fit any of the protocols. Those are the things that raise all kinds of questions of capriciousness, and as many people have pointed out, there ought to be a plan for dealing with those, but someone, somewhere wants to try this drug in a different tumor, that doesn't seem to raise too novel issues, that sort of in some ways happens all the time. This is more like a case where the company isn't directing it, but that's okay, they are not all-knowing.

DR. NERENSTONE: Ms. Linden.

DR. LINDEN: I would like to respond to a couple of comments that have been made around the table and also mentioned this morning and also at the December hearing.

First, I would like to respond to Ms. Platner regarding equity and justice, and that this is the time to move on from focusing on those issues. I am afraid--or I am not afraid--I actually view those issues differently as a bioethicist.

The way that I view them is that equity and justice are ideals toward which we strive and in any arena, whether it is experimental therapies or democracy or what have you, we never accomplish

fully our ideals. We use them as beacons toward which we are guided.

I would also like to respond to a comment that Mr. Erwin made, as well as Dr. Williams, in part of the discussion last December that has really stayed with me over these past five or so months, and that is the issue of communication.

Dr. Williams this morning proposed--perhaps "proposed" is too hard a version--suggested the possibility of a consensus conference at some point to lay a framework for the issues of treatment INDs and expanded access. I think that is a wonderful idea, but I do believe that we are very far from a time when it would be appropriate to hold such a conference.

Bob Erwin's comment about communication, I think is extraordinarily important, and the sort of communication that I am most concerned about is of the sort that was mentioned at the hearing last December, and that is communication between and among industry, PhRMA and its constituent members, large pharmaceutical companies, and small biotech start-ups, community members, activists, consumers, physicians, the FDA, the NCI, HMOs, which have a rather significant role in those communities where

they are dominant providers and how clinical trials are enrolled.

I hope that the call for meetings where these various stakeholders can get together and begin to talk about their concerns, the fiscal concerns that you mentioned, Dr. Taylor a few moments ago, so that we can really begin to hear each other and find out what our points of agreement are, what our common ground is, and where we have fundamental disagreements. That is not going to happen at a consensus conference. A consensus conference is for down the road in my view.

Thank you.

DR. NERENSTONE: Mr. Dixon.

MR. DIXON: Yes. We have gone around and around once again on this information and access, and justice and equity point, and I would like to remind everyone that we do have a statutory basis for a clinical trials' database, which is largely ignored by industry involved in FDA-related trials.

I would hope that this group would suggest strongly to the agency that it work more aggressively with industry to assure that those trials are available on a database, so that

patients can find out about them wherever they live. I think this would go a long way towards answering some of these access questions.

I also think that if all cancer trials at the FDA were within one office, so there were similar rules across the board, that that would also be a big step forward.

Thank you.

DR. NERENSTONE: Dr. Albain.

DR. ALBAIN: I do think, though, in relation to the concept of a consensus conference and national dialogue, that we are in a new era, though, with our new agents, our molecular targeted therapies, and, in fact, we are now seeing trials open and close in 6 to 8 months with expanded access trials opening before the investigators know even the toxicity profile of the agent.

So, I think it is clearly necessary that we rapidly reach some consensus about how at least an expanded trial process should proceed nationally.

DR. NERENSTONE: Dr. Sledge.

DR. SLEDGE: After hearing so many wonderful discussions here, it is hard to add a whole lot, but just three points, if I could.

First, the issue of justice. I mean in essence in this very wonderful philosophical discussion, we are basically talking about two very different concepts of justice.

One is sort of utilitarian justice of, you know, the greatest good for the greatest number, which would suggest that justice is best served by getting a drug onto the market as quickly as possible, and therefore doing the best trials as quickly as possible, and anything that holds it up will delay justice for the majority.

The other form of justice, of course, is individual justice, what can we do best for the individual.

These really are very different concepts of justice, we have got to recognize that.

Second, from a scientific standpoint, leaving aside the issue of expanded access, which I don't think is what we are discussing here, but rather the use of single patient use setting, can we get anything scientific out of single use indications? My bias is no. My bias is no because, first, the physicians who are involved in the system as a rule of thumb are not clinical researchers, and they are not used to or very good

at collecting clinical research data.

The patients, as a group, tend to be very poorly characterized, and therefore, even the adverse event data that you get out of these single use indications I think is highly flawed and is confounded by the patient's underlying disease in most cases.

Is it possible that we might be able to get some signal data from an efficacy standpoint in terms of rare tumors? There, I suspect, yes, it is possible. Certainly, if one looks at the history of, say, a treatable cancer like testicular cancer, where actually the initial signals did come out of Phase I programs, and out of individual patients responding remarkably well in a rare tumor, I think it is at least possible that there may be at least some potential for getting that sort of data.

Third, is a toxicity issue. We have talked a lot about informing patients, but the truth of the matter is that for drugs in early development, we really don't have much to tell patients about the drugs.

Talking about issues of informed consent with patients with a drug that has only been through a Phase I trial or very early Phase II

trial is pretty nonsensical, to tell the truth. Most of the time we just simply don't know anything about the range of activity of the drug, and we truly don't know very much about the toxicity of the drug. Most of the scary side effects that we end up discussing with patients down the road, we learn as a result of large Phase III trials rather than Phase I and Phase II trials.

So, my bias is that a lot of the bureaucracy that surrounds single use is pretty much wasted bureaucracy. The sending of a protocol to an Institutional Review Board, you know, the informed consent discussions that go around this, I think by and large really are done primarily for lawyers rather than for patients. I am truly not sure how much they benefit the average patient.

DR. NERENSTONE: Again, I have a question, a point of information. Somebody raised a question about centralizing the database for patient access to trials.

Would someone comment about PDQ and whether that has expanded access protocols listed on that, does anyone know?

MS. DELANEY: We request that the companies list their expanded access protocols in

the PDQ. Compliance with PDQ, in general, though, has been very poor, as Carl Dixon said. There are currently 1,850 clinical trials in the PDQ database, and the number of industry-sponsored trials in that database, the highest it ever got was 200, and it is now going down again in spite of the law that was passed.

So, this is the single largest place that a patient can find out about an ongoing trial or if they are not eligible for an expanded access protocol that may be in there, they certainly can find out about another trial they might be eligible for, the compliance with it has been poor to miserable.

DR. NERENSTONE: So, maybe one of the suggestions can be that because the mechanism exists, that drug companies should be encouraged--I don't know if we can say required--to comply with that in terms of helping them with their accrual, as well as patient information about existing studies. Because the mechanism does exist, we shouldn't have to reinvent the wheel.

Other comments?

MR. DIXON: If I could just supplement that, the statute on that particular database says

that they shall comply, so it is not a question of whether industry wants to do it or not, the database is there. It is just that they are not doing it.

DR. NERENSTONE: Could you please introduce yourself for the members of the committee?

MS. TOIGO: I will. I am Terry Toigo. Part of the law that Carl Dixon is referring to is a section of the Food and Drug Modernization Act, Section 113. FDA developed guidance and put out guidance about a year ago. We will have another guidance document available very shortly that will tell sponsors how to get their trials into clinicaltrials.gov, which is the database that the government developed to respond to Section 113 of FDAMA.

So, that will clear up any--we have already given guidance on which trials need to be put in that database. This will tell industry how to get the trials into the database. It is required, it is a law.

The reason they are not doing it--Dr. Temple asked me how come companies are not doing it--Congress passed a law, we are developing

guidance. We needed to get a mechanism in place for companies to submit their trials, and that has been now developed.

DR. NERENSTONE: Dr. Redman.

DR. REDMAN: Again, I am probably just going to reiterate what Dr. Sledge said, you know, there seem to be two issues here. The one that I came prepared to discuss, I guess was the access to investigational agents, not therapies, outside the context of a clinical trial.

I think that process, that access does co-opt the clinical trial, not that that person is not being put on a clinical trial, but the fact is you are making an assumption that the clinical trial is through and you know the answer, and there is some therapeutic benefit.

I really think that is a fallacy, and I tend to agree that the whole process of single patient use or access to an investigational agent is a lot of waste of time, both at the regulatory level and at the physician level, and there is no information that is gained from that.

Some of the other comments, though, are dealing with better access to clinical trials, and I do agree, and there have been meetings at the

NCI, at CTEP, regarding this process. I think that process definitely needs improvement, but I don't think this committee is going to improve it.

DR. NERENSTONE: Dr. Linden.

