true there have been tons of successes, and it is true that there have been people harmed, both from not receiving therapies and from receiving investigational therapies. In the context of clinical research there is a concept known as the therapeutic misconception. It is a belief that the experimental procedures are directed primarily at therapy. The process of science is not directly primarily at therapy. It is nice when therapy happens. It is hoped that therapy happens, but it is designed to create generalizable knowledge.

Sometimes the recognition of serving as a subject for someone who is sick can be challenging. The phenomenology of illness, being ill, doesn't let us believe that our decision-making -- that person in the white coat is making a decision based on a coin flipped. But it is also troublesome and challenging for investigators who are clinicians who, on the one hand are trying to behave like a clinician and, on the other hand, are trying to be an investigator and they also fall prey to the therapeutic misconception. In empirical work that has been done, both patients and investigators overestimate, for instance, the likelihood of any clinical benefit in a Phase I clinical investigation -- way overestimate it.

So, this has direct implications for the informed consent process. If you are being told or sold something

that is going to be likely more therapeutic than is possible, it makes it more desirable to have it but then, again, it may foreclose the possibility of other options.

Well, in the last few years we have witnessed the range of what we call novel therapeutics -- gene therapy, vaccines and biologics, and there are differences in the way the trial design, the trial questions, the outcome measures we can use but also in the language being employed. What does that word "therapy" mean? Even a therapeutic IND -- therapy means it is therapeutic. It is healthful. It hasn't been shown to be. It is a great scientific concept. It is elegant in its design. It is stunningly important science but at this time, probably in the proper terminology, it is gene transfer experiments. It is an experiment.

Vaccines -- we take vaccines. Some folks are scared of vaccines but vaccines are preventive. Cancer vaccines are not preventive. It changes our notion of what a vaccine is. Biologics -- they are natural. I had a secretary who came in one day with an enormous rash on her face. I looked at her and, you know, I tried not to overlap my roles here; she wasn't my patient but she had a huge rash on her face, and I said, "did you use some new soap or some new cosmetics, or something?" And she said, "no, no, nothing." I said, "are you sure?" "No. No, nothing." I said, "anything new?" She said, "well there's this new soap we are using. I

got it at the natural food store." She says, "it's natural. That couldn't be causing that." Well, so is a snake bite. It is natural too.

So, the language that we use for these things -- biologic is natural, vaccines, gene therapy -- can change our ability to communicate what it is we are trying to accomplish scientifically. Does this terminology cause a therapeutic misconception or add to it? It probably does. There is some research that suggests it does. I don't have time to share.

The discourse further in some of these routines, and up until the death of Jesse Gelsinger last year, discourse in gene transfer experiment protocols was -- and this was common and there was a common parlance at meetings of the recombinant DNA advisory committee -- it might help but it certainly won't hurt. Jesse Gelsinger's father who recently spoke at a national meeting and told Jesse's story was alarmed that he wasn't aware of the preclinical studies that led to what appear to be a similar toxicity in his son. Although his son had agreed and had signed papers to be part of that gene transfer experiment, according to his father Jesse wasn't aware of the information. What he thought is it might help and it certainly won't hurt, and for an 18-year old kid who spent the first 18 years of his life on diet control -- 18-year old boys don't like to be on a diet, and

as long as it wasn't going to hurt me, okays, try it.

So this kind of discourse contributes in some ways to our therapeutic misconception and also to the press on treatment abuse issues. There is enormous popular enthusiasm for things that come down the pike. I recently worked with some of the folks at M.D. Andersen when the endostatin trials were first announced. It was an extraordinarily effective agent in treating tumors in mice. Gena Colata bought into it. She said this is the greatest thing. M.D. Andersen received over 2000 protocols for Phase I based on mice data. They had maybe 15 spots -- I can't remember the exact number but that is about in the range, and how do you now take something where we have traditionally said let's protect you because this could be just toxic; it could hurt you; you could spend your life in a clinic instead of at home getting alternative therapy? How do they then allocate something that was unclear?

Well, what are our lingering obligations? Well, no surprise -- respect for persons in terms of informed consent. Beneficence and non-maleficence and justice, the need to treat people fairly; the need to balance protection and access; getting it right.

In terms of respect for persons, informed consent for clinical research in this area needs to recognize that therapeutic misconceptions exist and take measures to

overcome them so that when people give informed consent to trials they give meaningful and valid informed consent.

We need to ensure that all alternatives are recognized. Just because something gets good press and good adjectives doesn't mean those are all the alternatives that are available.

Beneficence and non-maleficence, honoring that fiduciary obligation that a clinician has to a patient, that an investigator has to maximize benefits and to minimize risks, that an institutional review board has in the design of a protocol, that a sponsor has for not hurting people in the process of bringing something to market -- the approach here is to use alternatives that pose the potential for benefit and to avoid harmful interventions.

In terms of justice, fairness in access, if we have data that suggests this is okay make sure that the access mechanisms are fair. Come up with a fair and appropriate mechanism to make sure that the bureaucratic issues are handled fairly and appropriately, that there are mechanisms in place to help those who may not be as empowered as possible to get access to things that might help them.

This whole notion of distributing what may be perceived as a scarce resource or may, in fact, be scarce resource is something new to the field and needs some

explicit deliberation.

Well, in conclusion, considering access to investigational agents borders on practices of medicine and clinical research, raising some unique ethical issues. An ethical framework provides a language with which to deliberate about these issues, and the enormous reservoir of trust that people still place on clinicians in a scientific enterprise makes it critical to explicitly address these questions and get this right. Thank you for your attention.

DR. NERENSTONE: Our next speaker is going to be Dr. Linden.

DR. LINDEN: You all must be very tired. You have been sitting quietly for a couple of hours, and I hope we will get up and stretch soon so that some air can circulate to our brains.

My comments will be brief, I hope, and much of what I have to say you will have heard reverberations of in other talks and I hope that my comments will bring things together for you and offer a different kind of framework for thinking about the issues that we are here today to discuss.

I am Ruth Linden, and I am very happy to be here today. I particularly want to thank the FDA and Patty Delaney and Dr. Grant Williams for inviting me to participate in this meeting, and I also really want to thank the public speakers who have offered crucial and incisive

insights, as well as the painful stories, to our deliberations.

I am Director of Curricular Performance, Stanford University School of Medicine, which means that I am intimately involved with the training of generations of medical students, and I am also on the faculty of the Department of Family and Community Medicine at UC San Francisco. I have been conducting research on policy issues in the breast cancer arena and working with treatment activists since the early 1990's. I am by training a medical sociologist and a bioethicist.

I was invited to speak with you today about my experience as bioethics advisor to a group of community-based activists associated with ACTUP Golden Gate and assisted by Project Inform. Both are San Francisco based AIDS activist organizations. The group negotiated with Genentech, Inc., about whom you heard earlier, to implement an expanded access trial for a novel, non-cytotoxic therapy for advanced breast cancer.

Now, as you know, an expanded access trial is an entirely different mechanism from a single-patient treatment IND. Even so, I believe that the Herceptin experience may offer a valuable insight as we think about treatment INDs this afternoon.

I would like to begin with a brief description of

the development and implementation of the expanded access trial and, in contrast with most or all of what you heard this afternoon, the story actually has a positive outcome. So, it is a bit up, I am happy to say.

Expanded access arms are by now routine in HIV AIDS clinical trials. However, this is not now, and has never been the case for clinical trials in cancer. Thus, in 1994, when I began working with this group of activists this coalition of community folks, community activists, came together to pressure Genentech to offer a compassionate access program. Herceptin, the name under which the product was eventually marketed, was the first biological therapy used to successfully treat some forms of metastatic breast cancer.

As many of you know, Herceptin was approved for marketing about two years ago, in September of 1998. The "Her Too" activists, as I call them, were greatly influenced by the highly successful approaches to treatment activism developed and deployed by AIDS activists. Expanded access is among the most notable reforms brought about by and through the efforts of AIDS activists.

The Herceptin expanded access trial, in which more than 700 people received therapy, was an extraordinary feat. Utilizing the direct action approach pioneered by ACTUP, the "Her Too" activists attempted to begin face-to-face

negotiations with senior staff at Genentech. Their efforts, however, went nowhere.

In December of 1994, to press their demands the activists held a demonstration with civil disobedience on the Genentech campus, in south San Francisco. The next month Genentech agreed to negotiate with them.

Negotiations continued periodically, yet the company stood steadfast in its refusal to consider any form of expanded access. Over the course of many months the activists devised a publicity campaign to press their demands for expanded access and finally, in August of 1995, Genentech agreed to implement such a program.

The trial offered 25 slots per quarter, or 100 slots per year, to women who met the entry criteria. The names of those who qualified for Herceptin were entered into a lottery. Every month lottery entrants competed against a computer for available spots. The protocol specified that clinically meaningful data would be collected.

Over the next two years the activists pressed Genentech to increase the number of expanded access slots and finally the company agreed. Through a treatment referral center protocol, the company entered into an agreement with the National Cancer Institute that allowed Herceptin to be offered though all NCI comprehensive and clinical cancer centers. As many as 100 new people per quarter, for five

quarters, could be enrolled in the trial, which also used a lottery system. There were then two expanded access trials. As I mentioned above, during a three-year period more than 700 women received the antibody through the two expanded access trials.

Now, it is important to understand that the "Her Too" activists pushed for an expanded access trial because, in no uncertain terms, Genentech refused to offer single-patient treatment INDs for Herceptin, as Jennifer Bryson mentioned earlier. The company did not want to be put in a position of having to respond to requests on an individual basis and with the appearance of favoritism. If Genentech had eventually acquiesced and agreed to offer single-patient INDs a full-scale expanded access trial might never have been designed. In this scenario it is virtually impossible to imagine that such a large number of people would have gained access to Herceptin outside of Phase III trials.

