DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE

Monday, March 13, 2006

8:00 a.m.

Gaithersburg Hilton
Gaithersburg, Maryland

PARTICIPANTS

Silvana Martino, D.O., Chair
Johanna M. Clifford, M.S.,
RN Executive Secretary

MEMBERS:

Bruce D. Cheson, M.D.
Antonio J. Grillo-Lopez, M.D.,
  Industry Representative
David Harrington, Ph.D.
Pamela J. Haylock, RN, Consumer Representative
Maha H. A. Hussain, M.D.
Alexandra M. Levine, M.D. (by phone)
Michael C. Perry, M.D.
Gregory H. Reaman, M.D.
Maria Rodriguez, M.D.

CONSULTANTS (VOTING):

Susan Bates, M.D.
Ralph D'Agostino, Ph.D.
Harry Long, M.D.
Stacy Nerenstone, M.D.
Tito Fojo, M.D., Ph.D.
Eric Kodish, M.D.
Chris H. Takimoto, M.D., Ph.D., FACP

CONSULTANT (NON-VOTING):

Edward Sausville, M.D.

Martha Solanche, New York, Patient Representative

FDA STAFF:

Richard M. Pazdur, M.D.
Robert Justice, M.D.
Patricia Keegan, M.D.
M. David Green, Ph.D.
John Leighton, Ph.D.
David Jacobson-Kram, Ph.D.
Karen Weiss, M.D.
John Johnson, M.D.
Martin Cohen, M.D.

C O N T E N T S

C O N T E N T S (Continued)

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order and Introduction of Committee

DR. MARTINO: Good morning, ladies and gentlemen. I would like to start the meeting. This morning the committee will discuss nonclinical requirements and Phase 1 trial design issues for the development of oncology drugs. I would ask all of you to, please, turn off your cell phones for the duration of the meeting. If you have personal needs, please leave the room and attend to them.

I would like the committee to introduce itself, and I would like to start on my left with the FDA members.

DR. PAZDUR: Richard Pazdur, Office Director.

DR. JUSTICE: Bob Justice, Acting Director, Division of Drug Oncology Products.

DR. GREEN: Martin David Green, Supervisory Pharmacologist for the Biologics Oncology Products.

DR. LEIGHTON: John Leighton, pharm. tox. team leader for the Drug Oncology Products.

DR. CHESON: Bruce Cheson, Georgetown University Hospital.

DR. REAMAN: Gregory Reaman, Children's Hospital, Washington, D.C.

MS. HAYLOCK: Pamela Haylock, oncology nurse, consumer representative.

DR. HUSSAIN: Maha Hussain, medical oncology, University of Michigan.

MS. CLIFFORD: Johanna Clifford, Executive Secretary for the meeting.

DR. MARTINO: Silvana Martino, medical oncology from the Angeles Clinic.

DR. RODRIGUEZ: Maria Rodriguez, medical oncologist, M.D. Anderson Cancer Center in Houston, Texas.

DR. PERRY: Michael Perry, medical oncology, University of Missouri Ellis Fischel Cancer Center in Columbia, Missouri.

DR. HARRINGTON: David Harrington, statistician, Dana-Farber Cancer Institute.

DR. D'AGOSTINO: Ralph D'Agostino, statistician, Boston University.

DR. FOJO: Tito Fojo, medical oncologist, Medical Oncology Branch, NCI.

DR. BATES: Susan Bates, also National Cancer Institute, Medical Oncology Branch.

DR. TAKIMOTO: Chris Takimoto, medical oncologist, Institute for Drug Development in San Antonio.

DR. KODISH: Eric Kodish, from the Department of Bioethics, Cleveland Clinic Foundation.

DR. GRILLO-LOPEZ: Antonio Grillo-Lopez, industry representative.

DR. SAUSVILLE: Ed Sausville, medical oncologist, University of Maryland, Greenbaum Cancer Center.

DR. MARTINO: Thank you. For the committee members, realizing that some of you may be new to us, when questions are to be raised I would ask that you raise your hand. You will be acknowledged in a quiet manner. Then, when it is your turn to ask your question I will announce your name. So, please recognize this will not be a

free-for-all. Next I would like Ms. Johanna Clifford to read the conflict of interests.

Conflict of Interest Statement

MS. CLIFFORD: The Food and Drug Administration has prepared general matters waivers for the following special government employees: Drs. Ralph D'Agostino, Maha Hussain, Silvana Martino and Chris Takimoto. In addition, Edward Sausville, M.D. has been granted a limited waivers matter. Dr. Sausville is permitted to participate in the committee discussions, however, he is excluded from voting.

The committee members are participating in today's meeting of the Oncologic Drugs Advisory Committee to discuss matters concerning preclinical requirements and Phase 1 trial design issues for the development of oncologic drugs. This meeting is being held by the Center for Drug Evaluation and Research. Unlike issues before a committee in which a particular product is discussed, issues of broader applicability, such as the topic of today's meeting, involve many industrial sponsors and

academic institutions. The committee members have been screened for their financial interests as they may apply to the general topic at hand. Because general topics impact so many institutions, it is not practical to recite all potential conflicts of interest as they apply to each member. FDA acknowledges that there may be potential conflicts of interest but, because of the general nature of the discussions before the committee, these potential conflicts are mitigated.

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

In addition, we would like to note that James Green, FDA's invited guest speaker, is participating as a representative of Biogen Idec.

We would also like to note that Dr. Antonio Grillo-Lopez is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Grillo-Lopez is employed by Neoplaatic and

Autoimmune Diseases Research.

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participant involvement and their exclusion will be noted for the record. With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they wish to comment upon. Thank you.

DR. MARTINO: Thank you. Next Dr. Pazdur will give us some opening remarks.

Opening Remarks

DR. PAZDUR: Thank you. This session will provide to the ODAC the current FDA requirements for nonclinical safety evaluation of new anti-cancer small molecules and biotechnology-derived drugs prior to their initial use in human subjects. Applicants submitting investigational new drug applications, or INDs, to the FDA for early clinical investigations of new

biological or small molecule drugs are required to include data from nonclinical animal and/or in vitro pharmacology and toxicology studies. This requirement is derived from the Federal Food, Drug and Cosmetic Act of 1938, and codified in the Code of Federal Regulations. The data resulting from these studies provide the basis for which the sponsor, and ultimately the FDA, must conclude that the product is reasonably safe for clinical use.

Although the nonclinical pharmacology and toxicology studies provide support for the rationale and demonstrate the safety of the clinical investigation, the type, the duration and the scope of animal and other safety testing varies with the duration and the proposed clinical use.

The FDA recognizes that novel issues exist in designing and interpreting nonclinical studies for small molecule drugs and biological therapies and has provided guidance documents to assist investigators in developing their nonclinical programs. Guidance documents are also available through the International Conference on

Harmonization, or ICH, that provide a framework for nonclinical safety studies with the objective of adequately achieving the requirements promulgated by the FDA and other regulatory agencies.

However, these documents do not provide a universal nonclinical paradigm by which all investigational drugs and biologics may be tested. Flexibility is required to address specific concerns related to the biology of the product itself and the patients to be included in the clinical studies. Ultimately, the nonclinical data must be sufficient to permit the FDA to conclude that patients are not exposed to unreasonable risk.

Not only will the patient population dictate the amount of nonclinical data necessary to support clinical testing, but the product class may also be a factor in determining both the type of studies conducted and the amount of nonclinical data required to initiate and continue clinical testing.

Biotechnology-derived drugs, such as monoclonal antibodies, generally differ from small

molecular weight drugs in the biology, pharmacodynamics, pharmacokinetics and the potential for cumulative toxicity. The pharmacological and the potential toxic effects of biologics may differ qualitatively and quantitatively from the effects observed with small molecules; may be more apparent with increasing exposure and may not be identified by routine non-invasive tests typically used to monitor clinical trials.

The agency generally believes that an individualized, science-based approach to nonclinical testing requirements across different product classes of anti-tumor therapies is appropriate. We will present current nonclinical approaches for both the biological drugs and small molecules, and attempt to point out differences that may exist and the rationale for these differences. An industry perspective on these studies will also be presented.

For most drug development programs, the FDA has recommended that the duration of

nonclinical studies match the duration of the proposed clinical trials, an approach supported by the ICH M3 guidance. However, an abbreviated duration of nonclinical testing has generally been accepted for small molecular drugs under development as anti-tumor agents. An abbreviated dosing duration has also been proposed for selected anti-tumor biological products.

We will be asking your advice on situations where the duration of nonclinical studies should either match the duration of the proposed clinical studies or may be abbreviated or postponed relative to the clinical duration. Your consideration should focus not only on the product under consideration but also the patient population that is being studied and the relative risk/benefit relationship.

The FDA has received applications that have sufficient nonclinical data to initiate clinical Phase 1 testing but lack adequate nonclinical testing to support prolonged clinical use of the product for individual patients enrolled

in Phase 1 studies. We will ask you to provide guidance on situations where extended nonclinical safety data are unavailable, yet clinical investigators and/or sponsors may ask for permission to continue prolonged clinical use of the product in individual Phase 1 patients. In addition, we will ask your guidance regarding matters to ensure patient protection where this extended nonclinical information may not be present. Thank you.

DR. MARTINO: Thank you, Dr. Pazdur. The next several speakers will educate the panel on various issues that relate to the questions that have to be asked. Our first speaker is Dr. David Jacobson-Kram, describing preclinical safety data for "first in human" clinical trials in healthy volunteer subjects.

Preclinical Safety Data for "First in Human" Clinical Trials in Healthy Volunteer Subjects

DR. JACOBSON-KRAM: Good morning.

[Slide]

My name is David Jacobson-Kram. I am the

Associate Director of Pharmacology and Toxicology in the Office of New Drugs, and I have been asked to speak to you this morning about preclinical safety data for "first in human" clinical trials. Typically these are in healthy subjects so this is not so much focused on oncology but on other classes of pharmaceuticals.

[Slide]

What preclinical safety data are required prior to giving a new chemical to human beings for the first time, and why do we require such data? Well, it is important to remember that most Phase 1 studies are performed in healthy volunteers, so in a situation like this there is no risk/benefit equation that one evaluates. Since there is no benefit to be derived for these healthy subjects, it is strictly a risk assessment. So, is it safe to give this chemical to these volunteers for the first time?

[Slide]

So, the preclinical studies define potential toxicities. We want to determine what is

an initial safe starting dose. Since this chemical has never been given to a human being before, where do we begin? What is a reasonable amount of this chemical to give to people for the first time? What is a potential safe stopping dose? What organs or systems may be at risk from exposure to this chemical? If there are toxicities associated with this chemical, are they monitorable in the clinical trial? And, are the toxicities reversible if there are any? And, is the chemical potentially carcinogenic?

[Slide]

So, for the minimal data set to begin a Phase 1 clinical trial in healthy volunteers generally toxicity studies are done in two species. For small molecules this is typically rat and dog, although there are exceptions, and for biologics this is most often non-human primates. The highest dose we expect would demonstrate a maximally tolerated dose, and also there would be included a lower dose with no adverse effect levels, we want to see the two extremes where we see some amount of

toxicity and also a dose just below that where no toxicity is being induced.

A single dose clinical study can be supported by a single dose animal study. The animals are dosed one time and then there is an early sacrifice, generally 24-48 hours after the drug administration, and then a second group is sacrificed after 2 weeks.

[Slide]

More typically though what we see are repeat-dose toxicity studies in animals, typically 14-28 days. This is really much more efficient because it enables repeat-dose clinical trials. A single dose clinical trial isn't all that useful. So, if you want to do repeat-dose studies in Phase 1, one typically does repeat-dose toxicology studies. This is also, in fact, more efficient since one uses fewer animals in a repeat-dose study, although it does consume more drug. So, for some new drugs that are difficult to synthesize, from that perspective it is a little less efficient. It is also useful to include recovery

groups so if you do see toxicity you can find out if the animals recover from that toxicity at time periods after exposure is terminated.

