue. First, I will make a few introductory remarks about the law and about FDA experience. Next, we will be hearing from ethicists who will provide us with principles and language that will be useful when having our dialogue. Then, we will be hearing from the perspective of industry, from two individuals representing drug companies involved in studying cancer drugs. Finally, we

will hear the perspective of patients as communicated by representatives from three patient advocate groups.

After hearing these presentations and the perspectives that they represent, the committee will be asked to discuss the relevant issues. We are looking forward to these discussions and to your advice, and we will consider them very carefully as we evaluate our approach to single-patient use of investigational drugs.

First I wast to begin with a few definitions. All use of experimental drugs is regulated by FDA under an IND. An IND is an investigational new drug application. There are several different individuals that may be involved in an IND. First, there is the IND sponsor. The sponsor is the individual, company or institution that assumes responsibility for overseeing the study for assuring that the regulations are followed and for reporting to FDA on the progress of the study. The sponsor may or may not be the manufacturer of the drug.

Next, there is the investigator. The investigator is the individual that actually performs the trial or administers the drug. At times the investigator and the sponsor are the same person.

The regulations stipulate that a sponsor shall select only investigators qualified by training and experience as appropriate experts to investigate the drug.

For most cancer drug applications, we expect the investigator to be a licensed physician and to have training and experience in treating cancer.

FDA may receive a request for treatment at any stage in the process of drug development. So it is important to understand something about the process. The stage of development tells you how much information there is about a drug. For those of you that are not oncologists, I will briefly outline the drug development process in oncology.

The first stage is the preclinical stage before a drug has been studied in humans. We may have data from laboratory studies or from animal studies. These data allow investigators to select a cost for the first studies in humans and to identify toxicities caused by the drug in animals.

The sponsor subsequently files an IND. This IND contains, among other things, a clinical protocol for a Phase I study. Phase I studies in oncology are generally small studies, done carefully in just a few patients to determine what is an acceptable dose of drug for future study, and to determine the most obvious toxicities of a drug.

The next phase of the cancer drug development is Phase II. Separate Phase II studies are performed in different types of cancers. Generally one or two studies

usually totaling 30-100 patients are evaluated in each disease. The purpose of a Phase II study is to see if there is preliminary evidence that the drug might work. Such evidence might be tumor shrinkage or often known as tumor response.

Finally, the last stage of development before drug approval is Phase III. Phase III trials are larger trials, designed to demonstrate whether the evidence of drug activity noted in Phase II actually translates into clinical benefit. These are usually randomized trials in hundreds or thousands of patients comparing the experimental drug to a standard therapy.

So, that is a brief overview of the development of cancer drugs. The stage of development is one important consideration in evaluating the request for treatment use of an experimental drug.

The usual purpose of an IND is to allow for clinical investigators to determine whether a drug is safe and effective. If the findings from the studies are favorable, the sponsor will submit all of the data from these investigations to FDA to determine whether the drug can be approved for marketing. In this way, the drug becomes widely available to the American public.

The FDA strongly endorses participation in clinical trials because it is in the best interests of the

American public to determine whether a drug is safe and effective. Individual patients also benefit by participating in cancer clinical trials. The best treatments available are selected for testing in these trials.

However, there are times when it may be appropriate to test make an investigational drug available primarily for treatment rather than for the usual purpose of investigating the drug's safety and effective. Generally, this unusual step of authorizing such use is warranted only for patients with serious diseases and conditions, such as cancer, and for whom there are no remaining satisfactory treatments.

The terminology surrounding treatment use of experimental drugs can be confusing because the regulations do not explicitly describe all of the practices. Different terms are frequently used for the same practices. Treatment use of experimental drugs can be divided into two main groups, single-patient treatment use and expanded access treatment use. Expanded access refers to the fact that multiple patients are being treated under a single protocol, whereas for single-patient use individual type treatment plans are drawn up for individual patients.

I will briefly describe expanded access. In oncology, historically there are two well-defined procedures for expanded access. Since the 1970's NCI has worked with

FDA to provide investigational treatment for use under a mechanism called Group C. In 1987 regulations were adopted that formalized this process and extended it beyond the treatment of cancer to all diseases that are serious and life-threatening. The name of this mechanism of expanded access is the treatment IND or treatment protocol. Both Group C and treatment IND are intended to allow for widespread distribution of a drug that is nearing marketing approval.