For the "Her Too" activists the goal of the expanded access trials was, of course, to provide treatment options for desperately ill people. But in the back of their minds, they had a larger vision, to transfer the technologies of large-scale expanded access from the world of HIV AIDS into the world of cancer clinical trials. They believed that expanded access, run in parallel with conventional clinical trials, was the simplest, safest and

most compassionate, just and rational way to offer an unlicensed therapy to people who have exhausted their treatment options.

When I began to work with the "Her Too" activists I was by no means convinced that their view was correct, reasonable or even plausible. Since that time, however, I have become firmly convinced that they were, indeed, correct. I can find no credible ethical, clinical or scientific data that indicates otherwise.

I suggest that in many cases expanded access trials could be a strategy for routinizing single-patient INDs. First and foremost, they offer a compassionate approach to those who have the fewest available treatment options. In addition, they streamline and may hasten the application process for manufacturers, physicians and their patients and the FDA alike. Each time a request is made for a single-patient IND the manufacturer must first agree to offer the product and each patient, or her or his physician and advocates, must seek approval. The manufacturer's agreement is sought in the process, as you have heard today, but is entirely separate from FDA approval, a process that may be arbitrary and, as you heard this afternoon, is often, in fact, arbitrary and that is, as far as I know, unregulated by norms or even community standards.

For each of the involved parties the process may

be extremely awkward, uncertain and time consuming. Manufacturers are under no obligation to offer treatment INDs, and when they refuse to do so, they need not justify their reasons. These circumstances are extremely unfavorable to the policy-making process.

Successful negotiations with the manufacturer occur before a single-patient IND is submitted to the FDA, at which time a second formal process is initiated. I suggest that a policy should be designed to streamline these two separate steps, i.e., approval from the manufacturer and then from the FDA. This could be accomplished through several different approaches. With such a policy we could look forward to conserving scarce resources, reducing uncertainty, minimizing unintended redundancy and, most importantly, setting a just decision-making procedure in place that guarantees equal access, equal opportunity and the exercise of compassionate judgment.

In closing, I would like to pose a number of additional issues for our discussion. Sound policy is necessarily guided by data. In order to make recommendations, I -- we, in fact, need to know more about the FDA's experience with single-patient treatment INDs, as a question earlier was noted.

A white paper, in my view, needs to be developed to answer the following questions, and I am going to tick

off a number of questions. How many applications has the agency received during the past year? Two years? Five years? How are these applications reviewed, and by whom? On what grounds are some applications denied by the FDA? What is the distribution of applications by cancer site and type? Obviously, all of the applications that the FDA receives are not for cancer but we are just looking at the dancer domain right now.

Why are some manufacturers unwilling to offer any mechanism for expanded access? How might outcome data be collected on approved treatment INDs so that we can begin to learn about the conditions under which this mechanism does and does not make a difference, and what kind of difference it makes in life extension or palliation?

Additionally, we need to explore how the FDA, industry and trade organizations, and activists and consumers can cooperate to develop policies and practices that facilitate expanded access and single-patient INDs, while simultaneously ensuring that the collection of meaningful data in clinical trials will not be compromised. There is no doubt in my mind that these two goals are fully compatible.

A conference on expanded access could be the ideal setting in which we could begin this work. The white paper that I mentioned above could be distributed in advance of

such a meeting, whose purpose would be to set an agenda to evaluate the FDA's expanded access programs for cancer drugs and biologicals.

Single patient treatment INDs were instituted in a period that was significantly different from our own time, the post-genomic biotechnology era. The players in the research and development sectors have changed dramatically, with pharmaceutical and biotechnology companies taking a leading role, and the NCI less prominent.

The range of therapeutic approaches from antibodies, immune-based therapies and other biologicals to novel drug delivery systems will continue to expand in ways we simply can't imagine at this juncture. Cytotoxic chemotherapy and hormone therapy are being joined by a new generation of specific targeted therapies. It is incumbent upon the FDA to set policies responsive to this new generation of therapeutics while remaining grounded in the values about which we just heard -- compassion, justice, autonomy, beneficence, respect for persons and informed consent.

Finally, the principle of informed consent must be extended to include an informed and educated public. This would allow compassionate mechanisms to be accessed and utilized before people have become too ill for promising new therapies to improve their health status and/or quality of

life. Does public education fall within the FDA's mandate? If so, then how can it be accomplished? If not, then within whose jurisdiction does it lie? At this time we are a great and painful distance from reaching this goal. Thank you very much for listening.

DR. NERENSTONE: Yes, I know we are getting a bit short of time and there are a number of members who have planes to catch, so I would like to continue on, before we take a break, with our industry representatives. Dr. Spiegel will be the next speaker.

Perspective from Industry

DR. SPIEGEL: Thank you very much. I also extend my sympathies to those in the audience who have been sitting for so long, and I also wish to certainly thank the members of the public and I hope at the end of the day we can say "we've heard you," and I certainly want to thank the FDA for organizing a conference like this to share information. I think as we have heard already, and I think we will hear more, there is a great need for understanding of the different stakeholders, if you will, who are in this enterprise.

I was tempted, as we went around the room a couple of hours ago with introductions, to say that I am Dr. Robert Spiegel. I am the medical oncologist, as well as having other titles behind my name today -- the Senior VP of

Medical Affairs and the Chief Medical Officer at Schering-Plough, a large pharmaceutical company that has been involved in developing cancer drugs for many years.

I do want to begin by saying I am speaking today for myself and for my company and, although I have talked to colleagues in other companies over the years and even recently on this topic, I by no means am speaking for PhARMA, for BIO, the organizational groups of companies, or to echo a consensus statement in any way.

But having said that, I do want to say that I mentioned my own background of medical oncology and that began over twenty years ago when I was an associate at the National Cancer Institute, and I think that was the first time I realized, despite of going through medical school and specialty training, that cancer drugs didn't come from the NCI. At that time, I was on the phone asking drug companies if we could get experimental access to drugs for patients who had no alternatives. I then spent a number of years in an academic setting as a practicing and research oncologist, again talking occasionally with companies and being on the other side of trying to get access and release of drugs before approval.

Now, for the majority of my career I have been on the other side of that table, and I just wanted to say I am the face on the other side of that phone that many of our

patient advocates try to get through to. And, my real goal today is to try to help you understand and help the committee understand what goes on in the internal workings of one drug company, but I don't think an atypical drug company, when we make a decision on an individual request for a compassionate use exemption or to start a compassionate use program.

Let me say the statement I want to leave you with, at least from our perspective, we think that in general the present system provides an appropriate set of options to address the various ethically and medically appropriate requests for access to experimental drugs before approval. When I refer to the present system I am talking about that set of terms that Dr. Williams presented earlier that include expanded access programs, and the special type of an expanded access program called the treatment IND, and I will be followed by Dr. Kennealey who will describe the specific, recently initiated expanded access program, as well as compassionate use single-patient exemption which, as Dr. Williams mentioned, can either be sponsor initiated or initiated by a physician.

Now, having said that we believe that the present set of options that are available as appropriate, there is no question that the issues that were laid out in the ODAC briefing document as issues are very real. Pharmaceutical

sponsors in particular are very concerned about issues of, number one, limited drug supply, and I hope during my presentation I can explain that that is not a smoke screen to try and deter interested patients. That has very real consequences to the entire drug development process, and I will explain in a subsequent slide that every company makes a decision on every drug as to when they will scale up and make a major investment to move from having enough supply to test in a limited number of patients to have a commercial facility that can provide adequate drug with a much lower cost of goods to us, to move it into a commercial phase of development.

Number two, our companies are very concerned about the potential for a compassionate program to compete with the pivotal regulatory drug development program that has been agreed to. Although we almost always pose that argument as not trying to get competition for eligible patients, there is also competition for internal resources. I certainly want to try and help you understand the diversion that is created of resources and the incredible burden that is created within a drug company once a decision is made. I am not looking for sympathy but I am looking to help you understand what happens when a company crosses that line and says we will begin to entertain requests for compassionate use.

Finally, companies are extremely concerned about jeopardizing the safety profile of their drug in a less controlled situation. Again, there were a number of references earlier by speakers to the recent gene therapy experience. While that didn't occur -- and I would underline that, that did not occur in the setting of compassionate use, I think it was a recent example of a feeding frenzy by the press, trying to uncover more and more cases of safety problems with gene therapy that, frankly, did result in some immediate pause in studies until the FDA could be comfortable and the NIH Rat Committee could be comfortable that adequate protections were in place, and it did give pause to a number of companies about the attractiveness of immediately going forward in this area. So, unexpected safety toxicity that can occur when you have a wide-open program that is separate from your focused program, we believe, can have adverse consequences.

Secondly, I would like to note that contrary to the prevalent notion, we generally believe that we don't learn a great deal from a true individual compassionate use program. We learn a great deal from potentially an expanded access program where a larger number of patients with fixed entry criteria and description of the disease might be treated and give us an early look at efficacy. I think it is even more treacherous to think that we are going to learn

something about safety in a meaningful way through a compassionate use program.

So, I am distinguishing. And, I think you will be hearing from some other speakers that expanded access programs do have the potential to enhance our knowledge of a drug for efficacy and safety, but we generally believe that a true compassionate individual exemption program does not.

Finally, I just want to emphasize again that as doctors -- I appreciated Dr. Sugarman's framing of the question, we are taught to do no harm, and I think within a company the doctors who are following a drug know a great deal about it. Contrary again to some allusions earlier, not every company is interested in protecting its stockholders and increasing its stock price. We don't want to deceive ourselves about the efficacy of a product. I would venture to say that in many regards, in many stages of development the doctors in a company do no know more at any single snapshot in time than even the FDA reviewers do because the FDA reviewers get annual updates. They get sent immediate adverse events that qualify under regulations, and they get interim reports about the efficacy of a product but they really don't necessarily have their pulse on just how efficacious or lacking in efficacy a drug is in development at any given time.