DR. LINDEN: In response to the comment, the clarification of the regs for the database, as with any requirement, requirements don't hold a lot of water unless there is enforcement, and I wonder if there is or will be enforcement of entering trials and updating information as it is appropriate. That seems to me that it would be quite essential.

DR. NERENSTONE: Mr. Erwin.

MR. ERWIN: Leaving the broader questions of clinical trial design and expanded access and just going back to individual access for a moment, I think there is an additional perspective to consider, and that is the hope by a lot of scientists, and certainly families and patients, that newer technologies will lead to more efficacious products and the sometimes very reasonable hope that what an individual is trying to get access will, in fact, turn out to be one of those.

For example, had it been necessary,

although I guess in many cases it wasn't, for an individual to attempt to get access to Gleevec, there is a good chance it would have been beneficial, at least with the data that is currently available today.

So, as more and more targeted therapies, as they have been called, come along, the importance to an individual of individual access might actually increase.

I think that the mechanism that is in place now, which the FDA very infrequently blocks, where an individual's physician and a company can choose to voluntarily provide individual access, certainly works sometimes, and what we are talking about is how to, one, make it fairer, to make it perhaps less complex, perhaps streamline it, but more importantly, to integrate it into the broader context of the two forms of justice that Dr. Sledge referred to.

The additional perspective I think we ought to keep in mind is that the drive by families and individuals to survive a disease like cancer is going to go on no matter what policy decisions we make, and, in fact, if individual access were completely blocked, there would still be consistent

persistent attempts at access to something.

In fact, in the United States right now, patients can get access through the legal clinical trials mechanism, drugs that most of us in this room probably believe do not work, and for which those patients pay thousands of dollars in full compliance with FDA regulations or at least close to full compliance, and many of us consider those particular kinds of trials to be fraud, but they happen to fit within the legal framework that has been set up.

Alternative therapies are another whole category. People fly overseas for all sorts of bizarre treatments. So, that demand and that drive for a cure, as unreasonable as it may be, needs to constantly be factored back into the decisions that are made, particularly when there is an attempt to provide guidance and education, because they are not going to go away and in the face of advancing technology, that hope will continually be fueled whether it is false or not.

DR. NERENSTONE: Dr. Spiegel.

DR. SPIEGEL: Listening, I would concur with some other speakers that there seem to be a lot of issues on the table including general access

to clinical trials, participation in either the government or there are many--I think there are still some around that are trying to make public databases and for-profit companies that have some very clever ideas about how to overcome some of the issues that have been raised with the government databases and providing a third party who could screen patients for companies who could post their trials, but I think that is a different consensus conference.

What I wanted to mention was I think both in the December meeting and on 60 Minutes, but what we have heard is probably a very appropriate level of frustration that it is hard for people to penetrate both Big Pharma and little biotech companies to understand what stage drugs are at and whether any single patient exemption is available.

I am certainly taking home something that we could all do is to just challenge our own public relations departments to see if our web sites or 800 numbers could be more clear, so that people could even get a fast answer, that we do not at this time have a compassionate use or an expanded access program for any indication for a drug if it is at a very early stage of development, just to

give people answers, so they don't feel they have to keep knocking on doors.

I would like to raise a different issue, though, and I guess I would ask Dr. George or maybe, I know Dr. Temple has thought about this often, is just to go to the concept of equipoise that we apply when we do a clinical trial, we convince ourselves that it is ethical to randomize to standard therapy versus experimental because nobody knows the answer, that one arm of the trial is better than another.

But somehow when it comes to a compassionate use, we seem to be saying if I am doing a trial that has 25 inclusion and exclusion criteria, and a patient is not eligible, but I am doing the trial to find out if it works in that disease, somehow I should be considering compassionately that somebody whose creatinine is too high or had too many prior therapies should have access to compassionate use when there is really no evidence, you know, by the usual criteria of evidence, that it is likely to work. So, I don't know if our statisticians or people who have thought about clinical trial development would want to comment in that.

DR. GEORGE: A brief comment. There is one issue that you brought up obliquely there is the issue of eligibility criteria in clinical trials, which is something else off the topic here, but I guess it is relevant in some indirect ways, that I think it is true in cancer particularly that the eligibility criteria are often too rigid.

That is, there are too many eligibility criteria. That, of course, then leads to the situation of people saying, well, not many people are entered on clinical trials in cancer, and one of the reasons is they are not eligible for the clinical trials that are available. I mean there are trials that are there, but they can't get on them because they have a long list of eligibility criteria.

But it is just the issue of whether, then, not meeting the eligibility criteria, why people seek these compassionate use or whatever we call them mechanisms is just a human one, I think.

DR. NERENSTONE: Dr. Williams.

DR. WILLIAMS: You may wonder why we titled this single patient use. It was really to try to focus on the questions we asked here, which is the dilemma that we are often faced with, is

when should we say no, the FDA say no, you know, according to following the guidelines and law that there is there isn't adequate safety and efficacy to allow this person to receive the drug. That is our responsibility.

I think many of the questions we are hearing addressed, but what we do need to address in the future and may or may not be our responsibility, but I would like to make sure we have time to ask--I think we have good groundwork for it--but the questions about when should we absolutely say no, when is it basically, I would say, unethical or unwise or unsafe for us to allow use.

The only reason we put single patient use is because it avoids the likelihood it is going to interfere with the trial or all these different issues that industry might be concerned with, the cost, et cetera, and more, in the time remaining, perhaps focus on when should FDA say no, and then in the future, we hope that there will be a process where we can address some of these other issues.

DR. TAYLOR: I would like to make a comment to answer yours, but also about what was said earlier about frustration. I think what I see

as much as frustration about not being able to get an answer is frustration about dying. I think that is the whole basis of a lot of this is frustration about dying and the realities of medicine and what man can do and what God can do.

I do think that that is part of what I am talking about in terms of patient education. I may not know what the toxicity of that Phase I drug is, but I do know the likelihood of response based upon other Phase I trials, and I have to be frank and honest about what man can do, and that is a very important part of this whole thing.

A lot of this is dealing with the frustration of dying and our inadequacies in medical care.

I would like to go back. I think that I would agree, that I think that a patient whose performance status is so poor that we don't consider them able to tolerate or to respond to standard curative therapy would be a very reason not to agree to provide that type of drug.

I also have a very hard time saying that we are going to give Phase I agents out when we have not even obtained a dose level that we know could be used in a safe fashion. I think in that

setting that we do give, as you alluded to, with your equipoise, we do give the implication that we think this drug is better and before the trial is done. We don't have the trial done, and we imply by allowing that, that we know it is better.

We don't know it is better, we just don't know, and it is a big zero in the column as opposed to a 10 percent response or a 20 percent response from the standard things.

DR. NERENSTONE: Why don't we then ask for Dr. Williams, focus our discussion more specifically on the questions, and we can further have discussion under that framework that might be more specific to what the FDA needs us to accomplish this morning.

I am going to just go to the Questions to the Committee. I think that we have had extensive discussion about just to very briefly the FDA is seeking advice from us in its role of assessing the risk-to-benefit ratio of treatment use with an experimental drug in an individual patient, and when determining the apparent risk-to-benefit ratio, the following are important considerations:

How thoroughly has the drug been studied in humans?

What do the preliminary results from these studies suggest about the safety and efficacy (or activity) of the drug?

What are the other therapeutic options available to the patient?

They feel that those are questions that need to be in the context of those kinds of issues.

I would like to go to our first Questions to the Committee.

For each of the following clinical scenarios describing standard therapy, please discuss the following question:

The FDA receives a request from an investigator to use Drug X under a single patient IND. The commercial sponsor of Drug X has granted permission for the investigator to use the drug and also has provided written permission for FDA to refer to the commercial IND, so that has all been taken care of. The patient's medical history is outlined in each of the scenarios below.

The investigator states that the patient is aware of the benefits of standard therapy but wants to receive investigational treatment with Drug X instead. The patient is ineligible or unable to participate in a clinical trial using

Drug X.

When would single patient treatment with Drug X be appropriate?

They would like us to discuss it in the context of the drug's stage of development, the level of efficacy and toxicity that would be acceptable in the following standard therapy cases.

So, that is setting the scenario.

The first is there is no standard therapy available, and essentially metastatic--I guess you mean extensive--non-small-cell lung cancer that has received all available therapy.

I think that probably we need to talk about what phase the drug is in, Phase I, Phase, II, Phase III, as to when that would be appropriate, so each of these.