[Slide]

What endpoints are typically looked at in toxicology studies? We look at clinical signs, that is, animals have very typical behavior and we look for deviations from that normal behavior. We look at the amount of food that is consumed. We look at body weights and, in larger species we do clinical pathology during the in-life portion of the study.

[Slide]

Post-life macroscopic evaluations are looked at, at necropsy, so we are just seeing if the organs or tissues look abnormal to the naked eye. Certain organs are weighed to see if the drug has had effects on organ weights. For clinical pathology we look at hematology and clinical chemistries. Then we look at histopathology in all the tissues and organs in the animals and often toxicokinetics so that we have an understanding of

what the exposure was like during the study.

[Slide]

Also, to initiate a "first in human" clinical trial in healthy subjects we ask for safety pharmacology studies. We look at the cardiovascular system. Often this is done in non-rodent species, typically a dog. Endpoints such as blood pressure, heart rate and ECGs are monitored. In the ECGs we look at rhythm and morphology, arrhythmia analysis and also QT interval to see if there is any prolongation of QT interval associated with exposure to the drug.

[Slide]

Other kinds of safety pharmacology studies that are done are NCS. This is typically done in rodents and this is a functional observation battery where we are looking at spontaneous locomotor activity, motor coordination, proconvulsive effects and analgesic efficacies, and also a pulmonary safety pharmacology study were we are looking at minute volume, tidal volume and respiratory rate.

[Slide]

In addition since, again, we are dealing with healthy subjects or volunteers, we want to be sure that this chemical isn't potentially carcinogenic so we ask for genetic toxicology testing. Typically, this is a bacterial reverse mutation assay, often referred to as an Ames test, and here we are looking at the induction of point mutations in the DNA. We are also looking at an in vitro assay for chromosomal damage. Typically, this uses cultured mammalian cells, and we look at metaphase chromosomes, for example as you see in the slide here, and we just look at the morphology of those chromosomes to be sure that they haven't been altered or broken. Also an in vivo test for chromosomal damage, often referred to as the rodent micronucleus test, is not required by our guidelines but typically is often done.

[Slide]

I am going to switch gears a little bit. That is the basic battery of tests required for a traditional IND. I am going to spend the last

couple of minutes just talking about exploratory INDs. Exploratory INDs are very early in drug development to be able to choose a lead candidate to get a series of drugs into the clinic to find out which appears to be the most promising. Once one has completed the exploratory IND, it is closed and then one proceeds with a traditional IND along the normal drug development pathway which leads to an NDA or BLA.

So, in January of this year FDA published a guidance on exploratory INDs. It is intended to make drug development more efficient by expediting early Phase 1 clinical trials. So, these will result in increased understanding between a specific mechanism of action and the potential to treat a disease. It provides very early pharmacokinetic data in humans. And, it selects the most promising lead candidate from a group designed to interact with a specific human target, for example as you would do in an imaging study.

[Slide]

In exploratory INDs clinical studies have

no therapeutic intent. This is simply a method for choosing the most promising drug candidate. So, keep in mind that, again, this is done in healthy subjects and, again, this is just a method for choosing the most promising drug. When a lead compound is selected the exploratory IND is closed.

[Slide]

The toxicology evaluation recommended for an exploratory IND application is more limited than for a traditional IND. The basis for the reduced preclinical package lies in the reduced scope of an exploratory IND clinical study.

[Slide]

This slide compares the advantages of a conventional IND versus an exploratory IND. One of them, and probably the most significant, is the preclinical resources. For a traditional IND typically one would have to do from 9-12 studies. That would involve the use of about 220 rodents and about 38 non-rodents, and typically takes between 9 and 18 months.

For an exploratory IND the number of

studies is halved. The number of rodents are reduced but not dramatically, however, the number of non-rodents is dramatically reduced, as is the time that is required to perform these studies.

So, the benefits associated with a conventional IND are that you get a full toxicological profile. You can escalate to a maximally tolerated dose in the clinical trials and you can progress directly into Phase 2. With an exploratory IND the benefits are that the amount of drug that you need to perform these studies is much reduced. You have faster progression to clinical trials; the capability to evaluate candidates based on target activity. Better development decisions are made more quickly and early and less costly attrition of candidates can occur.

[Slide]

Disadvantages--for a conventional IND a much larger quantity of the API has to be synthesized. Decisions are made more slowly and attrition is later and more costly. The disadvantages of the exploratory IND are that you

have potential delayed progression to Phase 2 clinical trials and you never find out what the maximally tolerated dose is in the clinic.

[Slide]

So, the bottom line--CDER assesses implementation of an exploratory IND guidance as an important part of FDA's commitment to improving the "critical path" to new medical products. The amount of preclinical safety data required for exploratory INDs is less than for conventional INDs, and the reduction in safety data requirements is scaled to the goals, duration and scope of the proposed clinical trials so that we can use less resources and generate less data but still not compromise the safety of the subjects in the clinical trial. Thank you.

DR. MARTINO: Thank you, doctor. On behalf of the committee though, I need you to clarify something for me. Realizing that there are these two pathways, who decides which of these two will be applied to a molecule? Is that a request from a pharmaceutical to you, or how is that

decision arrived at?

DR. JACOBSON-KRAM: That decision is made by the sponsor. They have a choice. They can go the traditional route and in a sense it is a bit more of a gamble because you have to decide early on which molecule you are going to pursue. So, you take that single molecule into the clinic and if it fails you have invested a lot of resources. On the other hand, if you have a number of lead candidates and you want to see how they behave in humans early in development, the sponsor can choose to open an exploratory IND and make the decision as to which molecule they are going to move forward with. But that is strictly their decision.

PARTICIPANT: [Not at microphone; inaudible]

DR. JACOBSON-KRAM: Active pharmaceutical ingredient; it is basically the drug.

DR. MARTINO: Again, if there are questions to be asked, please let me know and I will acknowledge you, otherwise we will not be able to hear questions. Thank you, doctor.

Our next speaker is Dr. John Leighton. His presentation is entitled nonclinical perspective on initiating Phase 1 studies for small molecular wight compounds.

Nonclinical Perspective on Initiating Phase 1 Studies for Small Molecular Weight Compounds

DR. LEIGHTON: Good morning, members of the advisory committee.

[Slide]

This slide shows the overview of my presentation. I will first discuss nonclinical studies conducted during the course of drug development for both oncology and non-oncology indications. I will provide a brief historic perspective, which the FDA had previously discussed with the oenology advisory committee, its nonclinical recommendations for initiating Phase 1 studies. I will discuss our current recommendations for nonclinical studies for drug oncology products to initiate "first in human" studies; briefly discuss the role of our pre-IND meetings on oncology drug development and discuss

some deficiencies in the nonclinical data set for small molecules that may potentially lead to a clinical hold.

[Slide]

Aggressive measures are usually required to treat cancer, and therapies often include combination of toxic chemicals and biologics that are intended to halt cell replication or kill tumor cells. It has long been recognized that therapies at doses high enough to kill tumor cells usually induce serious side effects in patients but that these side effects are less threatening to the patient than their underlying disease. Therefore, the nonclinical testing strategy for oncology drugs is usually less extensive, and allowable starting doses are much higher for oncology drugs than other non-oncology indications.

For drugs intended for other than immediately life-threatening conditions, we recommend that sponsors consider the recommendations outlined by the International Conference on Harmonization, and the guidance

document M3 addresses the timing and duration of nonclinical studies relative to clinical development.

[Slide]

This slide shows some of the nonclinical studies that are usually conducted to support drug development for both oncology and non-oncology indications. Pharmacology studies assess mechanism of action and provide some evidence of efficacy of a drug. I will discuss the role of these studies for oncology drugs in later slides.

Pharmacoknetic studies provide information on absorption, distribution, metabolism and excretion. These studies are strongly encouraged, particularly for drugs with extended expected duration of exposure, for example drugs administered by depot formulation.

Safety pharmacology studies provide information about vital organ function, particularly central nervous, respiratory and cardiovascular systems. Evaluation of these systems should take place prior to "first in

human," either as part of stand-alone safety pharmacology studies or as part of the general toxicology evaluation. Stand-alone safety pharmacology studies have not been necessary for drugs administered locally or for those drugs intended for patients with life-threatening conditions.

Toxicology studies provide the basis of initiating the start dose and information about the safety of a drug, and I will discuss the role of these studies in later slides.

Genetic toxicity studies provide information about mutagenic and clastogenic potential of a drug. Reproductive toxicology and carcinogenicity studies, when needed, are also important for drug development. Safety pharmacology, genetic toxicology studies, reproductive tox. and carcinogenicity studies are not generally necessary for drugs intended to treat patients with life-threatening disease so I will not discuss these studies further.

[Slide]

In the 1970s most drugs in development were your traditional cytotoxic agents. In an effort to streamline development and expedite the toxicology testing that was in place at that time, the FDA discussed its recommendations with the toxicology subcommittee of the oncology advisory committee in several meetings in 1979. As a result of these deliberations, the FDA then presented to the oncology advisory committee a revised testing paradigm.

This revised testing paradigm included a study in mice that was to identify the LD10, which is a lethal dose in 10 percent of the animals on a daily times 1 and daily times 5 schedule. These studies were to include a 28-day recovery period. A second set of studies in dogs was to assess the safety of one-tenth the lethal dose 10 on the same daily times 1 and daily times 5 schedules. A second dose in dogs should then produce over-toxicity. A 60-day observation period to look at delayed or irreversible toxicities was also to be included in the study design.

Histopathology was recommended for both species. It was not required prior to Phase 1, however, it was to be submitted from the dog studies to the FDA prior to initiation of Phase 2 trials. The FDA also stated during the course of the May, '82 advisory committee meeting that the data from nonclinical studies that would trigger additional testing would be clarified.

[Slide]

While the regulated industry was reevaluating its nonclinical testing strategy in the 1990s, the FDA toxicology group and oncology group was also reevaluating the nonclinical recommendations. As a result of this internal reevaluation, this was elucidated in an article by De George et al. in 1998. The article describes what is our current approach to toxicology testing for initiating Phase 1 trials. The article also discusses other issues, for example, studies required for chemoprevention and studies required at both the IND and the NDA stage, but I will focus the discussion on those studies required for

initiation of Phase 1 studies with end-stage disease.

[Slide]

According to the De George article the safety intended for "first in humans" is assessed to study the pharmacodynamics, pharmacokinetics, toxicology and their inter-relationship. At a minimum, we expect the sponsors to conduct toxicology studies in two species, a rodent and a non-rodent. This differs from the recommendations from the 1980s which specified a study in mice and dogs. The goal of these studies is to identify the start dose; identify organ toxicities and reversibility; and to guide dosing regimens and escalation schemes. We expect that these studies follow standard protocols. Standard protocols are publicly available and most companies have developed their own testing assessment. We expect that studies follow the clinical schedule, route and formulation as much as possible, and studies should be conducted according to Good Laboratory Practices, or GLPs.

[Slide]

Perhaps the area of most concern to sponsors is to make sure that their preclinical study schedule supports the intended clinical schedule. This slide shows some of our recommendations. The International Conference on Harmonization does not have anything specific about the preclinical schedules necessary to support oncology drug development, and the De George article is not comprehensive in this regard.

Some of the more common schedules seen by the Division include studies where drugs are administered every 21 days, studies where drugs are administered weekly, with one week off, and continuous daily administration. So, as a general recommendation, the Division would recommend that sponsors follow a one to one concordance between the toxicology study design and the intended clinical schedule, at least for the initial part of the clinical dosing schedule.