So, when we get a request we are, in fact, wearing

a couple of hats and one of those hats is to weigh the benefits of what we think is the potential benefit to a patient versus the very real risks. That is a tough equation. One equation that is not so different, and that is what we will get into, is that we definitely are buying a lot more work for our entire organization, work that could potentially divert us from getting a drug more quickly to the FDA for review and to the public.

I just wanted to add one further complication, as if there wasn't enough on the plate today. This slide shows the experience of Schering-Plough over the last twenty years with drugs, on the left-hand side, that represent drugs in the oncology arena. They actually represent a hormonal treatment, a biological and a conventional anti-neoplastic drug. Each of them at some point in time did have compassionate use experience that I will build on in my talk, but on the right-hand side is another topic that we haven't touched on, which is supportive therapies for cancer, which bring their own set of issues. I really don't have time and I don't think the committee today would be able to address them, but I wouldn't discount GM-CSF, which most people are familiar with as a hematologic support drug that can be utilized when patients have low blood counts, and it was an interesting issue in the development of that drug because we knew very quickly -- we had a good rationale

from the clinic that we knew in animals it could increase the blood count when we gave this drug. We knew as soon as Phase I, in a very clear dose-related manner, that we could increase the blood counts. And, there was tremendous interest even in Phase II, to respond to requests to help patients who had had a bone marrow transplant and were now 30 days past the transplant and still hadn't had any recovery of their blood count, or patients who had a life-threatening illness with infection, that we truly believed we could improve but hadn't yet finished our studies to demonstrate it convincingly.

Posaconazole is an anti-fungal compound that had shown activity in aspergillosis, which is a very serious fungal infection for which current therapy is not highly efficacious. We are still developing it and we have evidence that this is an efficacious product and we get numerous requests, particularly from the investigators who are involved in our studies for patients who don't qualify for the study when they have a patient with a life-threatening infection and nothing further to offer them.

This is the slide I want to spend a moment on, and I call it the logistics of a compassionate use protocol. This is really meant to address the pure single-patient exemption, not the expanded access program but I think Dr. Kennealey will next tell you how many aspects of this do,

nonetheless, apply to that program as well.

The exercise begins up here when a patient or a family make direct contact to try and get access, usually after going through a pretty good thicket of telephone tag and referrals, and not going to the right place in the company, get to the project physician. Every company might call that person something different but the person I am talking about is the individual physician who is in charge of that drug for us in the company. That physician has responsibility within the company to do all the real clinical trials that are going to get assessed and, hopefully, with completed studies will go to the FDA. So, it is a busy person who has some major responsibilities, but they are usually the best person to take the call when somebody wants to request immediate access, and it usually is immediate and a crisis.

That call can trigger a number of activities, but one thing we do is we ask whether we can talk to the physician. That is drawn with a couple of arrows because physicians are busy people so it might be a series of calls before we finally get to the physician who may or may not be an oncologist. If it is not the physician, we have to track down the referring oncologist.

There are two players who, for no special reason, I left off this slide but maybe they will be added in my

next version. One is up here and I will leave it to your imagination. Those are the VIPs, the congressional liaison officers, the investors in your company who all have a friend or a cousin who is the lawyer of the CEO or the senator's close friend who is also putting pressure on the company. The other player I didn't put here is the FDA. I put the FDA down here but there is no reason for me not to say that the project physician in our company could very quickly begin a conversation with the FDA to say, "we have received a request. What do you think?" Again, I would like to echo what a number of other people have said. In my personal experience I certainly would not bash the FDA. I think on almost every occasion we have had a very realistic discussion with the FDA about whether the stage of development of the drug justifies a request at that time, and we are usually in pretty good concordance with whether it makes some sense or doesn't make some sense.

That, again, is a couple of phone calls back and forth here. So, this project physician, who has been identified by the family and is getting calls regularly to find out where the drug is, if they agree -- if the company has made a decision that we will entertain requests, starts to ask for more information. As Dr. Williams pointed out, the regulatory requirements are -- we call it a patient synopsis. That could be a one-page description of the

patient and their previous treatment and their present condition. It could be a hospital discharge summary. Sometimes it is a three-inch hospital discharge record.

What we then say, if the patient qualifies, is we tell the physician you have to get us real fast a special type of curriculum vitae, with a 1572 form that the FDA requires for an investigator, a signed informed consent, a signed protocol and IRB approval. As you can imagine, if you are going back to an institution that has been conducting one of your trials, this isn't a great deal of additional trouble. If you are going to a new site or if you are going to an oncologist who only rarely has experience with experimental drugs it takes a lot of hand-holding to get through these procedures.

Once all these arrive, in our company our standard procedure is that this package goes through two places, our regulatory affairs group gets the package and forwards it to the FDA. Again, at that point we have had previous conversation with the FDA in most cases, although if we are starting to do a lot of the same type of patient we might be sending it to the FDA for notification and not having to negotiate each case.

And, we have an internal management sign-off. Because of this next step, which is packaging and shipping -- and this is a pretty important concept which might be a

little different in a small biotech company that has one product but in a company like ours and in any of the major drug companies, we have a department of trained people who follow FDA regulations for handling experimental drugs, and it is not the same as going into a pharmacy and pulling a couple of bottles of the experimental drug off the shelf and throwing them into a Federal Express package. The material that we have produced for the clinical trial is often labeled for a double-blind study. It is packaged in the amount that we use for the experimental clinical trial, which might be two weeks, four weeks or six months of exposure. We have to create a special packaging vial for the experimental drug that would be appropriate for a patient compassionate IND.

I am going to return to this but, within our company, that request to have that sent out as an emergency the next day competes with requests that that shipping department and packaging group has for every other experimental drug that we are developing. So, when they come in to work in the morning, they have a long list of studies that are about to start for oncology studies, cardiovascular studies, Alzheimer studies, AIDS studies. They have to make a decision of how much they are going to divert somebody from what they were supposed to do that day to get this shipment out. I know that sounds minimal, but even for a

single compassionate use request it is quite a diversion, and when you start to run a couple of these a week through your organization you can easily disrupt the entire planning process for the studies you want to start.

What are the follow-up procedures that we are committed to once we say we are going to supply one patient or a number of patients with the compassionate product? In our company -- this is our own SOP -- we send out quarterly letters requesting follow-up to find out what happened. We have an FDA regulatory obligation to file what are called alert reports, that is, any life-threatening adverse event or death has to get to the FDA real quickly. Again, if we are not working with experienced investigators, it takes quite a bit of education to make sure they understand what their requirement is as an investigator to get us not just the immediate report but all the follow-up information possible.

That is what we have to do on an ongoing basis any time something occurs. As you can imagine, in cancer patients who are usually quite ill it is not unusual to have a number of alert reports that are going to be kicked off with any compassionate use.

Then, on a yearly basis we have to report to the FDA, in what is called an annual IND report, everything we know about our product, every adverse event whether it is

mild, moderate or severe or life-threatening is supposed to go into our annual IND report. At the time we file the NDA, when we tell the FDA we are now presenting all the information we know for consideration of approval, we are supposed to get all the information back on anybody who ever received the drug. We also have a regulatory requirement to retrieve unused drug. If the patient stops responding and they don't want to take the experimental drug anymore, or if the patient dies the investigator is not allowed to just throw it away and they are certainly not allowed to use it on another patient who looks about the same. So, we have an obligation to track and be accountable for that drug and we have to get it back and destroy it.

Finally, there is an interesting new twist, which is what our obligation if the patient is doing well to resupply this patient indefinitely? It is of interest that in a recent reissuance of the Declaration of Helsinki there is a clause that actually says that there is an obligation to continue to provide a drug of value to the patient. So, we are aware that once we make a commitment to try and help a patient, if they are doing well we really have made a commitment forever.

Drug supply I have mentioned, and won't dwell on this but I do want to drive home the difference between a clinical manufacturing phase to a commercial manufacturing

phase. There has been mention by the last two speakers that we are in a new era of science. Many, many of the new products being developed for oncology are recombinant human proteins, monoclonal antibodies, gene therapy vectors. When you are in an early stage of developing clinical materials for the testing of these products, we do it at an extremely high cost of goods. We are making a very small amount, enough to get us through Phase I and Phase II. We have to qualify those facilities with the FDA to show that we can meet certain standards for reproducibly making the material that is stable. So, we set up a facility that will be adequate for the early studies and, at a certain point, when we think it looks good and we think the Phase II trials are going to be promising enough that we are really going to go to Phase III, or at some point in Phase III with enough lead time to have commercial manufacturing capability when the drug is approved, every company for every drug has to make a very critical business decision of when we are going to switch to a commercial site that produces much larger amounts at a much better cost of goods.

Having said that, in our company and I am sure in every pharmaceutical company, we have many examples of drugs that cost literally thousands of dollars per dose while we are producing it for the early stage of trials. Again, I am not looking for sympathy from the patient community, but to

start to produce more and more material before we know how good the drug is going to be is a tremendous commitment. Many companies I believe quite honestly say they just don't have the excess material at an early enough stage when patients might be excited because of something that was presented as early findings.

I have mentioned the packaging and shipping, and perhaps this is an exaggeration but, again, I have been told in our company that if you start to send in a request for more and more compassionate shipping what don't you want me to ship today, because it takes the same amount of work to slap labels on 200 vials or 200 doses of a drug for a clinical trial as it does to get that one shipment out the door for the patient.