The first would be Phase I. Would it be appropriate for a patient to receive a Phase I drug with non-small-cell lung cancer after all available therapy has been exhausted?

Discussion from the committee?

DR. WILLIAMS: Dr. Nerenstone, we are not really asking for votes on these. We really would just prefer to get discussion.

DR. NERENSTONE: I will lead off. I would

say no. I think in any of these scenarios, a Phase I drug is really not appropriate for widespread or even limited single patient use. We have no idea of the toxicity. How can you even do an informed consent if you not only don't know the drug dose, but have no idea of the toxicity.

So, I would say because of lack of data, informed consent becomes meaningless and therefore, the potential to do extraordinary harm remains high, the benefit remains most likely very low. So, I would say pretty much under no circumstances do I think a Phase I drug should be given out for single patient IND, single patient exemption.

Dr. Kelsen.

DR. KELSEN: I agree. I was thinking about this. If it is truly an experimental drug in Phase I, it is not a combination of conventional agents being used in a Phase I trial, which gets a little tricky, so if I put that aside for a minute, and it is really a new drug, you are at Level 2 or Level 3, you have no idea of the toxicity, you have only treated three or four patients, maybe up to six, to provide that outside of a carefully, carefully supervised trial would make me very uneasy.

DR. WILLIAMS: As a devil's advocate, there is an informed consent in your Phase I trial, and for that patient it is okay, but you are saying since you don't have a controlled setting, that would be another--

DR. KELSEN: Right, obviously. There is two settings this happens in. You are the investigator at the center doing the Phase I trial. The patient is not eligible. The level is not open, which is even more difficult, they are eligible, but the level is not open.

But you know very, very little about that drug. That would make me very uneasy, make me extremely uneasy. The patient is not at your center. They read the PDQ. They understand there is Drug X that is being studied in New York or California or wherever, and they want to receive that drug from a physician who is not even involved in the study. I think that is really a bad idea.

DR. NERENSTONE: Dr. Przepiorka.

DR. PRZEPIORKA: I would have to agree that anything that has not been studied or is still in Phase I or just completed Phase I and going to Phase II, should not be used in a single individual patient.

I don't disagree with the terminology "treatment IND." I think that pretty much says it exactly the way we intend it to be. It is not a single patient experiment. It is a single patient treatment. So, in the interest of time, I would actually suggest that we not even entertain Phase 0 or Phase I drugs in the rest of the scenarios.

DR. NERENSTONE: Is that the feeling of the committee? Mr. Erwin.

MR. ERWIN: I think it is useful to draw a distinction between single patient exception and a single patient IND, because that also addresses the confidence of the investigator and the quality with which that patient will be treated.

DR. WILLIAMS: You are suggesting that it might be acceptable at a Phase I center for someone who didn't fit on the protocol, that they might consider treating them off that protocol, is that what you are suggesting?

MR. ERWIN: Yes, that is my suggestion.

DR. NERENSTONE: Why, I guess is my question, why would you consider doing that?

DR. KELSEN: We should be very careful about that because the parameters for a Phase I trial usually involve very small groups of people

at each level, and it is a very common scenario to say, you know, you talked to me about Phase I studies and you told me that you might be opening another level, and it is not, but I did fit the criteria and I want to go into that. I could imagine that having a level of 20 people in no time flat without really knowing all the side effects.

MR. ERWIN: I would agree that it requires care, but in this case, a single patient exception to the study, you have got the primary investigator who is running the Phase I study, who may be the physician involved. You have got the patient, you have got the IRB. There are multiple levels of decisionmaking in this case which have all gone positive.

My suggestion is that you don't need broader government involvement in that decision. At that point, you have got enough competent people who have said yes, I want to do it. It comes back to that issue of patient autonomy.

DR. KELSEN: It implies that a patient can say I understand that the study is not open, I understand you don't know very much at all about this drug, you have only treated the first few patients, but I want you to treat me, and you could

have that situation, you could have a number of patients who are requesting that therapy when you know very little.

DR. TAYLOR: You don't have true informed consent because your informed consent for the Phase I trial says I am not doing this for a therapeutic benefit, I am doing this to find the side effects, and that is not the same as doing it for treatment.

The objectives of a Phase I trial are to determine the MTD and the toxicity of that drug, and by treating that patient off of the study, you don't succeed in getting your objectives, and the patient, in my opinion, is being treated with something that therapeutically, has a very little chance of responding, and they are not understanding that.

DR. SLEDGE: I can't accept that. You have to differentiate between why we do Phase I trials and why patients go on Phase I trials.

DR. TAYLOR: I don't disagree, but I think you still have to--

DR. SLEDGE: I mean the idea that a patient goes on a Phase I trial without any hope of therapeutic intent is ridiculous.

DR. TAYLOR: And I don't do it without any

hope of therapeutic intent, but I think the realities of it or the objectives of that trial are not for therapeutic benefit at that point.

DR. SLEDGE: I am well aware that that is your objective, it is not the patient's objective.

DR. NERENSTONE: Dr. Redman.

DR. REDMAN: Basically, this is for Dr. Kelsen with Mr. Erwin. Having reviewed off-site Phase I trials, what you are suggesting, many investigators have had their trials pulled for doing that. It is inappropriate, it is unethical, and not within the rights of the patient to demand treatment on an investigational trial outside the confines of that trial.

We are talking about allowing Phase I. I mean I can go all the way up to Phase III and say no.

DR. NERENSTONE: Dr. Albain.

DR. ALBAIN: I think we have the real potential of doing harm. That has been alluded to, and we cannot allow patients in these early Phase I trials that are designed very deliberately with rigid eligibility criteria to protect the patient.

We don't know the metabolism. You know, the creatinine criteria may be very, very

appropriate, and you put someone on with a creatinine of 2, you could kill them.

DR. NERENSTONE: I think that the FDA, that the take-home message that I see is that there may be a real division between the medical community and the non-medical community over this issue, and I do think that the medical community, many of whom around this table have been involved in Phase I research, is struck by how potentially harmful this could be.

In our role as physician, someone pointed out how research treating a group of people under research and treating patients individually sometimes come into conflict. Our fear is that in this particular case, it is the physicians who are worried about doing harm, and the non-physicians who perhaps don't understand our fear of doing harm to the extent that we are--I don't want to say horrified at this idea--but certainly strongly against Phase I drugs being released.

DR. WILLIAMS: I think that was a very good discussion, and it will be useful.

DR. NERENSTONE: Again, with the standard patient with metastatic non-small-cell lung cancer, what about a Phase II agent? Discussion.

DR. KELSEN: This is a little trickier because this happens also a great deal where there is an agent that is under study in a given disease for which we now know perhaps a good bit about toxicity. It may be a multicenter trial where there is information from a number of investigators, so that you have a better feel for the dose and the schedule. You know it well enough to go forward, and you are already beginning to see preliminary activity.

Now, you have made even maybe a preliminary report in some meeting, not necessarily an open meeting, which very rapidly begins to disseminate, and you have a patient who has no options, would ordinarily be a candidate for the study, but they have something that withholds from the study, which is not felt to be a safety issue, or the study, even worse, has now filled its accrual in that particular center, and the patient says, you know, I know that this drug is working in 22.5 percent of patients for Temple, and I would like access to this agent in my disease for which you have exhausted all the conventional options, and we face that every day.

DR. WILLIAMS: What about some patients

treated, but no activity, or just the first few patients have been treated?

DR. KELSEN: I think that is very important. So, even within Phase II, I guess the suggestion is even within Phase II, there are gradations as to when treating a patient with single patient use, it becomes more reasonable and less reasonable, and I agree with the implication that I have treated three people, I haven't a clue.

DR. WILLIAMS: I would like to hear the discussion. Is it just you need to know it is safe based on Phase I, or is it that you have to show some activity? Where do you find it reasonable or not reasonable?

DR. KELSEN: I am speaking personally for myself. I have only treated a few patients, I have no evidence of activity, what is the compelling reason that we should use this agent in this situation as opposed to the latter.

DR. WILLIAMS: It is a different question, though. It is not whether you have compelling reasons, you and FDA, you have come to work for us, and you would say no if someone wanted to. When should we say no, if there is no activity, should we say no in Phase II, or should we say yes?

DR. NERENSTONE: Dr. Redman.

DR. REDMAN: I think if the FDA is willing to approve a drug on Phase II data from 40 patients, I think the FDA should say fine, but if you are not willing to approve the drug, I would ask the medical members here how many agents that have gone through Phase II trials or to Phase III trials, have shown increased efficacy over and above that in a Phase II trial?