[Slide]

It is our expectation that studies be

conducted according to Good Laboratory Practices. This is described by the Code of Federal Regulations, or CFR, in Part 58. These are a set of organizational requirements to assure the generation of high quality, reliable safety data and include, among other things, for example, analysis of the test article, testing of dosing solutions, identification of qualifications of study personnel, adequate record-keeping, etc. However, if studies are not conducted according to Good Laboratory Practices, then sponsors need to explain deviations from these practices and discuss their impact on the study outcome. Draft, unaudited studies are acceptable for the initiation of the IND, but the final quality assurance study reports should be available within 120 days of the initiation of the IND.

[Slide]

This slide shows our approach to setting a start dose for patients with end-stage disease. This slide details the approach for cytotoxic drugs. We have adopted this approach for

non-cytotoxic drugs as well. It is expected that sponsors in their nonclinical studies determine the dose that is severely toxic to 10 percent of the rodents, also called the STD10. This is then converted to a body surface area basis, and some of the conversion factors are shown in the second box in the slide.

The question is then asked is one-tenth rodent STD10 on a body surface area basis severely toxic to non-rodents? In most cases the answer is no. Is the rodent an inappropriate species? In most cases the answer is no for small molecules. Therefore, the start dose is usually set at one-tenth the rodent STD10.

[Slide]

Another area of concern to many sponsors is what duration of nonclinical studies relative to the proposed Phase 1 is acceptable. For small molecules, in the absence of documented disease progression and acceptable toxicity, when drugs are administered on an intermittent schedule, as shown two slides ago, then in general multiple cycles are

acceptable in the clinical trial. For therapeutics that are intended to be administered continuously, then continuous dosing for 28 days in rodents and non-rodents is generally sufficient to support clinical trials past 28 days.

The rationale for this study was articulated in the De George article in that longer duration studies may lead to an unacceptable start dose. Shorter duration studies do not adequately predict potential toxicities. In addition, plasma half-life indicates that for most drugs there is little accumulation and that steady state is reached fairly quickly. Also, this approach depends upon clinical assessment of the safety of the appropriate interval to support continued dosing in individual patients beyond the duration of toxicological support.

[Slide]

Another area of interest to many sponsors is what studies are necessary to support combinations of drugs to be used in clinical utility. The FDA has issued a draft guidance on

this topic of nonclinical safety evaluation for drug combinations. However, the oncology perspective is that toxicology studies of drug combinations may not be necessary for patients with advanced disease if no pharmacokinetic, metabolic or pharmacodynamic synergy is expected; drugs are not packaged as part of a combination; and all components of the combination are well studied individually; and, information from pharmacology studies may be useful to assess whether additional toxicology studies are necessary.

[Slide]

Pharmacology studies are very important to many sponsors as they provide the initial proof of principle and are used to select lead compounds for further clinical development. However, the Division's perspective is that pharmacology activity, as assessed by models of disease, are generally of low relevance to the safety decision which is primarily determined in your toxicology studies, and the efficacy determination which is primarily determined in later stage clinical

trials.

The reasons for this are that efficacy in vitro and in vivo from nonclinical studies may not adequately and dependably predict clinical efficacy. The reason for this is because of heterogeneity. There may be inter-species differences in absorption, distribution, metabolism and excretion of the drug, and the role of the immune system in tumor biology can also be cited. Other factors can also be cited as well.

However, we believe these pharmacology studies are useful for assessing an appropriate clinical schedule for study; justification of the drug combination; and also understanding the effect of the drug at the molecular target. For example, what is the receptor specificity? Is an anti-estrogen going to cross-react with a group of corticoid receptors, for example? We think pharmacology studies are also useful for identifying and evaluating the biomarkers that may be used in clinical studies.

[Slide]

In order to help sponsors make sure that their clinical testing strategy and their nonclinical testing strategy are appropriately aligned, we recommend that sponsors meet with us prior to the filing of an IND, or investigational new drug application. These are highly recommended, particularly for unique products or if there are unique questions on which the sponsor wants to get feedback. The purpose of this is to get feedback from the Division as to the appropriateness of the initial clinical development plan. It is important to stress that this is not a full data review. Generally only study synopses are submitted, or the studies, both nonclinical and clinical studies, are still in planning. It is not a protocol concurrence including the start dose. This is a review issue when the full IND is submitted.

[Slide]

So, what are some deficiencies in nonclinical data that may lead to a clinical hold? I would like to stress that there are usually

multiple factors described on this slide and associated with any clinical hold. It is usually not just one issue. For example, there may be an inadequate study design; standard toxicology protocols are not followed; appropriate endpoints, for example, clinical chemistry, histopathology, are not adequately assessed; and there is an inadequate number of animals to assess the severely toxic dose to 10 percent so we can't really set a start dose. Study reports are not organized in a manner for review, or were not provided, meaning they either would not or could not be provided to the agency for review. Data could be provided in a single test species rather than the recommended two test species so we can't determine whether or not the start dose is acceptable. The studies were not conducted according to Good Laboratory Practices, and deviations from Good Laboratory Practices were not discussed. There is no data to support the intended route of administration. An example of this would be an IV drug and now the sponsor wants to go to intracranial administration and we have no

basis upon which to set a start dose for that route of administration. Studies are of inadequate duration to support the intended clinical trial. Both commercial and investigator initiated INDs have been put on hold for these reasons. However, the usual approach of the Division is to work with the sponsor to avoid the clinical hold.

[Slide]

So, in summary, what we request is that sponsors conduct two pivotal toxicology studies using the same schedule, formulation and route as the proposed clinical trial. A rodent study should be conducted to identify life-threatening doses; and a non-rodent study to confirm that non-life-threatening doses have been identified. Studies of 28 days should be provided for drugs intended for continuous administration. Studies of one of several administrations, depending upon the schedule of the intermittent schedule should also be provided and full histopathology should be provided in one of those studies. Other studies should be conducted as needed, and standard

protocols should be modified as suits the needs of the particular drug. Multiple cycles and continuous treatment are generally acceptable, assuming that there is an acceptable safety profile in the clinical setting. Pre-IND meetings with sponsors are encouraged to discuss problem areas and provide alternative pathways to initiate the Phase 1 trial, and most clinical holds are resolved through discussions with the sponsors. Thank you.

DR. MARTINO: Thank you. Our next speaker is Dr. James Green, presenting the industry perspective on this issue.

Industry Perspective: Preclinical Development Considerations for Biologics

DR. J. GREEN: Good morning.

[Slide]

My name is Dr. Jim Green. I am Senior Vice President of Preclinical and Clinical Development Sciences at Biogen Idec, and I am also currently the chair of BioSafe, which is an expert industry preclinical group in the BIO organization. I would like to thank Dr. Leighton today for the

invitation to speak to you about this important topic.

[Slide]

Before I get into my formal presentation I want to offer a couple of background comments, and these are indicated on the first two slides. First, as we sit here this morning, I think it is important to realize that we have literally decades of experience working with complex biologics, taking them from the preclinical setting into human trials.

Second, as Dr. Pazdur indicated in his remarks, we have a number of guidance documents which have guided these programs over the years, beginning with the FDA's "points to consider" document that was available in the mid '80s, and followed by the ICH guidance document which dealt with preclinical safety evaluation program design considerations and approaches. This guidance document, which was available in the mid to early '90s, dealt with pharmacology, toxicology, kinetic and unique considerations which differentiate

biologic drug development programs from small molecules. One of the key points of the S6 document was the case-by-case approach. What is meant by that is that one program design may not look like another due to product specific concerns, and I will be coming back to that point several times during my presentation this morning.

[Slide]

What I was asked to speak to you about this morning by FDA organizers, as indicated here, was to address specifically differences for preclinical development programs for small molecules and biologics, and raise for discussion how would these differences influence the determination of how much preclinical data is sufficient to support Phase 1 trials. Recognizing that this is an oncology focus, we are dealing with refractory patients that have no options, no treatment options and, in my view the benefit/risk scenario in that case is severe, and present examples which would influence the transition of programs from the preclinical setting to the Phase

1 point but overall provide useful information. It is that last point, provide useful information, where I have a fair degree of latitude with respect with what I convey to you this morning.

[Slide]

So, with that charge, what I have decided to do this morning is to speak to you about these four areas. First I am going to, as indicated or as requested, contrast small molecules and biologics with respect to important considerations that need to be considered. Recognizing that the focus this morning is on biologic drugs, I will not be speaking to anything related to vaccines, cell-based therapies or gene therapies. These are other considerations entirely.

For the committee's information, I will then, in a fairly didactic manner, convey to you what I refer to as general principles. These will be regarding the utility of toxicology assessments, the utility of pharmacokinetic assessments. With respect to pharmacokinetic assessments, because one of the most important considerations that we have

in going from the preclinical to the clinical arena is dosimetry, I will share with you some examples that I found interesting and I think need to be considered when you make that transition. I will then give you my perspective, which is shared by many of my committee members of the BioSafe group, regarding preclinical development requirements for Phase 1. Then I will have some summary comments.

[Slide]

So, the key messages that I hope to deliver to you in my presentation are indicated here. The first is that compared to small molecule drug development programs there are important differences for biologics that affect program designs and assessment parameters. Second, well-designed pharmacology, toxicology and kinetic studies are important to support the determination of safe use conditions for human trials with oncology drugs. Finally, four-week repeat-dose toxicology studies with recovery periods should be adequate to support extended treatment of responding and stable disease patients in most

cases. Again, a case-by-case determination is recommended for that latter point. In particular, I hope there is some consideration this morning regarding what we mean by stable disease and how we characterize that population because I think we have some work to do in that particular area.

[Slide]

To begin my presentation about important differences, first I think we have to realize that most biologics, if not all, are non-oral routes of administration, intravenous, extravascular, intra-tumoral, intracranial, as was indicated earlier.

Second is that these are large and complex molecules, which is indicated in this cartoon. This is a typical antibody construct. And, I think it is important to recognize that these have a complex three-dimensional structure. Because of that, early in development structure activity relationships that are typically explored for small molecules are difficult to perform. Also indicated here I think is a level of complexity which is not

shared by many small molecules.

Here we have essentially tumor-targeting bonding sites in the CDR region, but we also know that the Fc region can also interact in a specific or non-specific manner with intended or non-intended target sites. In fact, this area of the antibody is subject to glycosylation changes and these glycosylation changes, which are related to how the material is made, can affect pharmacokinetics; can affect pharmacodynamics; and can affect the interaction in biologic activity of molecules with this type of construct.

In addition, many of these antibodies are engineered to carry effector molecules, chemicals essentially which are targeted to particular tumor type. What is shown here are four but, in reality, these molecules vary in the number of pay-load molecules that are carried. There can be one, there can be ten. We usually hear a number on average reflected, but these are complex mixtures, mixtures meaning that they are variant forms and it is not one highly purified form as opposed to a

small molecule. This conveys a level of complexity which I think is important to consider, particularly in the early development stage.

Another important contrast is that there are no metabolites in a conventional sense. Small molecules are typically subject to complex metabolism. Here metabolism means something different. What is illustrated here is a disulfide bond. This can sometimes be cleaved. You have half antibodies perform. The half antibodies essentially can have their own activity, their own pharmacokinetics. Again, the point here I think which is important to consider is that these have a level of complexity which is somewhat greater than small molecules.

[Slide]

In addition, what is important is how the molecule is made because how the molecule is made affects what is referred to as key product attributes. These product attributes govern the potency, safety, efficacy or biologic activity of the particular molecule. Those, in combination,

affect the therapeutic ratio and the risk estimates which are performed and synthesized during earliest phases of preclinical development. As the manufacturing processes change, process-related contaminants can change to some degree the kinds of platform technologies that are available today. I particularly don't think this is an issue but it is something that has to be paid attention to, particularly in early development. Sometimes you hear the term process equals the product. I think, in particular in the early stages of development, this is very true. In later stages of development as we get an understanding of what these key product attributes are perhaps that becomes less important.