I mentioned drug accountability and retrieval. The second issue that I put on this slide is what I call expanded access program specificity. As a number of the people around this table know, this is a real-world example of a drug I mentioned earlier, called, temozolomide, which is a drug Schering developed and which has seen success in the treatment of advanced brain cancers. In our pivotal clinical trials we had very carefully selected patients who went through a pathology review to document that their underlying form of brain cancer was anaplastic astrocytoma or glioblastoma multiforme. When our studies completed

accrual, and we were waiting for follow-up, and submitted to the FDA, the word on the street and the word from many of our investigators who had done these studies in patients who met the protocol criteria was that this was a very attractive drug for patients who had failed prior therapy for brain cancer, and they wanted to get compassionate use.

We decided to respond to this request. You know, we could go through the mechanics of why this request made it, but we felt we had a good drug that was going to get recommendation from the FDA for approval, and we set up an expanded access program. I guess the watch words I want you to think about here is the proverbial Pandora's box because once you decide you are at the point that you can supply an expanded access program for a very limited indication, the question becomes what do you do with the call the next week for a patient with end-stage medulloblastoma or a neuroblastoma? Those are small variations of very rare forms of brain cancer that weren't in our original clinical trials, and is it ethical? Do we know enough medically about them to think it is a good idea to make our drug available for these patients?

This looks like a simple slide. It is a plea for a simplified case-report form. This is one that I have heard from peers about one of the ongoing issues, which is how much do we have to collect as follow-up information?

The second point is, if you really do have a drug that has been tested in thousands of patients do we need to collect all of the expected, well-known side effects, or can we create a case-report form for the compassionate use that is only looking for unusual, unexpected or serious side effects?

Finally, this is my final slide, and I think it is the point we are going to be leaving for the committee to discuss in the time that is left this afternoon, which is what is the appropriate point in development? Some people say after Phase II. I mentioned GM-CSF as an example where the scientific rationale was very clear. It made a lot of sense that if we saw translated into humans the effects we had seen in animals, it should work; it should increase the blood count. And, we did see that in Phase I. When we were in Phase II we had interim results that we saw blood counts improve; we saw patients clear infections. Even though Phase II wasn't complete, is that a scenario and is it a scenario that is generalizable that some drugs earlier in their development, at end of Phase II, could be candidates for such programs?

Our suggestion would be to avoid hard rules and do allow exceptions. However, I am saying that but I am also saying with trepidation what it does open up, and I think that is going to be the topic for discussion later. Thank

you.

DR. NERENSTONE: Dr. Kennealey?

DR. KENNEALEY: Thank you very much. My name is Gerry Kennealey. I am Chief Oncologist at AstraZeneca, and prior to joining the industry I was a practicing medical oncologist, and quite familiar with the NCI's Schedule C program as I gave cisplatin to my patients with testicular cancer and asparaginase to my patients with leukemia, when those were available through the NCI program.

I realize that many of you are sitting there with your legs crossed and Gary is going ahead and deleting some of my slides at the moment to speed things up a little bit.

I think this is obvious from what we have seen and heard today. Rising public expectations are clearly making earlier access to therapies necessary. Patients are really much better informed than they have ever been in the past. The worldwide web is giving more and more information on health and new treatments, new treatments in particular. Patient advocacy groups, and you have heard from a lot of them today, are more knowledgeable, more influential, and more effective on behalf of their clients than ever before.

I was going to talk a little bit about treatment INDs but I am going to skip right on to the main focus of my talk, which is expanded access program. That is because we believe that additional treatment approaches are necessary.

Patients with more common tumors are exhausting currently available approved and experimental treatment options and the sheer number of patients who meet description requires a more efficient method of meeting their legitimate medical needs.

For those of you who were here this morning, you heard about a number of patients who had multiple therapies for chronic lymphocytic leukemia and still had an excellent performance status. You heard about an hour ago from the wife of Mr. Tibbett who has had a number of treatments for colorectal cancer and is still working full time.

Now I will go on to describe our own experience, and our experience is with the drug called ZD1839 or Iressa. It is an EGFR tyrosine kinase inhibitor that is orally active and can be given only once a day.

We began our Phase I clinical trials in May of 1998 and just two years ago, in May of 2000, reported initial activity in a number of clinical trials, including a report at the plenary session. Following our presentations there was a lot of media hype from institutions that were involved in participating in these trials.

This is a montage of some of the publicity that was seen in May following the presentations at ASCO, as well as the presentations at AACR. Unfortunately, what happened was that the media took a drug that appeared to have some

real activity in non-small cell lung cancer and put it forth as a pan-cure for multiple cancers.

Our initial plan as a company, following those initial Phase I and Phase II trials was to initiate Phase III randomized, controlled trials which would lead to the registration of the drug. But our information center and various patient and professional groups received over 7000 inquiries about the compound between May and December. Calls came from elected representatives, celebrities and other high profile individuals expediting treatment with Iressa now. We stopped counting when we got beyond 12 senators' offices immunotherapy terms of phone calls, and calls came not only from celebrities in the United States but from the rich and famous all over the world.

There is plenty of precedence for expanded access programs and I am going to skip over this since this has been discussed amply by the representative from Genentech and the AIDS experience.

I will now go on to what I think is one of our most important slides, the principles that we used in driving this expanded access program. At the time we made the decision to go ahead with expanded access we had data in only 300 patients, some of whom had received a tiny dose; some of whom had received only a single dose. The majority of activity that we saw with this drug was in patients with

non-small cell lung cancer. So, we elected initially to limit the protocol, the expanded access, to patients with non-small cell lung cancer.

We also felt, and we had such a small database, that patient safety was a real concern and we were going to be very rigorous in collecting patient safety data. AstraZeneca is a global company, and we wanted to be sure that there was equal access throughout the world. It just wouldn't do if a pat in Germany could get Iressa for his or her lung cancer and somebody in France of the United States with a similar stage of disease could not. So, we wanted to make every effort to have equal access.

The other principle, and this was a tough one initially, was that we could not allow special cases. We could not allow preference for the senator or the movie star over the factory worker. We solicited and, indeed, received full backing from our senior management, up to the CEO, to enforce this policy.

Many people have referred to drug supply as a potential issue. We were caught a little bit by surprise with the results of our initial trials so we were a little bit behind in ramping up our drug supply. So, we were worried that that might become an issue and, as I will mention later, fortunately, it has not.

The other worry that we had as a company is that

we didn't want any interference with our registration program, which was also planned in non-small cell lung cancer. This is a very important principle in terms of expanded access. Registration is the best route to expanded access. It is the best route for patients because it allows them and their families to have unfettered access to new therapies without the paperwork that is involved with expanded access programs or single-patient INDs. It is best for physicians because it allows them to make their own judgment as to whether a therapy has benefit or not. It is best for the FDA because it allows them to devote their scarce resource to other new and promising compounds. Lastly, it is best for us because it allows us to spend our time further characterizing the compound and working on other promising compounds as well.

These are the initial steps. We decided right away that we could not have, as I mentioned earlier, this program interfere with our efforts to get the drug to market. So, we created a dedicated expanded access program or EAP team. We actually considered moving them to a separate building but rejected that as not being necessary.

We immediately involved the FDA Oncologic Drugs Division and exchanged e-mails and telephone calls with them over the month or so where we were putting the protocol together. We also worked closely with Patty Delaney, in the

Cancer Liaison Office, who provided us invaluable advice on dealing with sensitive issues concerning questions from patients, questions from physicians, and also gave us some background on the mistakes that other folks had made and so enabled us to, hopefully, not repeat other people's mistakes.

We also decided use a clinical research organizations that is an external company that manages all of the day-to-day activities, such as mailing out the forms, getting in the forms, getting the IRB approvals -- all of the things that take up just an enormous amount of time and we just didn't have the folks internally to do this.

We also elected to collaborate with the National Organization of Rare Disorders, or NORD, and you heard from them earlier today. Again, they had a lot of experience in dealing with phone calls from sick people and from their families, and our internal folks, our internal call center, is just not trained to do this, and we received a lot of phone calls about other drugs and about other aspects of this drug. So, we wanted to have a small group of people specially trained to answer questions about expanded access.

This is the protocol we came up with. As I mentioned before, we felt we had very good reason to restrict the program to patients with non-small cell lung cancer. We agreed with the FDA that it made no sense to

restrict the program to patients whose disease had failed to respond or who had relapsed on standard therapy. We also forbad concomitant therapy for cancer. We had absolutely no data on the combination of Iressa with any of the common cytotoxic chemotherapy drugs.

We also didn't want patients who were candidates for our registration trials to be allowed into the expanded access program because that would really slow things down, in our view. We wanted patients to have at least adequate general health because, again, we had no experience in critically ill patients and, obviously, we had to have informed written consent. Obviously, that is an issue that has been talked about by a number of folks earlier today, a really critical issue in dealing with a drug this early in its development.

These are some of the challenges that we faced. AstraZeneca employs 10,000 people in the United States and any one of them could be approached at a cocktail party or a soccer game with "my mother has lung cancer; how do I get Iressa?" We wanted to be sure all of then knew the pathways for patients and the pathways for physicians to find out what they needed to know about our expanded access program, really a critical issue from a public relations standpoint, and also a critical issue to see that patients and physicians got an answer quickly.

I have to say that when we started this we dealt with some of the things that you heard from the patient advocates earlier. Initially callers got into a loop when they never got an answer, and we had to break that very, very quickly because that was obviously very frustrating to people and their families who were critically ill.

We had to develop a single informed consent document that would work for everybody. Those of you who have been involved in clinical trials know that when a drug company sends out a consent form your IRB changes it around, changes the wording, changes the format, usually adds very little in terms of content but feels that they have an obligation to make some change and put their individual stamp on it. This requires an enormous amount of effort. So, we took our consent form, showed our consent form to patient advocacy groups, to the FDA, to NORD, reviewed it very thoroughly internally so that we were quite confident that we had a form that covered everything that was necessary.