Over the years expanded access protocols have also been approved for promising drugs not yet at this stage of development, that is, near marketing approval stage and treatment IND. The requirements and format for these other expanded access protocols are not really described in the regulations as a separate section, but the considerations for their approval are similar. In a little while you will be hearing from Dr. Linden and Dr. Kennealey about their experiences with such protocols.

Now I will describe single-patient use. In single-patient use treatment plans are drawn up individually for each patient. There are two mechanisms for handling single-patient use. In the first mechanism, the single-patient IND, a new sponsor files separate IND. We know that hundreds of patients per year receive drug under single-patient INDs. In general, this process is less desirable and involves more

paperwork for everybody. Also, there is not a single sponsor who communicates with all the physicians treating patients. Generally there is one sponsor per IND.

In the second mechanism, called single-patient exception, there is already an existing IND, an existing sponsor and an existing investigational protocol. Under the single-patient exception mechanism a patient who is ineligible for an investigational protocol is treated under a plan that is a slight modification of the existing protocol. The same IND and the same sponsor are used. This is a more efficient mechanism for single-patient treatment.

In summary, investigational cancer drugs are provided for treatment use by a variety of mechanisms. Over the years many thousands of patients have received investigational cancer drugs through treatment IND or Group C mechanism, by other expanded access mechanisms or by single-patient treatment use.

So, what are the legal requirements? Legal requirements for single-patient use are basically the same as those for any IND. There must be a drug manufacturer that will supply the drug. There must be a sponsor who reports to FDA. There must be a medically trained investigator and, again, sometimes the sponsor and the investigator are the same person. There must be informed consent and IRB approval, and there must be concurrence by FDA that there is

sufficient evidence supporting the drug's safety and efficacy.

Please note, however, that FDA cannot initiate this process even after a request from a patient or a patient's doctor. The FDA does not produce drugs and the FDA is not a sponsor.

You should be aware that if there is a problem with a requirement for treatment use, FDA may not always be able to directly communicate the reason for the problem, and I think you have heard that earlier. Legally, much of the information generated under an IND is proprietary and confidential and it cannot be communicated by FDA without permission of the sponsor. But we did find interesting the comments earlier, and we will look into what we are legally able to communicate in the future.

When evaluating any requirement for treatment use, these are the items one must consider: whether evidence suggests that the drug is active or toxic; whether patients have other acceptable treatment options; whether the sponsor is conducting clinical trials needed for marketing of the drug; and whether the proposed treatment is likely to interfere with clinical studies needed to prove whether the drug is safe and effective. These latter two issues may be less important for single-patient use, especially if such use is infrequent.

In summary, when evaluating a requirement for single-patient use of an investigational drug these seem to be the central issues: First, what evidence do we have regarding the drug's effect in people? One aspect of this question is to consider the stage of drug development. Do we have data from Phase I studies, Phase II studies, Phase III studies?

Then we need to consider the results of the studies. Are there data suggesting that the drug has activity or that it is toxic? The other important consideration is whether there is available standard therapy for the patient's cancer. For diseases where there is no standard therapy or where standard therapy is not satisfactory, FDA has usually permitted single-patient therapy if data suggests that experimental treatment is relatively safe.

Later in this session the committee will be asked to discuss when single-patient use of investigational treatment is appropriate. You will be asked to consider basically these three factors: Evidence of anti-tumor activity, evidence regarding toxicity and adequacy of available therapy.

We look forward to your advice. I will be glad to take any questions.

DR. NERENSTONE: Does the committee have any

questions? Dr. Przepiorka?

DR. PRZEPIORKA: Two quick questions. First of all, I know the FDA can, because I have read the warning letters on the web site, take action against drug companies when they are advertising does not comply with labeling requirements. But what about press releases prior to approval? Do you have any purview there in taking action against drug companies when press releases are not accurate?

DR. WILLIAMS: Well, first of all, we have a department that deals with press releases and a department that deals with advertising who I would consult with. But we do have interest in press releases and we are often asked to clear them. I don't know if Rachel has any other comments about that.