[Slide]

There is one important unique issue that affects the safety assessment of biologics and that deals with immunogenicity complications. These complications can sometimes limit the duration of repeat-dose treatment in toxicology studies. In practice, in my own experience and I think in the

broader experience, this has not been a major issue. All of these molecules are not like interferons, for example, which are highly immunogenic and can only be administered for very short periods of time in animal models. However, immunogenicity, as it occurs, can affect pharmacokinetics and can affect pharmacologic activity of the preparation. Sometimes the changes in pharmacokinetics can be reflected by increase or decrease in clearance, a change in dose and potency. Sometimes a change in pharmacologic activity can be attributed to a neutralizing response. But overall these are issues which have been dealt with, I think, very satisfactorily in the preclinical and the clinical arena.

[Slide]

I indicate that this also happens in the clinical arena. What is the experience to date? Well, the first four kinds of severe reactions, fortunately, are very rare both in animals and in the human setting. Immune response, however, generated to a biologic is more common. This is

commonly seen in animals and it is commonly seen in human clinical trials. The kinds of immune responses I have categorized on the next slide.

[Slide]

They are bucketed into what are viewed as the benign category, and a good example here is growth hormones and insulins where the rate of effect can be between 25-40 percent but it is a benign response and has no safety or activity consequences to a large extent.

The mixed response, where you may have a lower incidence, sometimes less than 10 percent and sometimes up to 20 percent, may be a benign response, a binding response, non-blocking response, non-neutralizing but, again, mixed.

The kind of response that you are most concerned about is the response where an antibody response is to the biologic. The biologic cross-reacts with some endogenous factor, renders the subject physiologically incompetent with respect to that particular physiologic activity but, fortunately, these are very, very rare. Many

times you hear that this is a major complication in biologic drug development. In my view, this is sometimes overstated and it is an aspect which is certainly different for biologics, not to the same extent involved in small molecules, but is adequately being addressed and handled.

[Slide]

So, what are the effects of these unique issues on the preclinical safety assessment? Well, you interpret the safety assessment data with prior knowledge of what these unique issues are. If the safety assessment is not compromised, there are no consequences. If there are uncertainties which remain, then these issues are communicated to the physician and the patient by the usual means--FDA regulatory review, informed consent, investigator brochure, IRB reviews, et.

[Slide]

Now I am going to turn my attention to some general conclusions or principles regarding the utility of toxicology studies. First, I think it is important to recognize that a range of

toxicology responses can be observed dependent upon the properties of the molecule. Toxicity is sometimes non-existent, sometimes mild and occasionally severe. Often the toxicity is limited to an extension of the known pharmacology. However, there are examples which are, fortunately, very few but where severe non-pharmacologic toxicities are sometimes observed and I will share one of these examples with you this morning.

[Slide]

I had indicated earlier that sometimes the duration of toxicology studies can be limited and, as has been indicated in Dr. Pazdur's and Dr. Leighton's remarks, the duration of toxicology studies is often linked to the duration of the intended clinical trials. This has to be a case-by-case determination for biologics, in my view. It has to be initially based on the planned duration of the clinical trials but, if there are considerations that arise related to unique differences, sometimes this has to be modified. For example, a blocking or a neutralizing response

that neutralized the activity of a molecule after three or four weeks of administration, testing that molecule for any duration longer than that is not going to provide any useful information.

I think it is important to recognize that four-week repeat-dose studies in one or two pharmacologically responsive species and standard a recovery period, are typical across many indications for biologics and historically are adequate to support IND filing and the safe initiation of clinical trials across a wide array of indications.

[Slide]

It is also important to recognize that many proteins are well conserved and pharmacologically active across species. Rodent models may sometimes be useful, as indicated by Dr. Leighton's presentation. Non-human primates are sometimes used for biologics. Sometimes other non-rodent species are used. Importantly, and this is a property which differentiates certain classes of biologics, single specie safety assessments are

sometimes scientifically justified.

What do I mean by that? Many times for the specie that you are characterizing you find only one representative specie that the molecule is pharmacologically active in. So, you study that specie. You profile that and you try to relate that essentially to the human disease condition. If all other species which are typically used are pharmacologically active there is no value in studying in that particular biologic in that particular setting. Therefore, sometimes applications for biologics do contain only one specie and these should be acceptable if properly justified by the sponsor.

[Slide]

Often dosimetry and toxicity profiles established in animal models are directly relevant to humans. What do I mean by that? Well, here is a slide, which I was shown a number of years ago by investigators at Roche, which attempted to correlate observations between rodents--in this case non-human primates, and the human setting at a

very high level, meaning were the same kinds of pharmacology or the same kinds of biologies observed? I think you can see here that there are more pluses than negatives. I would say that my own personal experience reflects this as well.

[Slide]

One last point with respect to toxicology assessments that I would like to share with you this morning is that the level of initial--I say initial--oxicology concern should extend beyond the pharmacology and immunogenicity concerns. The reason for that is that sometimes unexpected target organ toxicity and dysfunction can be seen. I have an example which involves a thromboembolic complication which I will review with you.

[Slide]

Here is an excised lung from a primate that was treated with weekly doses of human monoclonal antibody to a CD40 ligand. You can see an infarct there in this particular lobe of the lung.

[Slide]

Upon dissection, there was a subacute thrombus that potentially was pulled out of the pulmonary artery.

[Slide]

Upon microscopic evaluation, you can see loss of vessel patency and occlusive vasculopathy which was seen in the majority of treated animals.

[Slide]

Why is this important? Well, this was at that time, and still is today, a finding which was unrelated to the expected pharmacologic activity of the molecule. It was clinically silent in animals. It was observed in animals and clinical trials. From my perspective, it underscores the relevance of well-designed and conducted nonclinical studies to identify relevant human risk factors.

[Slide]

For pharmacokinetic studies, simply stated, clinically relevant disposition profiles can routinely be constructed in pharmacologically responsive animal models. These studies employ the clinical route and dosing regimen. The studies

cover the dose range employed and toxicology studies.

Therapeutic ratio estimates are supported on the basis of either body weight surface area, exposure extrapolation or some mixture, depending upon the preferences of the reviewers or departments of the agency. Techniques of inter-species scaling regarding kinetic data and toxicokinetic data are sometimes useful. And, on the basis of this data multiples of the projected human dose and exposure or safe starting conditions are developed. Well-designed kinetic studies are important and relevant, and can be helpful in the support of Phase 1 trials in patients.

[Slide]

What is illustrated here is a simple relationship and this illustrates this point. The right-hand corner is human data and in the lower left corner is animal data. What you can see on this particular plot is that clearance is predicted based upon work that essentially was performed in lower animal species. If you establish this

relationship early in a particular development program any kind of regimen change or modeling change which you anticipate in clinical trials can be modeled essentially on the basis of this relationship. Does it work all the time? No, but in my experience it works more often than not, and is an approach that is useful and should be considered.

[Slide]

Now I would like to turn my attention to a couple of examples which have a direct relevance to Phase 1 starting conditions in the area of dosimetry. These deal with issues of non-linearity and changes in site of injection and route of administration. I think it would be important to keep these in mind when you are setting dose conditions and you are considering what is necessary essentially to support the initiation of Phase 1 trials in patients.

[Slide]

Bell-shaped dose response profiles are sometimes observed. This is a cytokine wound

healing agent, TGF-beta, which is administered in an animal model. What you can see here is that lower doses promote wound healing; higher doses retard it. All right? So, the issue here is if give more, you don't get more, a concept very, very common to maximum tolerated dose for small molecules that sometimes does not apply to biology and biologics. This should be kept in mind.

[Slide]

This doesn't project that well, I am sorry, but it is in your handout. This is a kinetic profile which was done early in the development of a humanized monoclonal antibody against a particular integument that we have in development. Animals were administered the drug on one day, then serial samples were taken over time. What you can see, going from low to high doses, is a readily apparent change in residence time. All right? So, the drug essentially at the high dose here takes a longer time to clear from the body--and these are essentially days down here--than lower doses that cleared it over a much

shorter period of time.

What does this tell you and why is this important? Well, this may be one of the first indications that you don't have a linear relationship in extrapolating dose. If your therapeutic dose area here, your dose range--this is micrograms on this scale and this would be 10--let's say you wanted to target a dose that was above this level you could say, well, any of these three doses perhaps would give you that level and essentially perhaps saturate the receptors that you have of interest. So, that is one point.

[Slide]

Is this relevant essentially in the clinical setting? Well, this is the same antibody that was studied in Phase 1 trials, and what is expressed here is clearance over a dose range of 0.03 to 3.0 and what you see is a dramatic change in the clearance over that dose range. So, if you had projected your therapeutic dose to be in the lower end of this range where you have wide swings in clearance why would you expect there to be any

kind of uniformity of response?

So, I think this is one of the most important observations early on that you can determine, but it also speaks to a level of complexity with some of these antibodies which gets to the issue of how you are considering dose, and you are determining biologically effective doses or dose ranges.

[Slide]

Well, what is happening here? As I said, this is a humanized antibody, and if you remember from the earlier slide that depicted the antibody with the multiple binding sites, both on the Fab region and the Fc region, you have differential competing receptors. So, the clearance essentially that is occurring at the lower doses is an apparent clearance. The antibody is not leaving the body; it is just essentially being taken up by receptors. So, this is an important point to keep in mind when you are considering dose extrapolations.

[Slide]

Route changes--well, this is essentially a

subcutaneous route, varying the subcutaneous route within the animal between the leg and the intrascapular region. If your biologic effect is related to peak concentration, just by this simple change in location of the same subcutaneous route of administration you have a change in peak exposure, and perhaps a loss of biologic activity. That is something to keep in mind when you are making this kind of determination within a clinical study and determining where to administer drug in a particular patient.

[Slide]

Dr. Leighton indicated about the change in routes, going from SC to IM. Well, this shows essentially the same kind of change in peak concentration from IM route of administration of growth hormone to SC. Inadvertently, if this had been made without consideration that you are affecting the peak concentrations you could have loss of pharmacologic activity in that particular setting.

[Slide]

When we are considering the output of a preclinical development program, the one question that is first and foremost on our minds is can a new drug product be used safely in early clinical trials. Typically, for a biologic development program for a cancer biologic intended for some kind of repeat-dose treatment, this is the kind of study selection that you might typically see. Again, a number of studies to identify the relevant specie based upon pharmacologic response; a tissue cross-reaction study to identify non-specific off-target binding sites; single dose kinetic studies in one or mores species to get a handle on dosimetry, as I described earlier; and single and repeat-dose toxicology studies with some type of recovery period in one or two relevant species. You can see that the total number of study types is on the order of 8-10. This is based upon a background of information that is put together in the pharmacology of the drug discovery area that addresses efficacy, mechanism of action, availability of biomarkers, availability of

response indicators for example. The time frame, interestingly, for preclinical development for these studies is usually on the order of 6-12 months where the discovery period can range from 2-3 years.

[Slide]

What does our experience tells us is necessary and reasonable, reasonable length of toxicology studies that should be required to support repeat dosing of responding patients in Phase 1/2 oncology trials? Historically, as Dr. Leighton had indicated, for small molecules that are intended for daily administration 4-week repeat-dose studies are sufficient---have been viewed as sufficient for many programs.

Historically, 4-week repeat-dose studies for biologics have been viewed as sufficient to treat responders in early drug development programs. My own experience is with Rituxan and Herceptin to support that.