We also -- and this goes back to Dr. Spiegel's talk -- had to determine what data had to be collected. Safety data at this point is very, very important. With only 300 patients who had received the drug, we needed to know everything possible even though the data would not be collected with the same rigor that was to be collected in a randomized clinical trial.

These are some of our concerns. We really worried about the potential impact on our registration trials. Again, so far that does not seem to be happening. We worried about the potential impact on submission and, again, because we dealt with a separate team, the submission team is moving ahead without being distracted by the expanded access program.

Drug supply was a real issue, a real worry in August and September. It looks like it is much less of a worry for us now. However, the demand created by the media, should we bring forth new results, could again make drug supply a potential worry.

Equity I have mentioned before and I put it up here again because of its importance. There has to be no difference between the United States and France. There has to be no difference between the factory worker and the movie star.

The next question, and again this goes back to what Dr. Spiegel talked about, is what about other tumor types? Most or many malignancies express EGFR on the surfaces of the cancer cells. So if a drug like Iressa works in lung cancer, it might work in other tumors that express EGFR or over-express EGFR. We made a decision that we would delay expanding the program to other tumor types until we had a little more information about the drug and currently

our plans are to convene an ethics board in the spring to review this very important issue.

What about the future? Cancer drug development now clearly operates in the public eye. As you can tell from the speakers who started off this meeting, there is a lot of awareness of what goes on in developing a drug from the first preclinical studies in rats to drug approval. An expanded access program, in our opinion, should be considered to meet patient needs, particularly those with advanced disease, especially when there is the likelihood of a large number of patients who would want the compound. And, successful programs require commitment and cooperation from all parties involved, in this case the drug company, the FDA, the patients, he patient advocacy organizations.

We are do need some guidance from the FDA on a number of unresolved issues. The role of these data in NDA filings -- are they of benefit in terms of getting the drug approved quickly, and is there a potential for early registration, something, again, that was talked about this morning?

I would like to finish by thanking what are now 200 patients enrolled in this program, our expanded access team, NORD, the various patient advocacy groups, like ALLCASE, who have helped us, Patty Delaney in the Cancer Liaison Office, the Oncology Drug Division, and those who

have consulted on this program. Thank you.

DR. NERENSTONE: Thank you very much. What I would like to do now is take a brief break and allow everybody to get up and stretch and do other things, and come back at 4:05 because we are immediately going to want to start.

[Brief recess]

DR. NERENSTONE: Because we are so strapped for time, the plan will be for the patient advocacy community representatives to address the committee, after which time we are going to open up for questions to the speakers from the committee. We are going to have to save ODAC discussion until our March meeting, at which time this obviously very complicated and very important issue will get the time it really needs to give the FDA some direction.

We do have Susan Weiner, of the Children's Cause, who was able to make it now and she will address us first. Then the patient advocacy community participants will speak.

MS. WEINER: Thank you very much. I will be brief. I am Susan Weiner. I was the parent of the child with a brain tumor who was diagnosed in infancy and then died just short of his 14th birthday.

I am the founder also of the Children's Cause, which is an education advocacy group whose mission is to accelerate access to innovative therapies for children with cancer.

I will be very brief. As we all know, the successes in the treatment of childhood cancer over the past twenty years really are due directly to high rates of patient enrollment in high quality clinical trials that are conducted through the national pediatric oncology cooperative groups. Improvements in outcomes for children whose cancers have not experienced these kinds of treatment, positive treatment outcomes, notably those with solid tumors, will depend on the clinical trial system made even more robust through a partnership with the Children's Oncology Group, the FDA, the NCI and the pharmaceutical industry.

Evaluating standards for single-patient use in pediatric oncology must be considered in this context. The consensus of the pediatric oncology community, including parents, is that the hope for curing these children lies in more clinical trials that can evaluate new agents and treatment regimens, hopefully, made even more available by the newly unified national cooperative group and by a vigorous application of the pediatric exclusivity provision of FDAMA. For our children whose disease is resistant to available treatments, special exemption and single-patient access is really the last resort. We really have to include our children in more clinical trials and make more clinical trials available, and we would hope that that would be the

direction that all of these new development would go in. Thank you very much.

Perspective from the Patient Advocacy Community

DR. NERENSTONE: Thank you very much. Mr. Carl Dixon?

MR. DIXON: Good afternoon. Thank you for this opportunity to speak to you about compassionate use of drugs for cancer patients. I am Carl Dixon, the President and Executive Director of the Kidney Cancer Association, a voluntary patient organization which, for over a decade, has been dedicated to helping kidney cancer patients and their families deal with the physical, emotional and social impact of kidney cancer.

As the only national kidney cancer patient organization directed by patients for patients, the association realized the importance of a national policy encouraging efficient development of new oncologic drugs. We commend the FDA for holding this important meeting to discuss patient access to unapproved oncologic drugs outside of clinical trials. The association believes that it is important that the voices of patients and their advocates be heard in this process.

Kidney cancer is an uncured disease. Today there are approximately 200,000 Americans who have kidney cancer. Each year 12,000 Americans die from kidney cancer. It is one

of only three types of cancer with an increasing incidence. There is only one FDA approved treatment for kidney cancer, the biological agent interleukin-2. Unfortunately, this treatment only works in about 20 percent of the patients who develop metastatic disease. The second-line therapy, the off-label use of a different biological agent, alpha-interferon, offers only modest promise of success. The standard of care after these treatment is participation in a clinical trial.

We are very concerned about the availability of high quality clinical trials for kidney cancer patients. For a variety of stated reasons, some of which are different to understand, many patients who want to receive new oncologic drugs in clinical trials are not able to meet the often highly technical eligibility requirements. In particular, many are barred because of trial designs that call for only patients who have not received prior therapy or for patients willing to perhaps be randomized to a placebo arm.

While we understand the need to make certain that drug sponsors scientifically prove that their drug is both safe and efficacious, kidney cancer patients, in search of hope, want compassionate access to these drugs even knowing that the safety or efficacious is unproven. In other words, they are willing to take more risk. These are the patients who seek compassionate use or a single-patient use of an

[Slide.]

Let us look at the problem of evidence of efficacy. First, the original protocol did not specify time of final analysis based on events or a specific data cutoff date. However, in the statistical plan submitted by the sponsor in November of '99, an arbitrary cutoff date of March 8, 2000 was chosen for final analysis. As for this date and NDA submission, there is no difference between the two treatment arms with a p of 0.1255 and a difference in median survival of 0.9 months.

Note that the data by this March date was reasonably mature with approximately 80 percent occurrence of events. Even in subsequent analysis with updated data, unadjusted p-value has remained above 0.05 level with 88 percent of events already occurred.

[Slide.]

The second problem refers to multiplicity issues. This graph illustrates that repeated analyses result in different p-values. This emphasizes the importance of prior specification of time of final analysis based on number of events.

Per sponsor's statistical plan, March 8th should be technically considered as the final analysis date. It appears that the nadir p-value was reached with September 8th data cutoff date.

assistance to patients by referring them to other clinical trials or, at the very least, to the National Cancer Institute Clinical Trial Search Service. If the drug company is simply not allowing compassionate access, they should be prepared to justify that policy. Simply stating that it is a matter of corporate policy is not an acceptable answer to a patient with a life-threatening disease. Likewise, if the FDA has a procedure or rule about when new oncologic drugs may be made available, it must state that procedure publicly and in plain language.

One reason frequently cited by both the FDA and the drug companies for denying compassionate access is that the single user data might be used against the company when they file their new drug application. Balderdash! While, by statute, the FDA must track that safety data on every single patient, including compassionate use patients, if such patients die as a result of their cancer, the expected outcome in this group of really seriously ill patients, then the data is not used against the drug company. The only time that compassionate use safety data might be used is, for example, when every patient on compassionate use dies from an unexpected source or a remarkable adverse event occurs.

I am sure that the advocacy community will be more than willing to disseminate this important information on how to secure compassionate access for all Americans. I know

the association would do so. Once again, we commend the FDA for assessing and reviewing this complex subject of compassionate use and, in conclusion, I want to express thanks to Terry Tuergo, Patty Delaney and Joanne Minor for the excellent work that they do every day with patients seeking compassionate use. Thank you.

DR. NERENSTONE: Mr. Robert Erwin?

MR. ERWIN: Well, I am with the Marti Nelson Cancer Research Foundation. We have worked with patients with a variety of types of cancers in making treatment decisions and enrolling in clinical trials, getting access to experimental medicine through a variety of mechanisms.

The comments I want to make today are derived from that experience, which has varied across the map in terms of both success and failure. I would like to start with an observation that this rather complex issue should probably be dealt with in a much more extensive analysis than we have time for today, but really we can reduce it down to one simple consideration that I think should guide the rest of the debate, and that is that for some people suffering a terminal disease treatment with an investigational drug might be the only opportunity they have for an extension of life. That will not be true in most cases but it is true in some cases. I think if we keep that in mind as we go though the analysis and consider that fact, it may guide some of

interpretable and subgroups have to be studied individually.

In such a case, one can consider subgroup analysis. Since the sponsor presented Table 11b of my review, I would like to clarify that this model was considered to test for interaction and find a rationale for further subgroup testing.

This model was not intended to evaluate the treatment effect in either of the subgroups, that is, either the liver met subgroup or the non-liver met subgroup. A subgroup analysis was further performed in my review, as well.

[Slide.]

However, in this study, stratified randomization within liver subgroup was not done. Imbalances favoring histamine plus IL-2 arm in the distribution of patients are observed. Furthermore, liver metastasis subgroup hypothesis testing was added on to the original protocol after the study had completed enrollment.