DR. BEHMAN: In our discussion and between the Division of Advertising and General Counsel, it is not considered advertising and many in industry have, therefore, stated their position that we cannot take action on press releases.

DR. PRZEPIORKA: My second question is do you have a guidance document for use of a treatment IND for the treating physicians?

DR. WILLIAMS: The terminology is very confusing. We have regulations that discuss treatment INDs. The word treatment IND is a very special word in the regulations. No,

we do not have a guidance document, that I am aware of, that discusses what we are talking about today, that is, treatment use, no. But that could always be considered, and input from meetings such as these could always help in that process.

DR. NERENSTONE: I have a brief question. Do you have any idea of the magnitude of the number of requests that you might get if this were opened up?

DR. WILLIAMS: Well, you know, it depends on what you mean by "opened up." We get hundreds and thousands of treatment use every use clearly. It is hard to look at statistics because they come in so many different forms. Some of them under the INDs don't jump as treatment use but there is a lot of it and I have no idea if we did everything possible to make it easy how many there would be.

DR. NERENSTONE: Other questions from the committee?

[No response]

Thank you. Our next speaker is going to be Dr. Sugarman.

Ethical Considerations

DR. SUGARMAN: Thank you for the invitation to talk about this very important and vexing topic. As the stories we heard so far make clear, the stakes here are enormous.

What I have been asked to do is to provide an ethical framework, not to provide with the ethical answers from the outset. So, my task is still different because there are multiple ways of approaching ethical problems in research and health care. I am going to do my best to provide a framework so that at least we are sharing a language as we discuss some of these issues.

What is interesting about this topic is that it overlaps areas of traditional medical ethics with areas of research ethics, and the driving force behind the regulatory approach has been one that focuses primarily on research ethics. So, we need to understand what some of the competing claims are in those areas.

Scientific success has certainly change the calculi that we use in ethical decision-making and the implications of it have been social, political, commercial, personal, medical, etc., and need to be weighed in. Then, finally I will discuss what some of the ethical obligations are for the multiple players in this field.

Well, here is the medical ethics 101 course, with apologies to folks who have spent years of their life going through this one slide. But there is a new medical ethic that emerged over a couple of thousand years. As you probably are aware, the Hippocratic ethic, exemplified in the Hippocratic oath lasted from the 4th century B.C. up

until probably the 19th century. Now, in the Hippocratic oath, remember, there is the Hippocratic physicians practice on the Isle of Cos, off of Greece. They were Pythagoreans, the same people who brought you the triangle. Okay? They were an odd set of physicians, a weird group who had some strange notions about the way to practice medicine, but they were deeply committed to it. When one was a Hippocratic physician one swore an oath by Aesculapius, and Hygeia and Panacea -- the gods that were important in dealing about what these physicians did.

Now, one central notion of the Hippocratic oath has persisted today, the notion of beneficence; the notion of doing good by your patients; the obligation to help and at least not to harm. This persisted. There were changes in the way healthcare was delivered and, by the 18th and 19th century there was a series of writers, especially in Scotland, who came up with the notion of what it meant to be a professional; what being a physician meant, as having a fiduciary obligation, an obligation to look out for the rights and interests of the person who was sick. And, there was some competition around, and there was a need for doctors to take a hard look at what kind of competing forces were at work as they went about taking good care of their patients.

Go forward another 150 years or so and we begin to

have, especially in the '60's and '70's, problems with technologies. The one that is often cited is the availability for the first time of dialysis machines, or for the first time we have the ability to save people with the use of hemodialysis and there were only a couple of those machines around.

Groups tried to decide, with this now very promising, very early treatment, how to allocate it. There just weren't enough to go around. Committees were set up in different parts of the country, and Shana Alexander, in 1962, in a famous Tine magazine piece, witnessed the deliberations of committees, especially in Seattle. As this committee of good deed doers stuck around and tried to make a decision about who should receive this dialysis machine, some were horrified by the ways they were making decisions.

What was the best way to allocate it? Was it the person that looked like the good deed doers on the committee or was it someone who looked very different? One woman was quoted as saying, when a decision was made to give the business man with then, I guess, four kids and a station wagon, the dialysis machine and a guy who lived in the woods alone was not given the machine -- she said that Henry David Thoreau couldn't have gotten dialysis.