Recently we have been requested, to have longer-term studies. Sometimes three months,

sometimes longer duration is being requested to support treatment beyond one month, particularly in patients who are in the stable disease category. It is not required essentially to treat patients that are giving an objective response. I think the issue is how you are determining what stable disease means. I have my own view on that. For example, a patient that is perhaps not giving an objective response by typical measures but, on the basis of biomarker measurements, the biology is going in the right way and there is no untoward effect that the person is presenting, should that patient be allowed to continue therapy beyond the support of the limiting four-week animal toxicology studies?

[Slide]

The question to you is are the cited differences between the small molecules and biologics of sufficient concern to warrant additional requirements for biologics in all cases? In my view, and shared by many of the BioSafe Committee, this should not be a mandatory

requirement for all biologics in Phase 1, and we recommend the maintenance of a case-by-case determination.

Historically, as is continuing today, agreement between the FDA medical and pharm. tox. reviewers prior to the initiation of IND supporting studies is important. That harkens to the importance of the open, early and frequent dialogue with FDA scientists to ensure program alignment and to avoid unnecessary delays.

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So, in summary I would just like to re-emphasize the key messages that I delivered in the first part of my presentation. Compared to small molecule drug development programs, there are important differences that need to be considered. Well-designed pharmacology, toxicology and kinetic studies are important and should be utilized and designed maximally to support the initiation of clinical studies in refractory oncology patients.

It is our view that four-week repeat-dose studies with recovery periods should be adequate to

support the extended treatment of responding and stable disease patients in most cases. That is not to say that there aren't examples where there should be longer-term studies required. I think we would not debate that and we would entertain those kind of discussions be made on a case-by-case, individual-by-individual situation, but that we do not essentially extend that requirement based upon experiences in one or two cases to the broader population, unless the level of concern is such that it truly warrants it.

[Slide]

I would like to acknowledge my colleagues on BIO's expert nonclinical working group. They are indicated here, and also acknowledge my colleagues at Biogen Idec. That concludes my presentation and I would like to thank the committee for your attention.

DR. MARTINO: Thank you, doctor. Our next speaker is Dr. Martin David Green, presenting nonclinical on initial Phase 1 studies for biological oncology products.

Nonclinical Perspective on Initiating Phase 1 Studies for Biological Oncology Products

DR. M. GREEN: Good morning, members of the committee.

[Slide]

I am going to present a nonclinical perspective on initiating Phase 1 studies for biological oncology products. The products in the discussion that I am going to give today pertain only to the biology oncology products reviewed in the Center for Drugs and not in the Center for Biologics, and do not include discussion of those issues relative to important oncology therapeutics such as somatic and gene therapy.

[Slide]

My presentation today will have two basic parts. One will be a discussion of the concepts involved with the review of nonclinical safety data for initial INDs for oncology, and it will present the results of an internal review of initial INDs regarding nonclinical safety assessments and their impact on clinical hold decisions. This is

important because we are currently developing a new guidance for nonclinical standards for biologic oncology products, and this is due to the fact that we are now facing new molecular structures for which the toxicities are to be determined, as well as new therapeutic approaches which require us to rethink how we evaluate nonclinical safety using the limitations that we have, as was previously noted by speakers.

The purpose of today's presentation is to allow us to obtain your comments so that we may incorporate these and consider them in terms of the nonclinical recommendations for safety testing for biologic oncology products, and in particular the question of adequacy of duration of nonclinical studies relative to proposed clinical studies.

[Slide]

As was mentioned earlier and is available in the information on the web site, there are a number of relevant documents that both reviewers and sponsors can refer to, to understand what is likely to be an acceptable nonclinical safety

package. I won't belabor these issues but briefly go over them. The ICH S6 document is important and it develops the concept of relevant animal species and typically for biologic oncology compounds we are relying on a single specie rather than two species and trying to determine the most sensitive one.

The M3 document is one that pertains to biological products, although there is an escape clause basically for development of immunogenicity which negates exposure and, therefore, does not provide useful information after that. It is basically a timing and duration document, and it basically indicates or suggests that there should be a 1 to 1 calendar day exposure nonclinically for those products which are going to be studied clinically.

The CBER "points to consider" document for the manufacturing and testing of monoclonal products is particularly important because it relates information regarding the tissue cross-reactivity study, which is where human

tissues are used to assess the binding potential of monoclonal antibodies in particular and some other classes of compounds, and in some unique circumstances provides us with the only data that is available for nonclinical assessment. You will see an example later where this was a key point in determining the adequacy of information for the clinical study.

As was noted, the pre-IND meetings provide an important opportunity to discuss issues such as duration and frequency of dosing. In some instances these are intertwined. It is not a means of pre-reviewing the information that is provided under an IND but to get the best scientific advice and guidance, and allow for a dialogue between the sponsor and FDA about anticipated recommendations regarding nonclinical toxicity testing. We believe that in general this provides a broad and flexible approach to the issue of assessing nonclinical safety standards, and is one that has served well in general.

[Slide]

The nonclinical safety assessment in a conceptual way first considers molecular targeting and looks at sites of affinity and binding, and tries to determine how critical this will be in the expression of toxicity, particularly whether there will be issues of independence, in terms of dose-response curve characteristics in terms of toxicity, or whether the toxicities we are likely to observe will be extensions of the pharmacology. In some cases the non-specific effect even in specifically molecularly targeted biological products is overwhelming such as, for example, in ricin conjugates where blood flow to critical organs becomes the overwhelming manifestation and dose-limiting effect in terms of toxicity, rather than the molecular targeting.

Then we proceed with evaluating the nonclinical data in terms of the proposed clinical study, and particularly we look at the capability of the information that is provided to address the anticipated safety concerns. The number of animals that we are often provided in these nonclinical

studies for biologic oncology products is much less than it is for small molecules, typically because we are often dealing with non-human primates and they are difficult to obtain and they are a resources which has to be carefully husbanded.

The qualitative and quantitative aspects of the endpoints are particularly important regarding assessment of dosing and assessment of recovery periods, and biological oncology products are distinct in many ways in that we oftentimes emphasize the immune-based and immune physiological aspects of this class of molecules.

The range of doses that are studied is important to make sure that they include a clinically relevant dose range in terms of its conversion to exposure assessments, and oftentimes we are left with looking at a safe dose versus one that is backed off from for a frank expression of toxicity since many times the biologic oncology product will not produce independent frank toxicities. So, oftentimes a safe dose is a multiple of anticipated clinical exposure, one that

is backed off to avoid potential toxicity.

The duration and frequency of dosing in nonclinical studies is often selected to match that which is anticipated to be used clinically, although in certain instances sponsors have taken the opportunity to intensify the number of doses to make up for the duration. So, they basically lay one against the other--more intense dosing to get a longer period of dosing with a shorter study, although this is not commonly done.

There are unique aspects to nonclinical situations which we think can be addressed through nonclinical safety assessment. These are not necessarily conducted in toxicity studies. Oftentimes they represent a special form of pharmacology studies. We think that this is an important aspect of testing nonclinically for biologic oncology products. For example, for wound healing we would use a wound healing model to assess the effect of anti-angiogenesis for biological compounds.

[Slide]

Proceeding with the conceptual framework for the analysis of nonclinical data, we would analyze the data and extrapolate it in terms of was the data adequate in terms of the cardinal characteristics that are related to dose? Was the route of administration appropriate? Was the dosing regimen for the clinical population correct? What concerns remain unaddressed after we have gotten this data and considered it, and what were the consequences of failing to obtain some of these data which we might think would be important for patient safety?

Then we think about means of bridging the gap and oftentimes that involves modifying the starting dose, altering the dose escalation scheme, increasing monitoring or changing the inclusion or exclusion criteria for the clinical population. Our primary objective is to determine whether nonclinical data can be used so that the clinical study can go forward safely with the available nonclinical information.

[Slide]

The primary means of assessing nonclinical safety is through the toxicology study, and it is a widely understood industrial standard. It is comprehensive in approach by examining a multitude of levels. It provides a means for assessing the inter-relationship between various factors such as dosing and systemic exposure. It also allows a degree of ability to determine the adequacy of monitoring and the reversibility of effects.

It does represent a resource issue for some sponsors. Although it involves a small percentage in the overall development scheme, for companies that are in the early stages it can represent a significant resource issue, and often for sponsors it represent a resource issue with regard to time and the clinical development scheme.

It does have a number of limitations for biological oncology products, and they include the development of anti-product antibodies, particularly if they are neutralizing, but that is not the only effect that anti-product antibodies can create. They include carrier formation and

blocking antibodies. The development of anti-product antibodies can have a number of influences but, importantly, it can change the pharmacokinetics and access of the product to various target organs which would be involved in toxicity expression.

As I mentioned earlier, a limitation in some exceptional cases is that there are no animal models that are available, and that the molecule is human unique. Differences in the disposition can also occur, particularly if the disease burden is an important factor in clearance and, therefore, healthy animals do not really represent adequately the pharmacokinetic exposure and potential expression of toxicity. The accuracy of assessing the adequacy of nonclinical data revolve around dose and, as I mentioned earlier, dose should be sufficiently high to reveal potential adverse effects but oftentimes for this class of compounds it has to be a multiple of the intended clinical dose.

[Slide]

Important issues to consider are that it should be adequate in terms of the number and timing of doses because pharmacokinetics for many biologic oncology products is cumulative because of the long half-life. The clinical experience to date oftentimes has a dosing regimen which does reflect significant accumulation. Secondly, achievement of steady state to potentially deep compartments can be a difficult variable to elucidate since there are basically two stages to equilibrium. One is the short-term achievement of equilibrium in which the circulating blood volume comes to equilibrium, but then there is a longer-standing equilibrium where interstitial tissues and deep compartments also come to equilibrium, sometimes many half-lives after the initiation of dosing.

Additionally, there can be receptor modulation and this can be an important influence on the expression of toxicity. A historical example is the expression of toxicity relative to IL-12. There should be adequate duration in a

nonclinical toxicity study to express the toxicities that we would be interested in, and when we perform the review we try to differentiate between two general classes and their potential to express toxicity. One are molecules which are directly acting on cells to cause lysis or death, for example ricin conjugate, and those which are longer acting because they operate on systems which potentially affect cellular pools with slow turnover, such as the skin, or they affect physiological reserves with a great deal of redundancy, such as the immune system. So, we wouldn't expect that we would have the expression of toxicity until after significantly longer periods of dosing. [Slide]

As I mentioned earlier, we do conduct a review of INDs to understand how our general principles were reflected and how we conducted assessments for clinical holds. The time period for this review included July of 2001 to November of 2005. They represent a continuous series of 51 INDs. These INDs were included if they were new

molecular entities and they were proposed as anti-tumor agents. That is, they were deliberately selected to kill the tumor cells. The INDs were excluded if they were single-patient INDs or emergency INDs, if they were radiolabeled therapeutics because this has a separate means of assessing toxicity, if they involved approved products, or they were diagnostic or supportive.

[Slide]

The source of information that was used to compile the database and understand its implications included the pharmacology and medical reviews, official correspondence, the division files, as well as computerized records, and the primary source of information was contained in the original submissions as submitted, or in the 30-day period of time prior to the final decision regarding the clinical hold.

[Slide]

As I mentioned, there were 51 new molecular entities, and of these 73 percent were monoclonal antibodies; 16 percent were fusion

proteins which are distinct from the monoclonal antibodies for this exercise; and 4 percent were cytokines and 8 percent were others.

The data elements that were examined--I will point your attention in subsequent slides to jut the following, the duration of the nonclinical study as estimate of exposure simply computed as calendar days and then basically the number of nonclinical days that were assessed were compared to the number of calendar days that were proposed for the clinical study; the frequency of nonclinical dosing, that is, number of doses during those calendar days both clinical and nonclinical. As I mentioned, most sponsors chose to match the proposed clinical dosing regimen within the practical limits of the nonclinical study but in a few cases they did try to make up for that in terms of duration, that is, trying to gain a longer duration from a shorter study by just more dosing. In the end I will present how the safety concerns which arose out of pharmacology and toxicology data were considered, and then go to the clinical holds

and differentiate between those which were proposed and those which actually occurred.