No allocation of alpha for testing liver metastasis subgroup hypothesis was planned prior to the start of the study. A statistical plan was submitted by the sponsor prior to NDA submission with a plan for post-hoc adjustment of type 1 error for testing liver metastasis subgroup hypothesis.

[Slide.]

In this graph, red bars represent histamine arm and blue bars represent IL-2 arm. The message to be taken from this bar graph is that the red bars, which represent the histamine arm, have higher percentage of patients in all the better prognostic subgroups. For example, patients with less than 65 years of age, female, performance status of zero, no prior chemotherapy, et cetera.

Thus, this bar graph illustrates that the imbalances observed favors the histamine arm. It should also be noted that of the 14 characteristics presented in this graph, 13 of them favored histamine arm.

[Slide.]

Because of these imbalances in the liver subgroup, it is appropriate to further evaluate treatment effect using covariate adjusted analysis. Sponsor has submitted models which are different models with different data cutoff dates. They are also different from protocol specified covariate and covariate specified in the statistical plan.

FDA has used consistent model at all times and no selection was considered, that is, all characteristics identifiable with imbalances were included in the model.

[Slide.]

In the original model, only two factors were prespecified, presence or absence of liver metastasis, and secondly, whether the patients received prior chemotherapy

any risk, and it is impossible for any group, no matter how wise it is, to make the right decision for that broad range of individuals varying across all sorts of situations. I think that should be left to the individual.

However, it is very important to ask is a patient's expectation of benefit realistic, or is it only false hope. When we help patients to choose clinical trials for enrollment, our function with the patient and the patient's physician is to try to assess the probability of therapeutic benefit. It has been pointed out very clearly that research studies are not designed to provide benefit, but patients enroll in research studies primarily on the chance of receiving benefit, not as individual acts of altruism to advance the experimental status of science and medicine. Recognizing that duality I think is extremely important.

The expectation of benefit is something that has been a major factor, I think, in the hype and the interest has in coverage by the media. It is a circular argument -- does the media generate the hype or does the public draw the hype because of their hope that there will be these kinds of benefits? There are many cases where the only likely benefit that apt is likely to receive from a clinical trial is the psychological benefit of participating, but in some cases I think it has been demonstrated, although as people have

pointed out today there has not been a systematic gathering of data to evaluate this, that there have been individual cases of life extension and even dramatic recoveries, at least for short periods of time, as a result of early access to experimental therapies.

So, I think that it makes sense for the FDA to leniently approve individual treatment INDs and to distinguish between expanded access protocols and individual treatment INDs in terms of the expectation of benefit. An expanded access protocol is very appropriate I think for promising cancer therapeutics after efficacy data has been gathered in Phase II trials, and these should be based on a realistic possibility of therapeutic benefit. They can, and should, be designed so that they do not conflict with Phase III trial enrollment. On the other hand, in cases of rare cancer, very unusual situations, complex situations where patients may have multiple disorders expanded access protocols will not be appropriate. Patients will not qualify for those either. Because it is impossible to know the probability of success in these widely varying cases, I think there will be a role for individual exemptions, individual treatment INDs even if there is broad acceptance and implementation of expanded access protocols.

If FDA has data suggesting a safety risk that would not be known to the physician and the patient, I think

Furthermore, the p-values presented in the table are not adjusted for multiplicity, meaning multiple hypotheses or multiple analysis.

For example, adjusting only for two hypotheses, one in the ITT population and one in liver metastasis subgroup, the p-value is 0.1146 with the updated data.

[Slide.]

Therefore, the take-home message is that the adjusted model results are sensitive to inclusion and exclusion of a covariate. They are also sensitive to whether a covariate is used as a continuous variable or a categorical variable.

More importantly, it should be kept in mind that these p-values are not adjusted for multiplicity either for multiple subgroups or multiple analyses.

Thus, there is no robustness in the liver metastasis subgroup finding, and it is not possible to assess the true treatment effect in this subgroup given the imbalances from one single open label study.

Dr. Griebel will continue the presentation addressing further the single study issues.

DR. GRIEBEL: Good afternoon. My name is Donna Griebel and I am the medical team leader. We are here today considering an application that has as its foundation a single randomized controlled trial, and my job on behalf of

unapproved indications and in patient subpopulations that were not represented in the clinical trial. This is one reason that certain products have so significantly exceeded the sales projections of Wall Street analysts, and it is a phenomenon well understood by the companies that market the drugs.

I think the FDA has done a good job so far in addressing this important issue. I hope that in considering its policies the FDA will further foster a regulatory environment that encourages both individual treatment INDs and expanded access protocols, and I favor the FDA taking an active role and outreach to make the opportunities widely known and understood. Such outreach and education will probably require that the FDA have additional resources, and I think the patient advocate community and the public needs to take some responsibility for making those resources available.

The issue of fairness is a different one that should be taken seriously, but difficulty should not be an excuse to take no action. I think, as I mentioned earlier, the FDA should anticipate the possibility that a new generation of drugs is coming down the pipeline that will demonstrate better efficacy and also generate increasing demand for early access.

Perhaps the FDA can actively encourage the

development of better validated or surrogate markers for efficacy to shorten the clinical trial process, and develop guidelines for the incorporation of cross-over provisions in Phase III trial design so that patients randomized to the standard treatment arm have the possibility of benefit from the new agent if standard treatment does not prevent disease progression. The potential conflict between the need for randomization in clinical pivotal trials and a patient's desire to obtain treatment with an experimental agent is an important topic for further discussion.

The FDA could also clarify the circumstances and extent to which drug sponsors should be concerned about adverse events that might occur when patients are treated under individual INDs.

Finally, I would like to comment on my view of the responsibilities of the drug developers, and I appreciate very much the two presentations earlier from pharmaceutical companies. I think that if we can believe what the scientific, medical and corporate world tell us, then dramatic improvements in the treatment of cancer are just around the corner and, unfortunately, have been just around the corner for the past ten years. As optimistic as I would like to be, I don't believe the news is this good. Unfortunately, a lot of it is just hype promulgated especially, I think, and this is a little bit of a bias, by

smaller companies to increase interest in their stock but also by others to increase the dales of newspapers, books and research reports. For better or worse, the steady flow of good news, both the real and the misleading, is actually building a market for compassionate access to experimental drugs. The same companies that frequently resist providing access to investigational drugs outside of clinical trials are building this market. Companies need to reconcile the incongruence between the exuberant optimism they steadily foster on the press and financial community with the unfortunately pedestrian reality of most of their cancer products' performance. Demand for compassionate access will only increase as information technology, such as the internet, continues to expand and the real breakthroughs begins to show up in the clinic as they may be starting to do already.

Companies must be clear and honest with the public about their policies, and make it clear, if the answer is no, that that is their responsibility. There are a number of perfectly valid reasons that a company might choose to deny access to an experimental drug but, as has been unfortunately my experience in a number of cases working with individual patients, companies choose to blame the FDA and the FDA is, in fact, not the problem in this case. Companies should take responsibility, not blame the FDA, and

make it very clear what the process is if the answer is yes, and if the answer is no make it very clear that there is no recourse by getting into this continual loop back and forth between multiple physicians, possibly politicians, lawyers, the FDA and others. That kind of circle of misinformation is a waste of time but, most importantly, it generates false hope which is a very unfortunate thing in these sorts of diseases.

I appreciate the opportunity to address the issue and hope these comments have been helpful. Thank you.

DR. NERENSTONE: Thank you. Our last speaker for this afternoon is Miss Jan Platner.

MS. PLATNER: Thank you. I am Jan Platner, from the National Breast Cancer Coalition, and on behalf of our over 500 member organizations I want to thank you for the opportunity to comment today.

Since NBCC's beginning nearly ten years ago, our commitment to evidence-based medicine has been fundamental to all of our advocacy efforts. We need to know what works for women with breast cancer, and all breast cancer patients need access to what works. Women with breast cancer should not be given false hope by treatments that are unproven. Interventions must be based on the best possible science available, and the best way to achieve that is through well-designed clinical trials.

There are all too few truly effective treatments for most types of cancer. While the public is inundated with information about cancer breakthroughs and news of promising new drugs, the reality is that most drugs result in incremental improvement at best.

The research process seems agonizingly slow for those who have run out of treatment options, and pharmaceutical companies, scientists and the media each bear responsibility for creating unreasonable expectations about unproven drugs. This has created a climate where many patients mistakenly believe that access to an investigational drug is their last hope when, in reality, it is a false hope.

Public policy should discourage access to investigational drugs outside of clinical trials. The coalition believes that single-patient INDs should not be granted but, rather, in situations where there is a compelling reason to grant access to drugs outside of a clinical trial that should be done only in the context of expanded access protocols in which distribution of the investigational therapy is fair and data is captured that would add to the scientific base of knowledge about the intervention. Expanded access should not be the norm but, rather, protocols may be allowed in particular circumstances and only for those individuals who do not meet the

eligibility requirements for a clinical trial.

If an expanded access program is allowed, access to the drug must be fairly and blindly allocated and all individuals must be followed, and their data reported to the trial sponsor. Expanded access should not be allowed until there is safety data available from a completed Phase II trial, and data that provides some basis for determining the drug may be efficacious.

While it is compelling to argue that there is little harm in making investigational therapy available to a seriously ill individual for whom there is no effective therapy, if someone is willing to pay for it, this argument simply does not hold up under scrutiny. To follow this to its logical conclusion completely undermines research and the concept of evidence-based medicine. Where does one draw the line? It would mean that any individual should have access to any drug as long as she is persistent and willing to pay for it.