I think it has always been the exact opposite. It has always been in Phase III trials where the efficacy has either maybe been equivalent, but more likely has been less. So, I think, again, even if we have an ASCO abstract from the Phase II trial that suggests that there is a 25 percent response rate of an agent, that that still does not require it to be given out on a compassionate, single patient, however you want to define it, unless the FDA is willing to say, gee, based on that information, we will approve the drug, we recommend approval of the drug.

DR. NERENSTONE: I see this as a little bit more of a gray area, and I could see where patient pressure and physician pressure could be brought to bear after several, either one or

several encouraging Phase II studies are released.

I agree, the likelihood that this patient is going to benefit is indeed quite small, and I think no matter what, that you still have to have performance status criteria, and you probably have to have end organ criteria, because treating someone again with a bilirubin of 12 in a new drug is very likely to be toxic, especially if we haven't had a lot of experience with it, and you can set up those end organ targets as to what would be appropriate, but I think that later in Phase II, when you actually have some published data, I would make the argument that I could see at least the potential of releasing that.

My feeling would be that you would try and do it in open access because as soon as that kind of data becomes available, especially for something like small-cell lung cancer, it is not going to be one or two patients who are interested in it, it is going to be many patients who are interested in it.

Mr. Erwin.

MR. ERWIN: I just wanted to add one further perspective on that comment about indications of effectiveness. The reality is that a lot of times, particularly biotech companies,

don't even go to Phase II unless they have some indication of efficacy in Phase I.

I know that that doesn't fit the traditional and official criteria for Phase I, but they use non-validated surrogates to get some indication of efficacy before making that decision to go forward. So, the Phase I, Phase II, Phase III distinction in many respects is even less clear when it is now possible for a Phase II trial to be designed for and designated as pivotal.

I think, again, my opinion comes back to the individuals involved, the patient, the physician, and particularly a clinical trial's experienced physician making a decision about possible benefit.

DR. NERENSTONE: Dr. Spiegel.

DR. SPIEGEL: I would ask if Grant could clarify the position the FDA is in. If we are really talking about a drug that is in Phase II, I would pose that nobody knows during that period where you are.

If a company comes to the agency at an end of Phase II meeting and lays out all of the single study or all of multiple Phase II's, and then the agency could say it has knowledge of a level of

activity, but if you are called about a drug by an investigator, by a patient, who knows of one anecdote that looked great, or I think the last comment is very good, even if Phase I had a proof of concept aspect to it and some biological principle was confirmed in Phase I, into and end of Phase II, you don't know what the true response rate is.

So, I think you should be comfortable saying we don't know where we are if someone requests it during Phase II.

DR. NERENSTONE: Dr. Temple.

DR. TEMPLE: I guess I want to press you, Stacy, on the practicalities here. What I heard you suggesting is that until people are ready to provide quite wide access, treatment IND or its equivalent, then, it doesn't make much sense to have individuals do it, but there are some practical considerations.

Companies are not always ready to provide wide access, but they like to use the, I don't know, pressure-releasing ability of a few individuals getting the drug in the situation where conceivably, if asked, we might allow a treatment protocol, but nobody has actually asked for one.

That raises all the questions of unfairness and capriciousness and people being in the know and all that. Do you have any further thoughts? What you were suggesting I think was, well, once you know enough to have anybody on these things, you probably know enough to have a lot of people on these things, but what about the practicalities, should we be saying no until you are ready to do it for everybody, it is not really fair or equitable to do it for a couple of people? What are your thoughts about that?

DR. NERENSTONE: I think I was hoping in the best of all situations, and I am very sensitive to the fact that especially the smaller companies are not going to have geared up and are not going to be able to provide wide access, in the best of all situations, especially with a lot of patients with a disease like lung cancer, I just see this as opening the flood gates, and you have to be prepared for the flood gates to be opened.

Do I think we should absolutely prohibit single patient treatment in later Phase II, if they can't do that, no, I am not going to take that hard a stance.

DR. TEMPLE: Would you want it to be done

in some way that was fair even if limited? There have been lotteries, for example, where a company wasn't willing to do it for a million people.

DR. NERENSTONE: Absolutely, I think that is exactly right. Then, you have to be prepared for the flood gates to be opened, because I think they will be, and I am not saying that that is necessarily a good thing. I don't see it as a good thing, but I think that is bowing to the realities.

Dr. Albain.

DR. ALBAIN: You actually just stated what I was going to state, Stacy, that I we are in some of these situations right now with some of the new molecules and that the pivotal trials have completed, and we don't have all the answers, however, there have been abstracts presented in national meetings, and the companies have come forward with lotteries with expanded access programs, and I think that is the place to refer our patients to rather than going through the cumbersome process of a single use situation.

Although we weren't asked specifically to address that, that is why I said earlier that having a rapid consensus nationally on how to mount these trials, how to help some of these smaller

companies do these through perhaps a central mechanism when they cannot mount them individually would be very useful right now.

DR. NERENSTONE: Dr. Blayney.

DR. BLAYNEY: I think I would support the business of single patient exemptions, and I think you ought to build that into your drug development process. At the end of Phase I meetings, one of the questions you might ask the sponsor is if this really looks good, how do you propose a fair and equal expanded access and at what point would you feel comfortable doing that.

Some sponsors may have limited production facilities, and that needs to be known in advance, and I think it would give the agency, as well as the sponsor, as well as the physicians and patients who want access to these programs a better idea of what the ground rules are going in.

I think also, if I may say, there may be some compelling biologic reasons that may emerge that you may want to give expanded access if there are peculiar molecular targets that either are known in advance or known beforehand with individual patients whose tumors demonstrate potential susceptibility to these molecular

targets, you may want to build that into your thinking, as well.

DR. WILLIAMS: Could I clarify the rationale that several of you have expressed? I very clearly understood during Phase I, it was a patient safety issue, you didn't have the data on patient safety, but in Phase II, we do have the data on safety, and you are entering your patients with the hope of seeing a response rate or whatever, and now perhaps you have other patients that don't fit on that.

A company comes to you and says we are early in Phase II, but we have a patient here that doesn't fit, we would like to treat him by special exception use, and your rationale for not giving that patient an investigation agent, if they want to, if the company wants to, is what?

DR. NERENSTONE: I think in early Phase II, it is still a toxicity issue. You know, very few patients have been treated on that, and so it still could be much worse than placebo. So, the idea of, well, doing no harm, I think is still an issue here with early Phase II.

Dr. George.

DR. GEORGE: Actually, my comment is

related to that, and Dr. Williams' comment some, and that is just to remind people that the notorious unreliability of Phase I data, even with respect to toxicity, these are very small studies done with very restrictive eligibility criteria for safety reasons, and then at the later stages, those criteria change and just from a statistical point of view, these studies are known to be very reliable.

I have certainly been involved with a number of Phase II and even Phase III studies where we had to radically change dose and schedule because of unexpected things.

So, you can't say that just because the Phase I test is over, we know the toxicity, so everything is okay about that, now, all we are concerned about is efficacy.

DR. NERENSTONE: Dr. Linden.

DR. LINDEN: One argument I heard a little while ago was that because Phase I--I am going back to the Phase I question--because Phase I trials have scientific objectives only, not treatment objectives, under the scenario, treatment IND requests should be denied, but Phase II or Phase II/III trials also only have scientific objectives,

not treatment objectives.

So, there is a little bit of slippery ground there in this group as to whether treatment INDs should be permitted at all.

That is my comment.

DR. NERENSTONE: I think most people would say that Phase II studies where you are looking for disease response is a surrogate endpoint for patient benefit. You are perhaps right in that that is an abstract concept that we have not yet proven, but certainly the expectation is that tumor response, which is what we are measuring, is going to be correlated with symptom relief and more.

So, I think that most of us who do clinical trials would say that Phase II and Phase III studies really do have patient benefit as a goal of the treatment.

DR. NERENSTONE: Dr. Przepiorka.

DR. PRZEPIORKA: I just wanted to address two issues regarding the Phase II studies, and that is if we go back to the terminology treatment IND, if we are really going to treat the patient, then, we really do need to know not only safety, but efficacy, there is no question about that.

I just want to broaden something that Dr

Nerenstone said about having performance status requirements for those sorts of treatment INDs and that even when we pick up the journal and read about a new drug that has come out, we have to read the Method section to see who was the patient population that was studied.