[Slide]

The most commonly performed nonclinical study for biologic oncology products was a study duration of 1-4 weeks in 41 percent of the initial INDs. The next most common study that was submitted was greater than 4 weeks, up to 3 months, and that occurred in 27 percent of these INDs. Following close behind that, in 25 percent of the cases were nonclinical studies of less than one week. Lastly, in the minority of instances they were at 4 percent where nonclinical studies of greater than 3 months were performed and then 4 percent were INDs in which no toxicity studies were performed.

[Slide]

We did compute a number called the duration ratio, defined as the number of calendar days of nonclinical dosing divided by the proposed days of clinical dosing. As I mentioned, it was calendar days. And, it did not consider the number

of doses that were administered in that period of time. The mean for this value was 4.5. The 95 percent confidence interval was displayed and, basically this means to us that the average initial IND contains 4-5 times more nonclinical days of exposure for a biologic oncology product compared to that proposed for the clinical dosing. There was a wide range which often reflected the duration of the proposed clinical study.

[Slide]

We now look at the number of doses and look at the dose ratio. We will define it as the number of nonclinical doses divided by the number of proposed clinical doses and, again, it was oftentimes almost completely chosen by sponsors to match the clinical dosing regimen. There was a mean of 1.6 with a wide range of 0.27 to 7.0. The higher dose ratios were not problematic. It was considered acceptable to basically overdose in a nonclinical setting relative to the clinical setting. However, the lower dosing ratios were often regarded as problematic because inherently

the nonclinical laboratory animals often show a faster disposition of it because they have increased rates of clearance.

It is important to point out in this series of products that were considered for the dosing ratio that there was not a confounding variable or development of anti-product antibodies, and that the formulations in nonclinical settings were very similar to those proposed for use in the clinical studies.

[Slide]

Regarding clinical hold decisions, the majority of clinical holds that were proposed and ultimately those which were made involved multiple disciplines, including chemistry, clinical issues regarding monitoring or patient selection factors, as well as pharmacology and toxicology issues. But in the majority of instances these were resolved within the 30-day period, oftentimes by additional information provided by the sponsor or some modification of the clinical protocol, as indicated below--increased monitoring; staggering of dose

cohorts where one cohort completed the dosing experience before another was initiated; inclusion and exclusion criteria; or modification of the dose escalation scheme.

[Slide]

Continuation was allowed in many of these instances based on the acceptability of the toxicities. Some of the cardinal factors in acceptable toxicity included reversibility and also a decision regarding the degree of potential harm, and whether it was clinically manageable and monitorable. The decision to allow continued dosing occurred in approximately 90 percent of the INDs when requested.

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Of the proposed clinical holds based on pharmacology and toxicology issues, there were 9 that emerged out of this database. Less than half of these holds were resolved by discussions and modifications with the sponsor during the review cycle. Four involved adequacy of duration and the pharmacology and toxicology issues were often in

concert with other issues that developed from other disciplines, including chemistry and the clinical considerations.

[Slide]

Examples of the types of holds that were proposed from pharmacology and toxicology information included lack of stability of the investigational biological product used in the toxicity study because, basically, it invalidated the information that was gained from the animals; failure to demonstrate anticipated binding pattern in the human tissue cross-reactivity study, again demonstrating something was fundamentally wrong since known bindings do not appear in the binding studies; also potential clinical risk revealed by the animal findings and an inability of the sponsor to provide adequate monitoring and emergency resuscitative care for patients in the clinical study, as well as preclinical data suggesting tumor stimulation that could not be adequately addressed by the sponsor with traditional information.

[Slide]

Of the actual clinical holds from all disciplines, 13 occurred in this database. Six involved pharmacology and toxicology issues. Four were primarily based on concerns related to pharmacology and toxicology. Three of these involved duration. The average duration of these findings that involved duration aspects was 0.3 and these INDs often took the strategy of matching dosing frequency nonclinically with that proposed clinically. So, they did not attempt to intensify by number of doses. They all involved proposals for continuous dosing in the clinic.

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So, examples were two examples that were put on clinical hold for pharm. tox. reasons. In one, a 3-month toxicology study was submitted, however, it failed to use a relevant animal model and, therefore, the information was considered invalid. Additionally, the sponsor performed a human tissue cross-reactivity study which, again, failed to demonstrate binding by any characteristics and was considered technically

unacceptable for that reason.

In example B there was a 2-month toxicology study that was performed. However, we already had existing information from a similar molecule within that class which demonstrated that a nonclinical toxicology study needed to be conducted of greater duration, that is, at least longer than 2 months, to elicit the potential toxicities. In addition, there was a product contamination issue for this particular product. I want to point out that Dr. Pilaro's presentation, which will follow mine, will discuss, with an additional number of examples and greater detail, the relationship between duration and expression of toxicity.

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Summary and conclusions--assessing clinical risk from nonclinical studies is a matter which is evolving over time as our understanding of the clinical situation and potential toxicities is increasing and the therapeutic environment is becoming more sophisticated. We believe that the

current standards for assessing safety from nonclinical studies is broad and flexible, but it is based on general guidance for biotechnology products that does not specifically look at biologic oncology products. For that reason, we are developing such a guidance in the future and are requesting your input on that today.

[Slide]

The review of submitted biologic INDs has demonstrated to us that toxicity testing was a major component in approximately 50 percent of the clinical holds that were issued and a major component in about 30 percent of those clinical holds. In 90 percent, or a little bit greater than 90 percent of the cases where continued dosing was requested, it was granted. That was based on the clinical population, the actual and perceived risk to patients, and also an aspect which we haven't had time to go into today, is the acquisition of additional nonclinical data concurrent with the clinical study. So, animal studies would be basically the leading edge of the toxicity, get

toxicity gathering data and allow the clinical study to continue as long as the animal findings were reported with a lead time, and oftentimes it is just a month. Thank you very much for your time.

DR. MARTINO: Thank you. Our next speaker is Dr. Pilaro, speaking on nonclinical perspective of initial Phase 1 studies for biological oncology products: case examples.

Nonclinical Perspective on Initiating Phase 1 Studies for Biological Oncology Products: Case Examples

DR. PILARO: Thank you.

[Slide]

I am Anne Pilaro. I am the expert toxicologist in the Division of Biologic Oncology Products in CDER's Office of Oncology Drug Products.

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What I plan on talking today about is some examples. The nonclinical data actually identified different safety issues that arose with continued

versus short-term treatment. I will provide one example where the toxicity was actually observed during a very short exposure that resulted in modification to the clinical trial.

We also want to discuss today how the findings drove the need for studies of longer duration for other sponsors with similar products. Finally, we are going to request input from ODAC in the questions and discussion later on for appropriate nonclinical study duration to support Phase 1 studies of biologic oncology products, particularly for continued dosing in patient populations with stable disease.

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The first case study that I want to present today is monoclonal antibody that is directed against a growth factor receptor. Now, tissue binding and cross-reactivity studies have shown that this growth factor receptor is ubiquitously present on a panel of different tumor cells, but also on pretty much almost all normal cells. Several sponsors have proposed Phase 1

studies in advanced cancer with this monoclonal antibody and we currently have a number of INDs in-house and quite a few more pre-IND discussions with this product class.

Some of these sponsors have actually proposed treatment past the 4-5 weekly doses that have been supported by the animal data. This has been permitted in several cases based on the protocol being designed to continue treatment in patients showing an objective tumor response, specifically complete or partial responses.

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For all of these products, they have been basically active only in non-human primates so most of the toxicology study has been done in monkeys. Four week studies or, in one case where a sponsor did a 7-week study, have been completed and so far with every one of these antibodies that we have seen the only overt toxicity has been weight loss, and that has been dose related and it has been pretty much irreversible. However, when you get to histopathologic evaluation, you start to see some

effects coming up at 4 weeks of treatment and there is a dose-related thymic atrophy and lymphocyte depletion in all lymphoid organs on histologic evaluation.

In 2 of the 4 studies that we have reviewed so far, there has been no resolution of the lymphoid depletion so we don't know what really is going on here. We have recovery data that are still pending for one study and another study has just recently been received. One study was actually done as a pilot study and the sponsor contacted us while they were still in the pre-IND phase, saying that they had early histologic evaluations that showed that they had similar thymic changes at 4 weekly doses of treatment with the same antibody.

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So, several sponsors actually elected to conduct nonclinical studies with longer duration and to continue the treatment out to 13 week studies. One sponsor, still during the pre-IND phase, initiated discussion with the FDA we and

said that we would like to extend the treatment in a certain group of animals, and they actually agreed to add extension groups at the high dose and control animals to continue out to 13 weeks. So, they modified their animal study to build onto the 4-week study.

A second sponsor, actually based on the findings in their 4-week study, was concerned enough that they contacted us, again in a pre-IND phase, and said we are electing to conduct a 13-week study. We are going to use the same doses as we did before and we are going to continue it out but we are going to add immunotoxicology parameters to monitor, as per the FDA's guidance on immunotoxicology evaluations. So, in this particular case they added the flow cytometry evaluations at 4 weeks, 13 weeks and at recovery. Again, at the same dose levels as in their 4-week study they saw the same toxicity profile. There were no overt toxicities other than an increase in weight loss. It, again, was dose related but it was more severe in the 13-week study. The

histopathology revealed dose-related thymic atrophy, lymphocyte depletion in all lymphoid organs again, however, this time it was seen in all dose groups so that no-observable effect level could be defined.

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So, from the flow cytometry data, if you look at 4 weeks the lymphocyte populations don't really seem to be affected by the different doses, and this goes across CD3, 4, 8 and then NK cells.

[Slide]

However, when we get to 13 weeks there is a very different profile that is seen here. Actually, notice the difference in the axis on the X side from the previous one. There is a big increase in total lymphocytes in the control group and this is driving some of the effects that are seen, but what you are actually seeing is dose-related decreases in all lymphocyte populations. They are statistically significant at 0.05 when you get to the CD3, 4 and 8 levels, the mid and the high dose.

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But what is more important is that when you discontinue dosing and you go to a treatment-free recovery period, they are not coming back in the highest dose group. So, this is a toxicity that we kind of expected from this particular class of molecules. The sponsors conducted an appropriate study and built in appropriate endpoints. However, FDA felt that there were other toxicities that could be related to this particular class of molecules based on the target that it is directed to.

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So, in the absence of 13-week data, what FDA asked sponsors to do is to limit patient treatment and continue that only in patients with objective responses that were not having any dose-limiting toxicity. Because, again, of the potential of a long, delayed toxicity with this particular target, FDA has requested that all sponsors with monoclonals to this particular target submit longer duration animal studies, out to 13

weeks, prior to continuing to treat patients where the risk/benefit ratio is less justifiable. Dr. Green mentioned that we will permit toxicity studies to be submitted in advance of the clinical development so before patients are treated for 3 months we would have the 3-month toxicity data in. This is what we refer to as a rolling toxicology application.

[Slide]

The second case study that I want to discuss with you today is again another product directed at growth factor receptor. This time we are looking at a recombinant protein that is an antagonist of the growth factor receptor. It has been chemically modified to extend its half-life. The target receptor is present on vascular and other endothelial cells, including sinusoidal cells in the liver. But it is also present on some other cells, like osteoclasts in bone.

This particular product is biologically active in multiple species, including the rodent and the non-human primate, so toxicology studies

here were actually done in two species because they could be done in two species. The proposed Phase 1 study was in advanced or refractory solid tumors or non-Hodgkin's lymphoma, and sponsor had proposed duration of treatment out to 6 months continuous treatment in all patients in the absence of dose-limiting toxicity.