These kinds of questions, questions about the beginning of live, questions at the end of life, famous

cases, the "baby Doe" cases, the Karen Ann Quinlan cases, all argued that we needed something more. We needed an approach besides doctors trying to do good things, and there were several approaches that came to bear, some religious, some regulatory and some philosophical.

Here, what we would describe as ethics is the systematic examination of the moral life, a way of looking at competing moral claims so that there will be morality within medicine; there is a common morality. Those moralities may differ. It makes sense if you come and see me in my clinic, you tell me what is wrong as the first thing you tell me; what is the matter; and then you take your clothes off. The same thing doesn't happen when you are shopping. It is a different interaction, different expectations, different rules govern that approach. So, clearly there was something special going on in this field of medicine.

The ethical principles -- and this is only one of many approaches but it is a common one that was brought to bear on this problem, are four: respect for autonomy, beneficence, non-maleficence and justice.

Respect for autonomy -- "auto," self; "nomos," rule -- the right to self-legislate, critical component for the American health care system. It is based on the notion of liberty. Don't tread on me. Tax us, we throw your tea

overboard. Leave me alone. Our social distance in this country is extraordinary. We don't sit very close. We don't touch each other very much -- very different from when I was practicing medicine in Tanzania where we would hold hands on rounds to show that we were a team of physicians. It doesn't work with my medical students at Duke.

[Laughter]

I didn't try it either.

[Laughter]

The notion of autonomy, this liberty interest, the right to be left alone translates into medical practice of that ability not to be touched without permission, not to have medical care done on one without permission. Don't do that to me unless I say it is okay.

Beneficence -- second principle; some would argue the first principle. Anyway, Latin, good; "fica," do or to make. The obligation here is to make things good. It is not "volo, volare" to wish or to want. It is not a Hallmark greeting card. It is not that you want it to be better; you have an obligation as a health care provider, as a clinician, to make it better. It is a moral obligation; it is a deep-seated moral obligation. And, the notion of what counts as good is where we get into trouble, but the notion of good is generally measured in medical goods, the things that doctors can know about not the thing they can't know

about or change.

Non-maleficence -- "Non" is not; "male" is bad; "fica" do or make -- see, ethics is pretty easy; we have big words to describe simple concepts. Not bad make." Okay? Now, this comes out as do no harm and it goes towards minimizing risks.

This Hagar cartoon -- he is a famous medical ethicist, said you should trust doctors more. The first rule is do no harm.

Second slide -- it worries me that they needed a rule to figure that out.

Now, there is that notion that people say, well, that is "primum noli nocere," first do no harm. Well, I told you what was in the Hippocratic oath, to help and at least not to harm. Hagar is right here. Where did "primum noli nocere" come from? That is Latin. They didn't have that yet. So, with the best we can tell, unless Dr. Pellegrino corrects me, it was a lying monk somewhere in the Middle Ages who changed this around and changed the whole ethical scheme. But, first do no harm is sort of an adage we use about not wanting to hurt and to minimizing risks to people in the process.

Finally justice -- one word, not two; fairness; equal access, treating equals as equals; knowing how, if there aren't morally relevant differences among different

individuals who need that dialysis machine, how to allocate those.

So goes this framework for ethical principles. All come up in different cases in health care. Autonomy is informed consent. Beneficence is giving treatments that are helpful. Non-maleficence is not giving treatments that are harmful or untested. Justice is treating people fairly.

There can be competing in different cases. In ethics we use the term "prima facie," first glance binding. They all matter; not just one, not just another. When they come into conflict that is when you have ethical problems and you need to weigh them and balance them. Switch gears.

Research ethics emerged out of a different history. Hippocratic physicians didn't really do randomized clinical trials; they weren't invented yet. Unfortunately, part of the history of human experimentation, early history of human experimentation derives from tragic stories. Our regulatory approach and the way we approach the ethics of research ethics traditionally has been one which Carol Levine has said was born in scandal and reared in protectionism. We draw this from the horrible experiments that the Nazi doctors conducted. These were clinicians who somehow kept wearing their white coat but forgetting what it meant. They began to do human experiments that served no useful purpose, brought patients or subjects to death

leading to sort of political learning and not necessary medical learning. At the end of World War II the United States government, in a court case known as the United States versus Carl Brandt, announces the first ten principles of the Nurenburg Code in a court case. Nazi doctors were hung; some of the rest are in jail for the rest of their lives for the kinds of experiments they did.