When we sit down with the patient, we have to tell them the results based on whether or not they fit those eligibility criteria, so I would even suggest that for a treatment IND, the patient has to actually fulfill the eligibility criteria for the study from which the activity was shown.

Anything else is going to be a new study, and as was pointed out, even in Phase I studies, and Phase II studies, eligibility criteria have had to be changed because of that, and if you come to the single patient exemption question, you know, it would be valuable data to find out whether or not the safety of that drug in such a patient would be of value, but it has to be done in a controlled setting. That means another study. It has to be done with more than one patient.

DR. NERENSTONE: So, Donna, you are making the safety argument that even Phase II data may not be reliable enough to translate into a patient

treatment.

DR. PRZEPIORKA: If the Phase II study is completed, and we know the activity, we know the safety, and we know the patient population, then, I would say yes, that would be somebody who you would give a treatment IND to while you are waiting for Phase III or other progress and development, but if you are still within the Phase II and you don't have the results yet, then, no, there is no indications to treat someone with that drug.

DR. NERENSTONE: Dr. Kelsen.

DR. KELSEN: I agree, the issues for Phase I, first of all, all studies have scientific aims, they have primary objectives and secondary objectives. Most Phase I's or at least many Phase I's, the secondary objective is to look the therapeutic efficacy, but it is not the primary objective, it is the secondary objective.

The primary objective of Phase II and III is an efficacy objective. It is not a scientific reason you are not treating people on Phase I for the single patient use, it is really just safety. You just don't know the right dosing schedule, and you put the patient at risk.

DR. NERENSTONE: Dr. Averbuch.

DR. AVERBUCH: Mostly to respond to Dr. Blayney's comments, and I think to echo some of the last speaker's comments about it is only going to be at the end of Phase II where we begin to have a level of confidence about benefit-risk, and it will depend on the drug, on the patient population, on the trial design, but I think it is only at that point by which you can begin to make judgments about expanded access and whatever setting you provide.

The other point I want to make, I think I want to throw out a very extreme caution about trying to have different rules for these molecularly targeted, defined agents. I mean those are still hypotheses, and I think we still are bound by the principles of good clinical trials to either satisfy or refute those hypotheses based on clinical outcomes.

I mean the hypothesis existed that specific antiarrhythmics would lead to improved mortality in cardiovascular disease, and we know the outcome of some of those trials. So, I think we have to be very cautious about changing the rules for those molecularly defined agents.

DR. NERENSTONE: Dr. Temple.

DR. TEMPLE: I just want to observe that what you are all saying is entirely consistent with the rules of treatment IND. There has to be reasonable evidence of effectiveness, obviously not quite enough to get the drug marketed, but something less than that, but still some, and there is actually a slightly different expectation when the disease being treated is fatal, which I guess is the case here, and the rules suggest that it will be very unusual to do that until the end of Phase II or thereabouts where you have some evidence, so what you are saying is quite consistent with the current definitions.

DR. WILLIAMS: But not necessarily the same as what has been done in, say, single patient use.

DR. TEMPLE: Well, no, that is right. I thought what Dr. Nerenstone said earlier is that one should think of single patient uses that aren't to learn something, but to provide access as roughly similar to being ready to allow for almost everybody. That is what I heard before, which is an interesting formulation.

DR. NERENSTONE: Ms. Delaney.

MS. DELANEY: I would just like to say

something as a practical matter from the experience that we have in our office, that while the focus of our discussion is clearly advice to FDA and how we should handle single patient INDs, our practical roll up the sleeve experience with this is that companies usually start by saying yes to single patient INDs, and their entire, let's call it compassionate use until we change it, the compassionate use plan is unanticipated.

It is sort of like tumbleweed and it starts to roll, and then panic sets in, and many times also I think these are always good people caught in a bad situation, but nobody wants to say no to the patient, and so oftentimes companies will refer patients even today inappropriately to us, knowing that the answer is no, but we have to turn them right back to the company and say this is a decision of the company.

My request is that sponsors anticipate this ahead of time. Think ahead what will the triggers be to when they might consider a treatment IND, when will they consider an expanded access protocol, under what circumstances will you allow single patient INDs, and not get the patients and family members caught up in the phone calls back

and forth to FDA saying no, it is not our job, it's the company's job. It is really very distressing for people who are, for the most part, at the end stage of their life.

DR. NERENSTONE: Dr. Santana.

DR. SANTANA: One of the problems I have with this whole discussion is--and I think it was presented by one of the patient representatives earlier in a letter--was that we are really talking without having much data in front of us and we are trying to make these rules, if that is what the FDA wants us to advise them on, on how to put patients in these categories to allow this or not to happen without really knowing what the real world is all about.

It was triggered by Donna's comment in the sense that for a patient to get one of these drugs under the mantra that it is non-research, but it is still investigational blah-blah-blah, that they have to meet some eligibility requirements that are very similar to the patients that otherwise would go on the Phase II study, but the reality is that I bet you that a lot of these requests are because patients do not meet the eligibility requirements as stated in the protocol or for many other

reasons, that they may not have access, they live a long distance, so we are dealing with a whole heterogeneous set of reasons of what initiates the process to request a practitioner or a patient or a family to request these products, and now we are setting a brand-new set of rules that, in essence, will impede that process, if that is the goal of the process.

So, one of the questions that I have--it sounds like a little bit of a circular argument--but one of the questions I have for the FDA is when people request this, why are they requesting it, what are the reasons, is it because they are not meeting the eligibility criteria for studies or because it is their last chance hope, and they want to get a hand on anything, or is it because they don't have access to the trial. I mean what are the real reasons?

DR. WILLIAMS: I think all of those and more, and we may not even be supplied with it in that way.

DR. SANTANA: If that is true, then, we have got to be very, very careful that we don't set a set of rules to allow these special exemptions to be approved.

DR. WILLIAMS: Actually, you have not been asked to allow them. We are mostly interested in when we would say no, because we do have that responsibility, and clearly we do say no sometimes, not that often, but we are interested in your comments about not necessarily would you in various circumstances, but what is the basis for why you would say no, and I think it was pretty clear about Phase I, the reason behind it.

DR. SANTANA: Yes, for safety, I think that is very true.

DR. WILLIAMS: I would worry too much about we are not going to take these and set rigid rules based on a majority vote. That is why we are not even having voting, but we would like to understand your reasons and get your input, because we have to make these decisions on basically a daily basis, and we would like to have some input from the committee.

DR. NERENSTONE: Dr. Przepiorka, would you like to respond to Dr. Santana?

DR. PRZEPIORKA: Yes. I would actually not disagree totally with he said. I think there does have to be a mechanism available for patients who do not fit eligibility criteria and therefore

would not be considered, quote, unquote, "treatment," that is responding to the standard regimen and the eligibility criteria that was used to demonstrate activity.

This is where I think safety protocols in the expanded access setting have to be set up early, because most of the patients who will be treated, will be treated outside the eligibility criteria, and it is really important to get some of that information available.

I also want to address one comment that Dr. Williams said earlier, which was that he doesn't believe that some of the things that we were discussing earlier today were actually within the purview of the FDA, and one of the things that I am really concerned about is there is probably a lot of data from expanded access protocols and safety data, and information that we could possibly draw some conclusions about who should or should not be treated under these circumstances.

It is unfortunate that it is largely probably all on archaic medium, so we can't really access it very well, but I would hope that the FDA would have a plan to actually get that formalized in the future, so that we could use that data to

make more reasonable conclusions.

DR. NERENSTONE: Dr. Linden.

DR. LINDEN: The discussion so far has focused on the risk-benefit ratio and the toxicity factor and the activity-benefit ratio, and we have heard a lot today about the problematic use of the word "compassion," and yet it is my understanding that compassion is yet another element that needs to be figured, that does need or may not need depending on where you stand, to be figured into this pot of elements that need to be taken into account.

If that is so, if there is an element of compassion in this mechanism, then, number one, I would suggest that we not throw that term out of our lexicon, but that that needs to be wed in some way to these other factors because it is a significant factor.

DR. PAZDUR: Just to answer this question, and Dr. Santana's question, when we looked at this issue, the vast majority of reasons why people are looking to go onto the single patient is because of too many therapies. Basically, they are third, fourth, fifth, sixth line therapies, and they are looking for a treatment option here.

To answer Donna's question, one of the big problems that we have is just the uncontrolled nature of many of these expanded access, which makes really scientific conclusions very difficult to make. I assume she is referring to toxicity considerations in this aspect.