At the pre-IND meeting, they were actually advised that they should have toxicology studies of longer duration because we know that this particular class of growth factor receptors has some delayed toxicities with other products directed against it.

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The sponsor, however, elected to conduct a 4-week toxicology study in the monkey and in the rat. To address the issue of continued duration, they actually increased the frequency to 3 times weekly compared to the proposed clinical plan of once weekly dosing. What they saw at the end of the 28-day treatment was a little bit unexpected. That is, there was a dose-related renal pathology

in both species that was only evaluable by histopathology. It wasn't detectable by serum biochemistry. Many of the animals were still within normal limits for renal function markers like BUN and creatinine. Proteinuria was measured and it was only detectable in rodents, not in non-human primates where approximately the same degree of renal pathology was observed in both species. What we found in evaluation of this is that these changes didn't occur until you really had a significant amount of damage to the kidney, and the histopathology and urinalysis findings, at least in the rodents, were not reversible following the recovery period. Other toxicities that were noted in this were dose-related coagulopathy that appeared to be a consumptive coagulopathy. There were also cardiac findings, including myocardial degeneration and necrosis present in rats and in a single monkey in this particular product, and the other finding that was present in rodents was bone fractures and dental findings that showed up after the 4 weeks of treatment and persisted through the

recovery period. So, this is a case where we actually got a product where the clinical application was going to be for 6 months of treatment but at 4 weeks we were seeing significant toxicity.

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At the present time the mechanisms of the toxicities are unknown, We think that the potential bone and tooth effects, and possibly the renal effects, may be due to an exaggerated pharmacologic response. Also, because this product is a long-acting protein, it was highly immunogenic in the animals and it is very possible that the renal pathology is due to an immune complex deposition but we don't have the data to address that.

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So, what we actually did was work with the sponsor to amend the clinical protocol. First of all we wanted to address one of the issues, what Dr. Green called bridging the gap, which would be to exclude patients that had baseline renal and

cardiac pathology from the clinical study. The duration of dosing would be permitted to continue in those patients with objective responses, but the protocol was to include extensive monitoring for renal pathology by serum chemistry and serial urinalyses, serial coagulation evaluations and baseline and on-study evaluations of cardiac enzymes, cardiac function by echo or MUGA scans and bone and collagen integrity.

The sponsor was also required to complete a 13-week toxicology study to support continuous treatment. Because of the questions about the pharmacologic activity and potentially the immunogenicity of this product, they were asked to do these studies at a clinically relevant dose and schedule and, rather than going 3 times weekly, go once weekly in the animal studies. We also asked for specific studies to address the mechanism of the renal pathology since this is an irreversible toxicity and it may not be able to be evaluated in the clinic.

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The final study that I want to present today is actually one of our older products that was under development approximately ten years ago. This is a monoclonal antibody to a growth factor receptor. Its mechanism of action is inhibition of binding of the growth factor to its receptor with subsequent inhibition of tumor cell growth through blockade of growth factor-induced signaling. The target receptor is normally present on cells in the gastrointestinal tract, the salivary glands, as well as the skin and they eye.

This particular monoclonal antibody is biologically active only in monkeys and in humans. So, the initial IND came to us really with very short-term pharmacology studies done in human tumor xenograft models and a few short-term animal studies done in both rodent and non-human primate. However, during the course of development the sponsor submitted a pivotal toxicology study in the non-human primate that actually mimicked the schedule for clinical use, which was once weekly dosing.

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This study was actually conducted over a 9-month period and what was found was that there were dose- and duration-related toxicities and mortality observed for this particular monoclonal antibody. There were severe skin lesions that were evident in the highest dose group at approximately 2 weeks; in the mid-dose group at 3 weeks; and in the lowest dose group at approximately 10 weeks of treatment. These were also seen at doses that were clinically relevant. They were about 0.4 to 4 times the human dose. So, they were also observed in the clinical study and they required dose modification. Here is a case where we had data that actually came to us while the sponsor was conducting the Phase 3 study. So, some of these clinical events that were seen in the study were not available earlier on for us to make decisions about clinical monitoring. The nonclinical data actually related to the mortality in the monkeys, which was specifically sepsis, may not have been adequately captured in early clinical development.

[Slide]

We have several other sponsors who have monoclonal antibody to this identical growth factor receptor, again, for use in advanced cancers. Right now they are at various stages of clinical development, from Phase 1 all the way up through pivotal trial completion.

FDA has recommended that the sponsors with this particular monoclonal to this particular growth factor conduct longer-term toxicology studies, again, at clinically relevant exposure and duration, but now in advance of continuing to treat patients in the trials so that we can have the data to guide our clinical dosing and dose modification.

What we have found so far is that the previous findings have been corroborated with at least one of these antibodies where similar severe toxicities have been seen. In another antibody against the identical growth factor these toxicities are showing up earlier and they are showing up in monkeys in a 6-month study. The FDA expects that for this particular class of

monoclonals against this particular growth factor receptor the data will eventually lead to class labeling for this product.

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In summary, what I have presented today are three case studies where the duration of animal toxicological studies was less than what was proposed for the Phase 1. All three cases had clinical laboratory and histopathology findings that suggested cumulative toxicity. In the second case study--I apologize for the typo--renal toxicity may not be monitorable in the clinical population and suggests a clinical risk to patients who are not achieving benefit to justify that risk.

So the question that we would have for the advisory committee today, and that we will discuss in the session following, is what should be the appropriate nonclinical study duration to support Phase 1 studies of biologic oncology products? We have provided you with the questions for deliberation and discussion.

So, finally in summary, the FDA

understands the need to expedite development of novel oncology products, particularly the small molecule and biologics for treatment of cancer. To do this, we have offered several mechanisms to sponsors, including the pre-IND meetings and advice that you have heard Dr. Leighton and Dr. Green talk about. We have offered nonclinical study design features to facilitate sponsors getting their data in to us in advance of their clinical studies, including the rolling toxicology study designs, including submission of in-life data, not waiting for histopathology to be completed, as Dr. Leighton mentioned, and allowing for flexibility in the number of doses administered to the animals versus matching the duration of the study to that for the clinical study.

We would like to include in the discussion the approaches and any guidance that ODAC makes today to us in an upcoming guidance. And I would like to thank you for your attention.

DR. MARTINO: Thank you, doctor. Dr. Perry, I think you have one burning question that

you may ask, please.

DR. PERRY: In your discussion on slide 3 you talked about continued studies based on objective criteria, which I interpret to mean either partial or complete response. Why did you exclude stable disease since that is becoming a very important disease category for these type of agents?

DR. PILARO: That is actually one of the questions that we have for discussion for you. It is under question two. I think it is bullet (b), and that is something that we really need feedback from you at the advisory committee about, because right now we really handle it on a case-by-case basis and it depends on what the potential risks of the product could be and what the potential for being able to monitor those risks in the clinical population is.

DR. MARTINO: Thank you. Our last speaker for this morning is Dr. David Ross, nonclinical studies for initiating Phase 1 studies in oncology: small molecules versus biologics.

DR. ROSS: Thank you. Good morning.

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My name is David Ross. I am Associate Director for Regulatory Science in the Office of Oncology Drug Products. The previous speakers have given an excellent overview of the nonclinical foundation that we need in order to build a therapeutic structure for patients with cancer. What I would like to do in the concluding ten minutes of this morning's presentations is take us up to our sort of 30,000 ft. view and look at what we really want to accomplish in terms of taking these products from the lab into the clinic.

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The title of my presentation is small molecules versus biologics, but I think one thing to emphasize is that there are a lot of similarities between the two classes of therapeutic agents. One of the similarities is in the questions that we need to answer before we initiate

a Phase 1 study in patients with cancer.

What are the potential toxicities that we are concerned about in evaluating a new agent in patients for the first time? How should we monitor for these toxicities? In terms of trying to minimize risk to the patient, what is an acceptable starting dose? Implicit in that question is what is an acceptable stopping dose? What is an acceptable duration of dosing? And, finally, what is an acceptable dosing schedule? I think one thing that I have gathered from the presentations today is that the general rule is that there are no general rules.

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Having said that, I think it might be useful to contrast and compare what the Office and review divisions look for in terms of nonclinical studies to initiate a Phase 1 study in patients with cancer. Both small molecule and biologic INDs require pharmacology studies before initiating studies in humans in order to define the mechanism of action and provide a rationale for going on to

the clinical studies in patients.

Safety pharmacology studies may be necessary. Pharmacokinetics and toxicokinetics are encouraged in small molecules and for biologics, in order to define potential exposures, these are really necessary, the animal models. Toxicology studies are important in both classes. Genotoxicity studies are not necessary in the initial studies, and tissue cross-reactivity is important for monoclonal antibodies but not in general for small molecules.

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In terms of deciding what a safe or reasonably safe, I should say, proposed starting dose in Phase 1 studies is, in both instances we need dose-ranging studies, athough the intent may vary, trying to get a handle on what we think the maximum tolerated dose is, whereas, for biologics we may be looking at defining an optimal or effective biologic dose. For the pivotal toxicology study, in general the mechanisms for small molecules tend to be species independent

although, again, in certain areas this may not be true. For biologics, expression of a species-dependent epitope or receptor may be important and, therefore, choice of species may be critical and may limit studies of biologics to one species.

Then, finally, in terms of what the starting dose should be, Dr. Leighton has presented to you the algorithm for looking at this and, again, this is an algorithm that needs to be looked at in terms of the compound's properties and the available science. For biologics the same principles apply in that we look at the no-observed adverse effect level but we also consider the optimal biologic dose.

In terms of what pharm. tox. studies are needed to support a proposed duration of dosing, in general for any class of drugs, regardless of therapeutic areas, we are talking about initial dosing that is supported by nonclinical studies that are at least one to one. This is true for both small molecules and biologics. Again, this is

not specific to oncology. This is true for any therapeutic area under ICH guidance M3.

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In terms of what we do specifically in oncology however, as Dr. Leighton has mentioned to you, for small molecules we need nonclinical studies that will recapitulate the proposed clinical dosing schedule. For biologics it is useful to separate these molecules out into those with a short half-life, such as cytokines where we want to recapitulate the proposed dosing regimen, and the frequency and duration of dosing that is possible driven by immunogenicity, as Dr. Green mentioned. For biologics with a longer half-life, such as monoclonal antibodies, we would like to see at least one to one dosing in terms of trying to get a handle on what the exposure is on the animals versus what we expect to see in humans.

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So, I have given you a very quick side-by-side comparison of these. One question that comes up is why do these differences exist.

The first Dr. Green, as well as the second Dr. Green gave you a very nice summary of some of the complexities of biologics, and I think it is important to recognize that, as stated in S6, the ICH document for preclinical testing of biotechnology-derived products normally we want to see two relevant species. However, one relevant species may suffice where a biological activity of that compound is relevant only in one species. In fact, in non-relevant species toxicity studies may actually be misleading.

Biologic dose selection is based on the biologically active dose as opposed to cytotoxic compounds where the effective dose is generally near the MTD. And, it is important to recognize as well that biologic toxicities are an extension of the pharmacologic activity of the molecule. Finally, biologic dosing schedules are driven by both pharmacology and immunogenicity and, as Dr. Pilaro showed in her first example, you may get unanticipated effects even beyond the initial dosing regimen that is tested in animals.

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So, looking at a central question that is going to come up for discussion today, which is what data do we need to continue dosing in a Phase 1 study in a patient with stable disease? There is no hard and fast answer to that. Considerations include the disease and the disease setting; the nonclinical data that are available; response data; clinical toxicity data; and what is possible and feasible in terms of monitoring.