We move forward. Doctors in the United States and Europe did not see themselves as Nazi doctors. We were very different. Now, as an aside, I should say that I had the opportunity to work on staff on the White House Advisory Committee for Human Radiation Experiments. In this country physician investigators and investigators conducted over 4000 human radiation experiments without consent, after the Nurenburg Code was put into place and during the time of the Declaration of Helsinki was put into place.

Now, what they did, unlike the Nazis, was they paid exquisite attention to the risk/benefit ratio. Even though there were thousands of radiation experiments, it was very difficult to find any evidence that anyone was harmed. They were wronged in the sense that their autonomy wasn't respected but they weren't harmed.

The thalidomide tragedy is another research ethics scandal. It is a call for better research. It fueled the amendments for the Food, Drug and Cosmetics Act and said,

you know, we want to show safety and efficacy in drugs. And, we have an elaborate process in place to provide protections so that drugs that come to market can protect patients who buy this stuff or who use this stuff. So, it is not a scandalous notion but it is a protective notion, protective of the customer.

In the clinical center there are also other types of scandals, U.S. scandals where researchers didn't necessarily respect the rights and interests of vulnerable subjects. Very famous research conducted in institutions, hepatitis experiments in which retarded children at the Willowbrook School were injected or inoculated with hepatitis to figure out what the natural history of the disease was, and then to figure out how it might be treated. Elderly patients at the Jewish Chronic Disease Hospital, in New York, injected with live cancer cells without their consent to see if cancer was infectious.

This clearly said that doctors had overstepped their boundaries. The world, through the '60's, was not willing to accept that sort of behavior on the part of clinicians even in the name of advancing science, even though the hypotheses were good.

There was an initials et of rules put into place at the clinical center by Dr. Shannon, who ran the place, and then the revelation of the Tuskegee syphilis study,

probably the most embarrassing moment in federally funded research in this country, was revealed, not because it had been kept secret by the scientific community but because a journalist thought to tell the story as an ethics story. Tuskegee is revealed and there is a national commission to look into that, and then the formulation of the National Research Act in 1974.

In 1974, we have the promulgation of what are the basic federal regulations which we still use today, something that becomes the common rule and, you know, policy types -- this is fun stuff to talk about; I will spare you at this hour of the day. But, the National Research Act also brought you the National Commission for the Protection of Human Subjects and Biomedical and Behavioral Research. What the national commission did is find that the use of philosophical principles could also be helpful in research.

The national commission issued what is known as the Belmont Report. The Belmont Report is so named because it happened at the Belmont Conference Center in Maryland. In writing a government report you don't have to have a great title. No fancy advertising; people are still buying it.

They announced three ethical principles -- sounds familiar, doesn't it? -- respect for persons, basically autonomy; beneficence and the corollary principle of non-maleficence is there; and justice.

Well, scientific success changed this need to protect people from research. There was the availability now of effective therapeutic agents that bolstered a considerable amount of trust in scientific enterprise. Protectionism began to seem inappropriate, especially through the '80's with the advent of the AIDS epidemic where folks with AIDS lobbied hard and basically came to scientific meetings. I remember presenting at a 1990 international AIDS conference and people were protesting, not my talk, the ethics talk, but plenty of people's talks. Scientists didn't get it. Why are you protesting? We are on your side.

The argument went the other way. We want access. We are dying; we have nothing to help us. Let us have it. We don't care about Phase this or that, we care about access. Martin Delaney of ACTUP says that clinical research is treatment too.

This then fueled a series of debates. Cancer activism followed and now just about folks with every disease that is devastating have felt the rally cry, and a pendulum of justice -- this is still a question of justice; it is about the ethical principle of justice but it is no longer protecting vulnerable populations, the pendulum now is towards access.

Well, we now need to understand one piece. It is