Investigational treatments made available outside of clinical trials have the potential to undermine the clinical trial system. There is little incentive for a patient to participate in a clinical trial if she can obtain the investigational drug outside the trial. I think in the case of breast cancer, I hope, we have learned some lesson from the bone marrow transplant issue where that

intervention was widely available before it was ever proven to be effective, and we could have known years sooner that, in fact, it does not provide benefit for women over standard therapy. We could have saved thousands of women from going through that gruelling process, and perhaps thousands of women's lives.

Certainly investigational treatments by definition are unproven, and even the most promising data in earlier stages often does not hold up. Further, there may be significant safety issues that do not emerge until well into Phase III trials, and that was certainly the case with Herceptin where the cardiotoxicity issue did not emerge during Phase II trials and it was only when we had much larger Phase III trials where that issue surfaced.

Finally, single-patient INDs raise serious issues of fairness or, rather, unfairness. Patients who have access to them usually are very knowledgeable. They have access to physicians who have the ability to develop a protocol for them and are willing and able to implement it. This is not the case for most women with breast cancer. Resources devoted to funding breast cancer should be allocated fairly based on the best evidence available and, frankly, when drug availability is an issue, as it certainly was with Herceptin and it is frequently an issue, we can find no way -- we have thought of no possible way where you can really make the

single-patient IND process fair.

We recognize this is an extremely different issue. We all want to save lives. We must work together to develop the right public policy that will achieve all that, and that must include movement toward more and better research, expanded clinical trials and access to healthcare for all Americans. We believe that a policy supporting single-patient INDs would undermine those efforts. Thank you.

DR. NERENSTONE: I want to thank all the speakers this afternoon. I think you, all, have done a tremendous job in sort of outlining the problems. We are not going to have time to really get into the discussion of those problems. I do want to open it time for the time remaining for the committee to ask the speakers questions or clarification of their presentations.

I will start it by asking especially the representatives of the patient advocacy community, do you think that we can at least start this discussion by outlining who we know should not get investigational agents? That is, the community cancer centers, protocols and a lot of our research suggests that performance status 3 and 4 patients, no matter what you give them, are not going to benefit from continued treatment. Do you think that we can start by saying who really should not get treatment as a way to at least limit our discussion?

MR. ERWIN: I think that is a very important point and it is something that I have been very curious about. There have been anecdotal reports of patients at very late stage, with very poor performance, benefiting from access to experimental drugs. In fact, during the Herceptin expanded access program there were some very publicized, media-covered, individual cases. But, as far as I know -- this may be known to FDA or to Genentech, I don't know what the longer-term outcome was. I don't know if people really received benefit or not. The cases that I am more familiar with are cases where people received no benefit and, in fact, in some cases may have been harmed. So, I think that is a very interesting proposal and I think in general the patient advocacy community is interested in making clear what the risks are. If it turns out that there is a reasonably objective basis to say that risks are extremely high or benefit is essentially zero, then you will probably have broad support for those kinds of limitations.

DR. NERENSTONE: Other questions?

DR. PAZDUR: The industry and also perhaps the patient representatives may like to speak on this, and that is this concept of early hype of drugs and now is that developed? You know, we have seen a lot of publications that come out at ASCO with really interim analysis of data, of early findings of data that come out. I guess for Gerry, how

does the industry view that? You know, it is a double-edged sword in the sense of promotion of a drug, in a sense, for a drug company. But, on the other hand, you know, it does create this false hope. How is this viewed by industry?

DR. KENNEALEY: You have hit the nail on the head. It is a very different issue, less so for large companies like the Pfizer's and the Merck's, but certainly we have to draw a fine line between getting the information that is available into the public domain and becoming purveyors of false hope. It is often not an easy line to walk.

DR. PAZDUR: Many times these abstracts are actually presented while the trial is ongoing, some preliminary level of activity is noted in the abstract. People pick this up and it really becomes a very negative thing when it is reported, especially if these results do not hold up in the long-run and there is this creation of false hope that does exist. Even in scientific meetings we see this. I will just refer you to last year's ASCO where a picture of a single patient was on the cover of one of the publications that were circulated by that organization, a single patient response of an investigational drug, which I found somewhat alarming in a scientific meeting.

DR. KENNEALEY: Hopefully, most of the people who review these scientific abstracts will have a little better filter than that, but I think it is reasonable to bring into

the public domain early information from Phase II trials, especially if there are really dramatic differences. You know, there are a number of examples of that, dating back to the days of cisplatin in testicular cancer. I think all of us have a real obligation to keep information on Phase III trials strictly confidential until there is clear evidence that the endpoints have been reached or that the differences between the two arms are so dramatic that a body that is external to the company makes a recommendation that the trial be stopped.

DR. NERENSTONE: Dr. Williams?

DR. WILLIAMS: I don't know if I used the right terminology or not. I think you were talking about beneficence and autonomy, and it seemed to me I was hearing some conflict there, maybe some of the advocates and patients were suggesting that FDA should really be in the business of getting into the autonomy business. How does one begin to deal with this conflict between the patient who feels that they are totally informed and the FDA perhaps becoming involved in the safety analysis and saying that maybe there is a safety concern?

DR. SUGARMAN: I think you are right to point out where one of the conflicts are, and there certainly is, in this situation, a conflict of those principles to respect autonomy and to do good by patients.

There are a couple of pieces, as you sort of specify these principles, to do the work that they have to do and in a tough case like this one of the pieces that you need to understand I think is that the obligation to not have things done to oneself seems to be a slightly greater obligation than a request for something, for someone else to do something to you. So, it is a stronger claim to say don't touch me compared to the claim of I want that and, therefore, I can have it. They are both claims of autonomy but they seem to be somewhat different.

The second piece about the beneficence argument, as you tried to play that out a little bit, is the argument of the risk on the one hand and the benefit on the other. If you tried to sort of do the math, it wouldn't work; they are not commensurable, as we say.

I think it goes towards enhancing autonomy, and one of the possible solutions would be autonomy enhancing by providing accurate information about risk and what the concerns are as a clinician, as an investigator, as an agency, as a sponsor to understand do you know enough about the risks to provide counseling? Are the risks completely uncertain? Does the person know what these risks might be, and how that risk assessment goes? Some people are more risk seeing, other people are more risk averse, and that part they retain throughout the informed consent process.

Likewise, in terms of benefit, clinicians and investigators ought not give something that they know is going to hurt someone or be completely inefficacious. So, if someone asks for an appendectomy to be done because they thought it would cure their cancer, they just wouldn't do it regardless of how risk seeking they were. I mean, if it doesn't make sense, if there are no data to support it, it is not something that someone would engage in. I don't know if Dr. Pellegrino wants to take this on as well.

DR. PELLEGRINO: Just a word on autonomy. It has become absolutized. People fail to realize there are limitations to autonomy, several limitations. First of all, when your autonomy results in harm to some other identifiable person, harm which is grave, probable and identifiable so, therefore, if you are talking about an IND you can see scenarios in which the demand is not absolutized. That demand is limited if it has an impact on others, and we could go on to scenarios for that.

The second one I think is the failure to understand that the health professional and the person who has been required to satisfy your autonomous wish or desire also has a right to autonomy. And, I think we are seeing here increasingly in the clinical situation, as a clinician myself, a tendency to say, well, we will do it because the patient wants it and particularly in pediatric situations

because the family wants it. They don't always act in the best interest of the patient or the person who is the most vulnerable member of that decision-making constellation.

So, I think autonomy has to be taken very, very carefully and put into a context in which, first, there is a balance between the autonomous claims of the various individuals, particularly the professional and, secondly, the impact of an autonomous choice. Then, thirdly, as Jeremy pointed out, the move from autonomy which started as a negative moral right -- don't tread on me -- has moved to a right to demand and, as a matter of fact, in the clinical situation we find over and over again a right to feel that one might participate in the micromanagement at the bedside. That, I think, acts very often to damage of the patient, and we can't do that.

So, I think the whole question of autonomy needs to be reexamined very carefully. Just a last word on it, that is that more recent empirical studies show that when patients demand autonomy they are not really saying I want to make this decision by myself; leave me alone. What they are saying is I want to have the information. I want to have the privilege of saying no. I want to know what I am doing, but don't abandon me; I need help.

DR. NERENSTONE: Mr. Dixon?

MR. DIXON: Yes, I want to go back to the

information point for a moment. One thing we have to keep in mind is that there is another large government agency called the SEC, which has very strict reporting requirements and, while there is probably no one drug that is going to matter or be material to a Merck or a Pfizer, for many of the small companies, if they have a bad result in a Phase II trial that is very definitely material reporting event which they are forced by the SEC to disclose. Of course, many of us read SEC stuff because we find a lot more there than waiting for ASCO.

[Laughter]

DR. NERENSTONE: Dr. Lippman?

DR. LIPPMAN: I guess related point really following up on Rick's point of the ASCO report and so on. It seems as though the large major societies with tremendous credibility, like ASCO and ACR, are actually taking a much more active role in promoting these advances. It is a different issue. I think part of it is that we want the information to get out; it is important for congressional information, to put more money into cancer research. It has a lot of positive benefits but the downside is that although an abstract may be selected for a high profile presentation because it is extremely scientifically sound, very provocative, and what-not, but it is still very early, not really ready for prime time, and what happens is when that

comes out in a forum and ASCO has actually put their stamp on it as something that they feel is very important, in that context it will often get exaggerated in the press, and then it leads to the false hope and all the issues we are talking about. It is a change over the past several years, the more active involvement of these large societies. So, if the press want to exaggerate, or it maybe it makes sense that they would exaggerate because it actually has the stamp from these major societies. In other words, it is not just a presentation of someone's abstract; it is actually that a society is involved in that process.

I was just going to throw out a question. This is something that came up to me when I was listening, that we don't the want the exemptions to interfere with getting the drugs through definitive trials to find out if they really work and what the risk/benefit is, and if they meet that then, obviously, you will get an FDA approval and get it out to the public.