Because of the uncontrolled nature here and also the reporting many times of the information, it is difficult to make a really scientific conclusion.

DR. SANTANA: I hate to be simplistic, but if the majority of the patients fit in this category, then, maybe the clinical study should have a strata of patients that defines that subgroup. That may not be used in terms of the analysis of the approval process, but certainly would offer the clinical investigation to go forward.

If that is a big part of the pie, I hate to be simplistic, there may be a solution to that.

DR. NERENSTONE: Dr. Temple.

DR. TEMPLE: I just want to totally agree with that. There is no reason why the primary efficacy analysis couldn't be done in the subset of people who do have good performance status while

you maintain the other groups. I mean they are already in the institution, it should be little burden to include them, and you will get information on what the drug is like in those, and that is really an excellent idea.

DR. NERENSTONE: Dr. Spiegel.

DR. SPIEGEL: I wanted to respond to some of the comments that particularly the FDA members have contributed today, although I would resist Dr. Temple's provocative question should the FDA demand justice, I think we have enough trouble writing guidances and rules for things that are better understood than that. But I think it would be very appropriate for the FDA either at the end of Phase II, although usually we have a very limited time to talk about other issues about how we are developing the drug, but either in the context of that meeting or when the first request comes in and an important senator or somebody else has requested it, I think it is appropriate for the FDA to ask us what are we going to do with the next request.

The other thing I would say is the FDA is a wonderful source of good and bad experience to share with sponsors. You can't divulge proprietary information about other companies' products, but if

you have seen a very good ECAP program run, there is no reason why you couldn't challenge either a Big Pharma company that may have done things pretty well, but could do them better or might have done things lousy, or small companies that are here for the first time, to say have you considered, instead of an individual patient exemption, doing an expanded access for 20 patients and see what happens, or if you want to treat 200 patients, why don't you do it under these types of mechanisms that might help us all learn more about it.

So, I would encourage the agency to feel that it has the authority to have these discussions with big or small companies, although I don't want any rules.

DR. NERENSTONE: Dr. Carpenter.

DR. CARPENTER: I think I wanted to comment on compassion. It may be under-rated, but I think a number of the physicians in the field also feel a certain amount of compassion toward this group of patients, but feel very much on the spot when they get requests in people whose organ performance is bad or performance is bad where you wouldn't give more standard treatment because there is almost no real chance of benefit, then being

asked to give an experimental drug with a lot less knowledge and a lot more uncertainty to the same person.

So, the idea of some very general guidelines about organ performance and performance status, to give a person a realistic idea about the chance of improving on anything, much less the experimental drug, could well be part of the process at some point, and I don't know whether the FDA would want to say that for certain people this could be done, but really don't feel it's in usual guidelines of good practice. There is that person, and there are some who simply exhausted the usual things, does have good organ function and performance, for whom a promising new drug that is not yet widely available might be a very reasonable option. It is getting some balance in that, that I think that we are chasing issues.

DR. NERENSTONE: Mr. Erwin.

MR. ERWIN: I think these last few comments have been extremely good, and one in particular regarding inclusion of nontraditional patient groups in clinical trials, all of those patients for which people legitimately express concern about safety will ultimately be treated

once the drug is approved for marketing.

The more insight that can be gained into those populations early, the better, I would say, and it gets back to the whole question of what quality information do we have in this discussion, how many patients, if any, have ever actually received a survival benefit from individual access to a Phase II, Phase I, Phase III drug, how many patients, if any, have ever actually been harmed by that access, how does that compare to what happens after marketing approval is granted.

You know, there is a lot of information that is probably out there that we haven't compiled into a systematic way to help in these sorts of debates, and it keeps coming up over and over again, you know, access to god quality information, a retrospective analysis that could be very helpful through some mechanism.

DR. NERENSTONE: I suspect that that data does not currently exist, nor is it retrievable on the basis of discussions with FDA with single patient exemptions as it now operates.

DR. PAZDUR: Plus many of these trials are single arm, so it is going to be hard to determine any survival benefit from any single-arm study.

DR. TAYLOR: Right, and the reason we are doing the trials, and the reason that they have strict criteria is to try to get good data and to get good scientific answers, and I guess I am going to show my age, but many years ago there weren't the restrictions on treatment that there currently are when we put people on investigational trials, and what we have learned were those patients who had had multiple treatments didn't respond. In fact, the statistic I was taught was that after each treatment, your chance of responding drops by 20 percent.

So, we have done that before. I am not opposed to it. I have a lot less problem giving Phase II agents out in this individual basis, but I think that to criticize our trials, the reason they have been developed that way was to try to give a fair answer about a particular drug or a particular treatment, so that a patient would know it.

I don't also agree that I would necessarily, if that drug were on the market, give it to a patient, because I think part of compassion is to tell them when they are wasting their time and their money.

If you have had four treatments for

non-small-cell carcinoma of the lung, you are wasting your time and your money to do another one, and if you can say that there is a benefit to society because I am going to be on a Phase I trial or there is a benefit in some other way, that's fine, but I am not sure it is compassionate when I have people coming back and forth for blood counts and CT's and spending that time for something that I have pretty good evidence it is not going to work because they have had four prior treatments.

DR. NERENSTONE: Dr. Linden.

DR. LINDEN: Hypothetically, what if a study were commenced today to look at outcome measures for patients who are granted treatment INDs, and a second study on expanded access, and what if it were learned that the outcomes are virtually, unilaterally poor for both kinds of studies, and there is anecdotal evidence and more than anecdotal evidence, as Dr. Taylor just suggested, that people do rather poorly on treatment INDs because they come to them so late, because they have received so much pretreatment, et cetera?

If we are talking about safety, that is one matter, but if we are talking about activity

and efficacy, if there is no efficacy, is that a basis for--and I am speaking in late Phase II trials, for drugs that are in late Phase II trials--is that a basis for eliminating this mechanism? I am just asking this as question to try to help us focus on what our justifications or criteria are.

DR. NERENSTONE: I guess you are asking if we already know that the response rate is zero, do we as physicians, who are trained ostensibly as scientists, have the right to refuse treatment to a patient, and I would say yes. I would say I don't like including the word "compassion," because I don't think that that is appropriate for us to be talking about.

I think the compassion that we show our patients is at the individual level. I think we have to set guidelines, and oncology likes to think itself as being a part of evidence-based medicine, and just as physicians have too long given antibiotics for patients who walk in the door with a viral infection and said, oh, the patient wants it, and therefore they should get it, I think it is asking us to throw out all of our medical training to say we should be giving patients, and as I said,

it is not placebo, it is worse than placebo, because these are toxic medications, but even if it weren't toxic, should we be giving them medications that we know don't work because the patients are demanding it.

I would say no, as a licensed physician, that is irresponsible and unethical because I know from a science-based point of view that it is not going to work. So, I would say yes, we have a responsibility to tell patients no, that you should not be getting this drug.

DR. TEMPLE: Some of the suggestions that we might learn more from this experience are I think unlikely to be fruitful because they are uniformly uncontrolled in a population that is typically not terribly well defined, so that getting survival data, I think is going to be very difficult.

This sort of violates Grant's law, but I just want to throw out one thought that hasn't come up much, which is the possibility that some forms of expanded access could actually be done in the form of large, simple trials--that was on Grant's slide--especially if the likelihood of benefit is modest, that is, you are talking about people who

have failed multiple therapies, then, you really have to wonder what you are going to accomplish.

There is no requirement that treatment INDs and their like not provide useful data, it is just works out that way. So, there is the possibility of actually randomizing. There is at least one AIDS trial that randomized between two doses. There are very few similar examples, but that is another possibility, that the right form for wider access to take in people might be one that actually provides information of a somewhat different kind from what we are used to, not focusing so much on tumor size and things like that, but on things like survival outcomes, which would need large numbers and might support wider access, and might actually be economically feasible for companies, as well.

It is worth throwing into the mix although it doesn't get to Grant's main problem, which is single patient.

DR. NERENSTONE: Grant, do you want us to go back to the questions?

DR. WILLIAMS: Let's see, how many more do we have? Fifteen minutes.

DR. NERENSTONE: We are still on A. There

is no standard therapy. How about Phase III trials? The drug is already in Phase III trials. Should the patient be able to have a single patient exemption? Have we beaten that to death? I think the general consensus is that would be okay.

DR. REDMAN: I disagree for the record.