But one of the issues that comes up, and maybe I missed it, is the issue of the issue of the randomized trials where you may have, for instance, a 50-50 chance of getting the drug that you really want to get as a patient, and how would people view that because if you went on an exemption you could get the drug and you know you would get it, versus enrolling in a trial but when you are on the

trial you don't necessarily get that drug. I don't know if there are any thoughts on that.

DR. NERENSTONE: Go ahead, please.

DR. LINDEN: Well, double-blind, placebo controlled trials are always very problematic, particularly when we think of them as the gold standard, but there are some interesting ways to work around the dilemma you are describing, and one of them is the use of cross-over designs so that -- well, I will give you two instances of a cross-over design that could make such a trial more attractive to a person who would potentially enroll in that trial.

The first is that -- and this has been done in the HIV AIDS arena -- there are two ways to do cross-over. One is that when a person is in the control arm of the trial experiences disease progression, that person in the control arm can be unblinded and they can be given drug. So, they are not consigned forever to nothing or to not having any access to the study drug. So, that is one cross-over option.

Another cross-over option is the design of a trial in which people on the study arm get drug and then they cross over to a placebo arm and don't get drug for a period of time, and those who were initially in the placebo arm, after a certain period of time, cross over to the study arm and get drug. So, the performance of both groups -- you see a four-cell situation. The performance of both arms of the

trial can be observed with and without drug. And, there are other ways to work that as well, but it creates some more options that make trials more attractive to people who otherwise wouldn't want to take the risk.

DR. LIPPMAN: I agree with that, those kinds of designs though from a pure trialist, statistician or even FDA point of view are often criticized, particularly if survival is an endpoint, because it is almost impossible to assess that unless you are looking at the effects of early versus late therapy. So, it is an attractive aspect in one sense but it limits your ability for some of the other endpoints. And, I wasn't even just talking about placebo control. I mean, we have seen randomized trials today, in this couple day meeting, where everyone knew what they were getting but you hope that someone would stick with that.

The only reason I bring this up is because it seems as though the one thing everyone seems to agree on, at least the FDA and the industry, is that the number one priority is if there is a trial, then people, if they are eligible, have to go on that trial. I am not sure that patient advocates or patients see it that way if they have a 50-50 chance of getting the drug.

DR. NERENSTONE: Mr. Erwin?

MR. ERWIN: Mr. Dixon made my first point so I will skip that, and the second point about cross-over, I

think that this is a very important issue that should be addressed in parallel with the rest of this. I think, as you pointed out, there is disagreement. An individual patient will not like the possibility of being randomized to standard of care, but from a policy standpoint or a scientific standpoint, I am not sure there is a great answer as to how to avoid that at this point.

DR. NERENSTONE: Dr. Pelusi?

DR. PELUSI: In part of that, one of the things that I think we are all saying is that we want equal access to quality care, and the one concern that I have, and I keep hearing over and over again, is that we want access to drugs that we think are very safe. I think at this meeting we saw -- and at other meetings in the past -- that you may have a Phase II study that on the outside appears to have some great effective, to have a low toxicity profile, but when the true review is done perhaps that is not all of the information. So, what I think we need to keep in mind as well is if we are going to look at access in terms of compassionate use, single patient or group, is that are these good studies, and I think that that mechanism needs to be there as well, and I don't think that we can just say everything should be opened up. I think that is something that becomes very important as to who really looks at the studies, who really gives this overall blessing, if you

will, that this is something that needs to be looked at for compassionate use.

Just two other brief comments, it does show us that we all have great responsibilities. It is not a responsibility just of media, just the physicians and nurse and industry, but it is all of together and that is what makes it so complicated. But I think that we heard very strongly today from all of the patients and patient advocate groups that if we are going to have information out there it needs to be the right information. It needs to be good information and that there is a major educational piece that must go forward that each of has to do in our own arenas.

Thirdly, to me, what was blatantly missing today are the voices of our minority populations. As we all say, the standard of care is going to be obtained by looking at clinical trials, again, not only are we very low in patients being accrued to clinical trials, but even more so in our minority populations, which includes the elderly as well. I really hope that as this discussion goes forward and we begin to look at this we look at the issues of those voices that may not be heard at this table. Thank you.

DR. NERENSTONE: Dr. Carpenter?

DR. CARPENTER: I just wanted to pick up on the point of cross-over designs, particularly the cross-over design with standard therapy. Cross-over with placebo in

early disease is a little different. But frequently the basis for marketing may be an increase in survival, and if you have a cross-over design in a Phase III trial against standard care you will give up the ability of the trial to detect a difference in survival. So, the very basis for marketing a new drug and the very basis for understanding the impact of the drug on the disease, which in the long-run is what we all want to know, is compromised. So, there is a tension there that needs to be resolved in order for this process to be balanced because I think we want to make the system as open as we can make it, but we don't want to make it so open that we give up the very thing which we need the most, which is which of the drugs that in the long-run are really the most valuable for the people with that particular cancer.

DR. NERENSTONE: Dr. Sugarman?

DR. SUGARMAN: I want to pick up on this point about designs. There is a lot of confusion about the ethics of competing research designs, but it crucial to understanding the ethics of the whole process and, unfortunately, it is hard word, it is even harder I think than learning ethics sometimes -- big p values and little p values and now you properly design research. Issues of placebo needs to be separated from issues of randomized as well as alternative design mechanisms. The world is

currently confused about placebos. Witness the recent Declaration of Helsinki, which actually occurred in Edinborough, not Helsinki, which confuses me geographically.

[Laughter]

But there is considerable therapeutic misconception about the roles of placebos throughout. So, that is one set of questions.

The question of randomized becomes very important because what we have learned in the autologous bone marrow transplantation in breast cancer is the example. It is a very pertinent example about the use of innovation of a powerful story about why it would be inappropriate to randomized from the perspectives of people facing devastating illness. Scientists and investigators were convinced for a variety of reasons that this was going to be a good idea. It made sense to some folks and not to others.

I think as this discussion moves forward you need to get some of the design issues on the table. One of the approaches I would hint towards, and that is all there is going to be time for without stealing all the rest of the time, is a notion of one way of understanding ethics of randomized, a notion called clinical equipoise in which there is uncertainty in the community about whether treatment A versus treatment B or treatment A versus placebo is appropriate, and if it is okay that is a starting place.

It is not the be-all and end-all. There are some contraindications to randomized after that. That needs to be understood. It might be worthwhile to consider playing that notion of clinical equipoise out through the informed consent process, through the public notification process so that the potential research subject, the patients with this who cannot be enrolled or could be enrolled can be in equipoise to understand that uncertainty about the scientific question, to realize the inherent biases to their requests or their clinicians' request for treatment off or on protocol. It is really when you are uncertain, you just don't know and you are going to fooled unless you randomly assign. So, I would think -- it is hard; this is tough stuff to communicate, but I think that would be helpful as a public education effort.

DR. NERENSTONE: Mr. Dixon?

MR. DIXON: Mr. Erwin made my point.

[Laughter]

DR. NERENSTONE: Dr. Lippman?

DR. LIPPMAN: Yes, I would just like to underscore that last point and hope that that could be used. I mean, if you want to pick a couple of examples -- you know, you showed elegant examples of different things but that would be a very good example of where the community and the people felt so strongly about uncontrolled data that if the

randomized study hadn't been done we would have had a self-fulfilling prophecy and it is a very good example of where when we abandon the normal way that we develop drugs -- you know, they may not turn out. So, I think this is a good example to bring up as we move forward.

DR. NERENSTONE: Dr. Linden?

DR. LINDEN: Into Dr. Sugarman's muddle, if I may, of placebos and randomized and -- what was the third point? -- placebo, randomized --

DR. SUGARMAN: And Helsinki.

DR. LINDEN: Yes, right, there is yet another variable that complicates things, and that is the question of surrogate markers and how impoverished we are at this point with surrogate markers to make sense of trials as they progress. It is an area that is in grave need of advancement.

DR. NERENSTONE: Dr. Taylor?

DR. TAYLOR: One of the things he said was about equipoise and I think it is one of the most different things since we are dealing with a vulnerable population, and that vulnerable population wants to get well, and understanding equipoise is different when you are in medical school in your third year. It is almost impossible when you are in a position of a life and death situation. So, I think it is really very different to do it and get the appropriate

informed consent. It is the right way to do it, but I think it is different, and I think it is another reason why people are always seeking the brand-new drug and not willing to accept that the standard of care may be the best care and the new drug may not be the best.

DR. NERENSTONE: Any further comments? Dr. Lippman, last comment?

DR. LIPPMAN: These great ideas are coming at the end of the two days, but the other great examples -- when you start thinking of examples where we all assume that they were better than the original -- the other great example to use would be the lymphoma work. You know, if ten years ago someone would have given CHOP -- it was absolutely accepted to be inferior. There are editorials written about first generation, second generation and all the other things and then, of course, the definitive randomized trial shows that CHOP is the standard. So, one could think of a lot of very good examples where, when we did not follow this path, we got burned.

DR. NERENSTONE: I would like to thank all the participants for coming and the committee, and we will take this up again in March.

DR. TEMPLETON-SOMERS: I would like to thank everybody else for being patient with our ambitious agenda, and mark your calendars for the March meeting, which is on

the 13th and 14th, exactly three months away.

[Whereupon, at 5:05 p.m., the proceedings were adjourned.]

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CERTIFICATE

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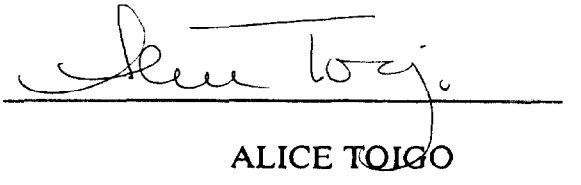

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