DR. NERENSTONE: B. Available treatment shows a marginal survival benefit. Non-metastatic lung cancer, 1 to 2-month median survival, produces moderate toxicity. Should they be able to get--Phase I, we have sort of talked about, Phase II or Phase III? I don't think it is really a big different discussion actually than we have already had.

DR. WILLIAMS: It is because we are no longer talking about whether they have used all available therapies. Here, we are saying available therapy has 1 to 2 month survival benefit. What would you have to see in a drug to allow you to substitute it for that, or does it even play into your consideration?

DR. NERENSTONE: Dr. Albain.

DR. ALBAIN: I guess I would ask you, Grant, at least we have numerous in untreated metastatic non-small-cell trials that have shown an

improved survival benefit, not just measured in median, but we are talking about significant 1- and 2-year survival benefit, and quality of life benefit versus best supportive care.

These trials have been conducted in Canada, the United States, and Europe, so that I would personally have a problem making a broad statement that one could allow someone to go off onto experimental therapy when you had standard therapies that not only improve survival, but improve quality of life, and that is where the education of the patient comes back in, and the public, on what can be achieved in this disease.

DR. WILLIAMS: That is this agent is nontoxic, it seems to be relatively nontoxic, let's say, and has a response rate. Would you allow it or not?

DR. ALBAIN: Right now I thought we were talking about Phase I.

DR. NERENSTONE: No, we are moving to end of Phase II.

DR. WILLIAMS: Where would you draw the line, what amount of efficacy or proven efficacy or toxicity of this drug, in what setting would you allow it, or would you never allow it?

DR. ALBAIN: I think I would work very hard first to educate the patient and the family about what we can achieve with standard therapy in this scenario where not only do we know that we have an improved statistical survival benefit, but we have quality of life data over and over now that is compelling, that it is better with treatment.

DR. NERENSTONE: Dr. Taylor.

DR. TAYLOR: I would disagree a little bit. I would say that in this setting, I would not be opposed to giving them a Phase II agent because I don't have a curative treatment, and it is a very small group of patients that gain that benefit. I don't disagree that because there is something standard available, that that shouldn't be brought up to them as one way of doing it, but I have no problem with giving Phase II agents to patients with non-small-cell lung cancer.

DR. NERENSTONE: But remember off study.

Dr. Sledge.

DR. SLEDGE: This actually is an area where we have a little data, actually from your group, Kathy, in breast cancer, where there was several years ago a randomized trial in breast cancer between novel Phase II agents--

DR. ALBAIN: It was not my group, it was the CALGB.

DR. SLEDGE: --CALGB--between novel Phase II agents and standard therapy.

That trial was done with very strict criteria, which is if you progressed after a couple of cycles of therapy on the nonstandard regimen, you went to the standard regimen, but there was identical survival between the two groups.

It is hard for me to imagine that if you had it under that sort of carefully controlled sort of setting, that it would be a danger. The real danger, of course, comes up due to the fact that most of these settings are not carefully controlled.

DR. WILLIAMS: George, that was with progression, going off study if you did not respond?

DR. SLEDGE: Correct. My recollection of the trial was if you got two cycles, six weeks, 10 weeks of therapy, and had evidence of progressive disease, you immediately crossed over to the standard therapy.

There was identical survival between the two arms.

DR. WILLIAMS: How large was the trial, do you know?

DR. SLEDGE: It was actually a set of rotating Phase II trials compared to a standard arm. It was a fairly large database.

DR. ALBAIN: I was not disagreeing, Sarah, with offering this end of Phase II investigational drug, but my concern would be if that was a broad policy, that some patients would not derive the benefit of quality survival for 1 to 2 years with extensive small-cell, and to go back to Dr. Sledge's point, we don't have that data from that breast trial available in extensive non-small-cell lung cancer now that we have therapies that can improve quality of life in the standard setting, although one could argue the breast standard agents did do that, so it's a good point.

But I think it is education. I would be very nervous about letting a message get out that this is an appropriate setting when we have worked so hard to educate the lay community about what we can achieve for lung cancer survivorship.

DR. NERENSTONE: I think that is a very important point because I think all of these scenarios are when the FDA is approached with this

problem. That is not to say this is something that we advocate as treatment at all, and I think that is a very important tenet, to make sure everybody understands, because this is going to be disseminated widely and this is for the patient who has decided after a lot of counseling with their private physician why this is probably not a great idea and insists on it anyway.

DR. NERENSTONE: Dr. Carpenter, did you want to add anything?

DR. CARPENTER: No.

DR. NERENSTONE: Dr. Blayney.

DR. BLAYNEY: I would be reluctant to advise the FDA to allow a single patient exemption at the end of a Phase II, I think in this setting, because I think it may jeopardize further drug development both because of accrual to clinical trials and it may uncover some toxicity that would take some time to explain and impede the timely development of a potentially rational and useful therapy.

DR. NERENSTONE: If we can go on then to the third scenario. Standard therapy provides a substantial prolongation of median survival. That is a patient with advanced ovarian cancer, 1 to 2

year median survival benefit, but is generally not curative.

I would be happy to start this conversation. I would find it very difficult to approve someone who is not going to take standard treatment, which in general is not life-threatening, does not have prolonged severe permanent side effects, and instead, wants to use a single patient exemption for a drug that is in Phase II where we have no idea of its activity and its survival benefit or even duration of median response benefit as a single agent.

So, I would be hard pressed to think that this is a good idea.

MR. ERWIN: I agree with you this time.

[Laughter.]

DR. ALBAIN: Stacy, what do you say if it is in Phase III, though, what is your reply?

DR. NERENSTONE: Single agent treatment is not a standard in the United States, and I would be hard pressed to think that a single agent is going to be better or even the same as our current upfront treatments.

So, usually, when you are talking about Phase III, it is in combination with something else

by the time it gets to Phase III, so as a single agent, I don't see the scenario where that would be appropriate.

DR. WILLIAMS: So, you would like to see results from the randomized trial showing a similar sort of outcome.

DR. ALBAIN: The reason I jumped to that, as we all know, the new agents, the small molecules are going from Stage 1, quasi-Phase II, and oftentimes not a true Phase II trial, into Phase III, leapfrogging, so that I don't know that we want to give the message that we are all saying that Phase III trials, if it is out there, that we could go ahead and justify, so I wouldn't in this situation.

DR. KELSEN: It does get a little muddier when you have a study--I will disagree with you on that--when we have a Phase III or a Phase II trial, we have an experimental drug plus conventional therapy in some of these settings, so what they are saying is, oh, well, I have this small molecule, monoclonal antibody, and it is being used in combination with proven, approved, approved for that indication chemotherapy, but I don't fit entrance criteria into the study, and I would like

to get that drug. That makes it a harder decision.

The easier decision for me is the patient perfectly fits criteria for the trial, but says I don't want to be randomized to that arm. As soon as you do that, then, it would be very hard to do Phase III trials.

DR. NERENSTONE: I think, though, that that is the problem. When you start allowing that drug to be given out as the adjunct, you will completely shut down your clinical trials, and again, these are molecules not without very high cost, some toxicity, and you are going to get into the same problem you had with the bone marrow transplant situation, which is everybody got it, no one went on to study, and you never knew what the real answer was to your question.

DR. KELSEN: I agree with you. I am just saying it's an even trickier situation.

DR. NERENSTONE: Dr. Przepiorka.

DR. PRZEPIORKA: Just to underscore that, I think if you are writing rules for yourself, one rule to say no is patient is eligible for a study. Then, they should not be under treatment IND.

DR. NERENSTONE: Dr. Linden.

DR. LINDEN: And that is precisely part of

the regs, that is written in stone. If the person is eligible for a trial, they are not eligible for treatment IND or expanded access.

DR. WILLIAMS: It may or may not say that for treatment IND, but it doesn't even cover expanded access. I mean some of these practices, there really aren't regs for at this time.

DR. LINDEN: Well, treatment IND.

DR. WILLIAMS: Right.

DR. TEMPLE: Actually, it says that we can stop a trial that is interfering with the randomized trials. It doesn't actually say that they can't both coexist. Maybe it could, but it doesn't.

DR. BLAYNEY: I think, Grant, you also raised the issue if the drug is nontoxic or very close to being nontoxic, I think the response to that is we don't, if it's nontoxic, it is likely that the pivotal trial or the licensing trial will move along and accrue very quickly, and you can, by granting a single patient exemption, you can perhaps impede that, and you don't want to impede the completion of the pivotal trial, so I think you also have an easy answer even if the drug has zero toxicity.

DR. NERENSTONE: Moving on to the next question, then. The standard therapy provides a substantial rate of cure. The example is a patient with acute leukemia who does not want to receive chemotherapy that is associated with a 40 percent rate of cure with substantial acute toxicity, but that produces few lasting toxic effects.

Would some of our leukemia doctors like to comment?

DR. SLEDGE: How about if the leukemia was CML?

[Laughter.]

DR. WILLIAMS: George, you have been wanting to say something.

DR. SLEDGE: What I am asking is the obvious question. I mean we have a drug that basically was approved on a Phase I and early Phase II trial basis. We have a disease where we have a proven long-term cure rate with albeit a very toxic therapy. The ethical considerations must have entered into your approval process.

DR. WILLIAMS: It wasn't approved for initial therapy.

DR. SLEDGE: But you know darn well what it is going to be used for.

DR. NERENSTONE: Other comments from the committee?

DR. WILLIAMS: George is unhappy we didn't bring it to the committee.

DR. BLAYNEY: What I said three minutes ago applied to that, and that is approved for principle. If it is a relatively nontoxic drug, the trial was done very quickly, and you didn't need this individual, a single agent exemption, and fortunately, the company was responsive and had an expanded access program in place, so that is exactly what is approved for principle, that is why you don't need the single patient exemption for such a home run, a nontoxic home run.

DR. NERENSTONE: Dr. Przepiorka.

DR. PRZEPIORKA: I think perhaps a more germane example would be the alternative drug for a treatment IND is one that has no cure rate, but a lot less toxicity and perhaps can just keep things under control for an extended period of time.

I think there you have to start weighing the risk and the benefit if the patient really and truly says no, I don't want toxic therapy, period, which patients can do especially elderly patients. Then, the question is what do we benefit from the

investigational drug, and if the investigational drug has shown efficacy or rather has not shown any safety problems and does keep things under control for a period of time, then, this may be something that we are going towards palliative care.

So, it may be appropriate for a treatment IND for a palliative care setting, but if this is another drug that doesn't have a good cure rate, and we are really not too sure whether it has any efficacy at all, then, I would say no, there is no reason to give something to the patient that doesn't harm him, but we really don't know if it is going to help him either.

DR. NERENSTONE: So, you are saying there has to be some clue of efficacy even in this situation.

DR. PRZEPIORKA: Yes.

DR. SPIEGEL: I am just curious on that last comment, what you are accepting as evidence of efficacy. At the end of Phase II, we have activity. We sometimes call it efficacy, but we usually think only at the end of Phase III, where you have compared it to a standard therapy and showed long-term benefit of some type, it could be quality of life benefit, not just survival.

But at the end of Phase II, you know you have activity unless you have CML with Philadelphia chromosome disappearing, you usually don't really have that much confidence that whatever you saw as a response is sustainable and better than standard therapy.

DR. PRZEPIORKA: That is a very good question, and I would actually like to turf that to Dr. Taylor. If you have a patient, an elderly patient with leukemia who really doesn't want to undergo toxic therapy, how much activity would you look for to give him something palliative?

DR. TAYLOR: I don't know that I think I have to give him some anti-cancer treatment to palliate him, and I think you have to decide that with the patient whether it is going to be palliation with symptom management, pain control, nausea control, or whether you are truly going to try to palliate in terms of lowering white counts and lowering the complications of that disease. I think palliation can be done either way, and it is going to be dependent upon that patient and what their goals are. I think they have to determine their own goals, and some of them choose, their goals are just to be comfortable, and others want

to try some less than aggressive treatment.

In that setting, I don't know that I have to have great response for efficacy data if I have good toxicity profile and which I am not going to aggravate my palliation.

DR. NERENSTONE: I guess the question is, if you don't need any efficacy data, and it is a drug that hasn't been studied in the leukemia, but it has very low toxicity, is it reasonable to have that patient call up and say I want that drug, and essentially tell you what to give them, because it is not toxic?

DR. TAYLOR: Well, I guess the practical part says I rarely have that happen, that when someone has chosen that they don't want to be aggressive, I don't have them asking for new agents.

DR. NERENSTONE: But they do, the FDA does.

DR. TAYLOR: But is it in the setting where they have really chosen to not be aggressive?

DR. WILLIAMS: This specific question was set up. We have a few examples where people have very good curative treatment, we are not talking that person who really doesn't have good option,

really do have curative treatment, they don't want it. They want investigational drug, and we have felt that going along with that was not in the patient's best interest, and there has been autonomy issues.

DR. TAYLOR: I agree with you on the autonomy, but I guess what I was hearing is I have an elderly patient, I am sorry, I don't like the response to acute leukemia treatment in elderly patients, they don't do well, so that is a little bit different.

DR. WILLIAMS: But that is a different value judgment, a little farther on down the line toward the lung cancer, I would say, or even before that. The answer to this is probably pretty obvious, even what you said with ovarian cancer, I mean this is even higher level of benefit that someone might be deciding they don't want, because they want this new treatment.

DR. NERENSTONE: What I would say is that somebody who has a treatable pneumonia, but they want echinacea, and they want you to prescribe it, and I would say no, I am a doctor, I prescribe antibiotics, that is the appropriate treatment. You can't get echinacea from me.

DR. TAYLOR: Right, and if this is a young person who has no reason for avoiding his acute leukemia treatment, then, I agree, I would not want to go with any.

DR. NERENSTONE: Dr. Blayney.

DR. BLAYNEY: There are plenty of other nonexperimental alternatives for that person, prednisone, or whatever fits into their value system, but I was also going to go the CML one step further, that if hidrea was the experimental agent, it is nontoxic, it is largely palliative, I think that is a reasonable palliative maneuver.

But anyway, to your specific example, there are plenty of non-IND requiring agents to mistreat acute leukemia.

[Laughter.]

DR. NERENSTONE: Do we need to go to E?

DR. WILLIAMS: No.

DR. NERENSTONE: You get the general sentiment.

Question 2. As noted above, the FDA strongly endorses participation in clinical trials. Patients should first consider entering a clinical trial before pursuing treatment under a single patient IND. If a patient is eligible and able to

receive Drug X as part of a clinical trial, but is unwilling to do so, should that patient be allowed to receive Drug X under a single patient IND?

Again, we have answered that. No is the sentiment I think of the committee.

Mr. Erwin?

MR. ERWIN: I definitely agree the answer should be no, but as a separate topic, I think there needs to be consideration of how and when to use crossover provisions in clinical trials. I think that that can definitely accelerate accrual and for the right agents and the right clinical trial design. It doesn't have to interfere with getting efficacy data.

DR. NERENSTONE: Question 3. If FDA has sufficient evidence to conclude that a drug is ineffective for treatment of a particular cancer, discuss under what circumstances, if any, single patient treatment use should be permitted.

You know how I feel about this, though. I will open it up to the committee.

DR. TAYLOR: I agree, it should not be used.

DR. NERENSTONE: Any other comments?

Do you feel that you have gotten what you

need?

DR. WILLIAMS: Yes, very much. Let me just ask one question. There was a lot of discussion about whether we should have a consensus conference, who should be involved, et cetera. I would just like to hear a little discussion about where should we go in trying to move forward the discussions about the justice of how to do these programs.

We have talked about when you shouldn't, when FDA should say no, but is there maybe a different level for the industry and the community when should it be provided, and how should it be provided.

What do you think about how we should go forward, who should be involved?

DR. NERENSTONE: Dr. Albain.

DR. ALBAIN: Grant, I just want to make clear that we have been saying a lot of no's for the single patient query to you, but I don't think we have been saying no's to proper design of expanded access programs or treatment IND programs, that the companies can start planning very early in their process of drug development as we are into this exciting era of small molecules.

I think the time is ripe to have dialogue about that issue at a national level.

MR. DIXON: I think, by and large, the advocacy community would very much welcome a consensus conference on this. The community itself does not speak with one voice, and even more reason why a consensus conference would be beneficial for all of us.

DR. PAZDUR: We had entertained, and we will be talking to people from the NCI, ASCO, advocacy in general, and industry, PhRMA, to bring this together, because we really think that this needs further really voicing and looking at where we would go with this whole topic.

DR. NERENSTONE: If there are no further comments, thank you, everybody, for that discussion and we will re-adjourn at 1 o'clock. This is a closed session only, so it is just the committee members and FDA.

Thank you.

[Whereupon, at 12:10 p.m., the Open Session adjourned.]

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Lawyer's Notes