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So, to summarize, there are a number of fundamental differences between small molecules and biologics. These differences are reflected in the nonclinical testing strategy for biologics. Guidance documents recognize these differences and support a different flexible testing strategy for biologics. Finally, continued dosing in stable disease depends on a variety of factors.

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With those issues in mind, we will be grateful for your guidance on the following

questions: For most development programs FDA recommends that the duration of nonclinical studies match that proposed for the clinic and this is supported by M3. However, for small molecules an abbreviated duration of nonclinical testing is generally acceptable for anti-tumor therapies. Such an abbreviated dosing duration has also been proposed for nonclinical studies for selected biologic products for treatment of patients with cancer.

It would be very helpful for us for you to discuss scenarios where the duration of nonclinical studies may be abbreviated relative to the proposed clinical duration or should match the duration of the proposed clinical studies.

We would ask in your response that you address the anticipated nonclinical parameters such as PK/PD and toxicity profiles that should be considered in determining the minimum duration of toxicity testing.

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Second, the Office has received

applications that do not provide adequate nonclinical data to support continuation of dosing for an extended duration in a Phase 1 clinical study. We would be grateful for your guidance on the following questions: In what clinical setting and/or patient population, for example refractory disease, indolent disease, no prior treatment, would the risk of continued treatment in the absence of long-term nonclinical safety data be considered acceptable?

In situations where extended nonclinical safety data are unavailable for long-acting biologic therapeutics, such as monoclonal antibodies, the agency believes that continued dosing in the Phase 1 study is appropriate only in patients who have demonstrated an acceptable benefit/risk ratio, for example objective tumor response or symptomatic importance. Should extended nonclinical testing be available prior to allowing continued dosing of patients who have not had clear evidence of benefit? We would like to ask that you ask that you discuss the following

scenarios, the patient with stable disease and the patient with progressive disease.

Then, finally, how should patients who continue dosing in the absence of supporting nonclinical data be informed of the limitations of nonclinical data and potential risks? Should they sign a new consent form? If so, what information should be conveyed? For example, lack of information about cumulative or delayed onset of toxicity; the lack of information on how best to monitor patients; or the potential for irreversible toxicity. What additional information should sponsor obtain during the clinical study to minimize the risks to study subjects in the absence of supporting nonclinical safety data, such as interim reports of ongoing nonclinical studies? Thank you.

DR. MARTINO: Thank you, doctor. At this point the presentations are completed. I will give the group about 15 minutes for a break. We will then return to this room and at that point we will start with questions from the committee to the

various speakers. Thank you.

[Brief recess]

Questions to the Committee

DR. MARTINO: Ladies and gentlemen, the next portion normally would be the open public hearing meeting, however, there are no persons who have asked to address us at this time and, therefore, we will go directly into questions from the committee members, to pretty much anyone that they want to address their questions.

Before we do that, I just need to be sure in my own mind that I am understanding what the actual issues are here because I actually find that this is one of the more complex meetings that this committee has been asked to deliberate on, primarily because it almost comes down more to an ethical rather than a scientific question. That is really how I see much of this. But I just want to be sure that at least I understand what the questions are.

I have sort of boiled this whole concept down into what scientific information do we need

before a Phase 1 human trial is allowed and, perhaps more importantly, what do we need in patients who are going to be treated longer than originally anticipated, those patients generally being those who are presumed to do well, and one can't ever anticipate what their number might be or what their length of time of doing well and, therefore, being continued on a particular therapy is. I think we all have experiences even with very early agents where some individual will be doing well for six, eight, nine months where you never anticipated such a behavior.

So, in my mind, I sort of break it up into two issues. One is what is required prior to starting your typical Phase 1 trial. But perhaps more importantly, what do you want knowledge-wise in a patient who is going to be on longer than anticipated, and how do you let that person know that, in fact, they are having an experience for which none of us are quite prepared and, therefore, none of us can anticipate what the toxicities might be. So, that actually is how I have conceptualized

these questions. Is that fair, from the FDA? Is that, in fact, what you need?

DR. PAZDUR: Yes.

DR. MARTINO: Then with that, we can start questions from the committee. Dr. Hussain?

DR. HUSSAIN: I want to ask first for a clarification and then, if it is okay, I have a couple of questions. The clarification is why biologics, specifically meaning monoclonal antibodies? What difference is there if you block a receptor by a small molecule versus using a monoclonal antibody? This is the clarification request.

DR. M. GREEN: This is Dave Green. So, the question is how do they work differently that is meaningful?

DR. HUSSAIN: No, why do you make that distinction?

DR. M. GREEN: Having a common site of action, is there a distinction?

DR. HUSSAIN: In terms of your requirement for the amount of safety testing that you need,

preclinical safety testing I guess. That is what I am asking.

DR. M. GREEN: Basically, the biologics have a longer persistence in terms of half-lives, and because they are restricted oftentimes in what sites of potential toxicity they reach it takes a longer period of dosing to establish access to those sites in some cases, for example, slowly turning over compartments or those which are not readily available from the circulation which may be clinically apparent as patients are dosed. So, we think that the longer dosing period nonclinically is important because it models the clinical situation in terms of gaining access to potential sites of toxicity.

DR. MARTINO: Patricia, go ahead.

DR. KEEGAN: I think the other thing to be emphasized is, in fact, the persistence after one stops dosing. A half-life of the small molecule is measured in hours, whereas, for the monoclonals they are measured in weeks. So, you stop the drug and the drug is present for weeks to months

afterwards. That is I think a major difference that we want to highlight.

DR. HUSSAIN: So, I guess my two questions would be one to Dr. James Green and the other one is to the FDA. The one to Dr. Green is what, in terms of real terms, are the costs to doing adequate prolonged placebo-controlled testing? A month versus, say, three months, what does that actually mean in terms of costs, and why is that such a gig deal?

Then the question to the FDA is why is the burden of safety any less for responding patients? If a patient is going to respond he is going to go on for six months or eight months. Is that the same concern as in someone with stable disease that is going on for six months? Why do you make that distinction?

DR. J. GREEN: I think to the first point with respect to the differential costs between a three-month study and a one-month study, speaking as a sponsor, we would only like to do one study. All right? So, the differential, essentially that

two-month delta and then including a recovery period--there is some time cost which is probably another 20 percent in a study that might be $600,000, $700,000.

A bigger issue though, and this impacts different companies differently depending on their scope, size and capability, a company like Biogen Idec where we have reactors that go between 200 liters and 20,000 liters, we can make grams of material. So, that two-month delta essentially in animals, and particularly if it is a non-rodent and these are larger animals, consumes an awful lot of material, particularly for a monoclonal antibody that is dosed on milligram/kilogram levels and you can oftentimes get up to between 50-100 mg/kg. So, that is a significant cost.

To give you an idea of what these cost estimates might be, years ago it was not unusual to have $100,000 estimates for material. You can do the math. Take the number of animals multiply it by the dose, if it is weekly dose, the number of doses by cohort, and you can actually go through

millions of dollars worth of drug. Some small companies just don't have that capability early on. So, that is a significant consideration.

DR. MARTINO: Dr. Hussain, your second question was to the FDA in terms of distinguishing why we are looking at patients with stable disease versus a responding patient differently.

DR. KEEGAN: you are correct that there are risks to both, but we look at it in light of a risk/benefit assessment. Patients with tumor shrinkage are, in fact, deriving a benefit, whereas patients with stable disease may or may not be having any drug effect whatsoever. That was the basis of the distinction.

DR. MARTINO: To ask a clinical question again to the FDA primarily, in setting up a Phase 1 clinical trial, my memory is that in years past a Phase 1 trial was very specific. You sort of looked at toxicity primarily because we didn't want to confuse issues and we dealt with drugs that were primarily cytotoxic. So, it was actually quite clear what your endpoints were. It has become less

clear to me with these newer agents what the actual endpoints are when you are doing a Phase 1 trial. So, the question I am posing is when you are dealing with these smaller molecules, these biologics, how do you actually word the end of the trial for a patient? What is the objective that is stated, and what does the patient understand? So, it gets to how we convey information to the patient.

The other issue in my mind is that we now also have Phase 1/Phase 2 studies. In the past I think we were more straightforward. If I can be blunt, we were more honest with ourselves and patients in the sense that we knew that it was parameters of toxicities and side effects and those kinds of issues that were the endpoint of a Phase 1, and we really didn't promise patients that these were drugs that we were looking at to look and see whether they would get a response. That really is the job of a Phase 2, as far as I am concerned. We now have brought those two together, in part because it is easier for us to tell patients that

we are primarily interested in what they get out of this rather than what science gets out of this.

So, the question I am asking is how are we now wording endpoints, both in the study itself when we call it a Phase 1/Phase 2, and how do we describe this to patient when they enter a study? Because what to tell them when they continue a study, to me, has something to do with what you tell them at the beginning.

DR. JUSTICE: I think from a small molecule point of view, the Department objectives of Phase 1 studies is still to determine the safety and the maximum tolerated dose, pharmacokinetics. But studies are done with a therapeutic intent even though we realize that the odds of a patient benefiting are relatively low. Trials do measure response and progression. Progression in particular is important because you want to stop therapy if a patient is not benefiting.

DR. MARTINO: So, do I then understand that the endpoint for most patients is progression of disease, or is it reaching some

pharmacologically measurable event?

DR. JUSTICE: Well, in general the doses are escalated in cohorts of patients. Although there are some trials that use every patient for dose escalations, most trials escalate in cohorts where patients continue at a particular dose level, and the objective is to determine the toxicity and pharmacokinetics at that dose level.

DR. MARTINO: Do we actually believe that patients understand that? That that, in fact, is the intent? See, this is where the Phase 1/Phase 2 combination, to me, becomes very confusing because it allows you to have one goal, yet the patient, I suspect, primarily understands the second goal, which leads to the problem that I am seeing here.

DR. JUSTICE: Well, I really wouldn't call it a Phase 1/2 combination. The Phase 1 trials still generally don't focus on a particular tumor type. They take different tumor types for which there is no effective therapy.

DR. KEEGAN: I would say, having reviewed these recent 51 NMEs, sometimes we have protocols

that are as typically seen in small molecule which are advanced refractory and it is a tolerability study, a dose-finding study. But we also frequently see studies in a single type of tumor of the Phase 1/2 variety where the goal is determination of an optimal biologic dose based on some pharmacodynamic parameters, such as saturation of receptors, binding to a circulating antigen--pharmacodynamic effects but not truly toxicity, and it is sort of to see are you in the ballpark of where you intended to be, and does this build on, for instance, the animal pharmacology studies that were done.

DR. MARTINO: What I am getting at is when does patient participation end in such a study? Is it, in fact, that they are treated to the point where there is an obvious progression or not? Is that when it is stopped?

DR. KEEGAN: I think it varies, and I think all of our studies do say that patients would be taken off for progressive disease or for unacceptable toxicity, but primarily it is for

progressive disease. Where our concern lies is for patients who are not meeting the criteria for progressive disease but also are not meeting the criteria for response where it is unknown as far as whether they are deriving any benefit whatsoever. We also are unclear about what the risks are for continuing.

DR. MARTINO: And from the group's experience to this point with this family of drugs, how often is it that you have a patient who actually presents with the question that we are addressing, which is to say that they have either a response or stable disease? How often is that, in fact, the case? Are we talking about the exception, as I suspect we are? But I would like a sense of that.

DR. KEEGAN: I have to say that we have not reviewed the information from those INDs to tell you how often that occurs. I think it probably is variable, and it may depend upon what you are looking for. If it is pharmacological effect, like an anti-DC20 antibody showing

clearance of lymphocytes, that happens pretty frequently.

DR. MARTINO: I am referring to the clinical benefit to the patient because that is the issue we are struggling with here. So, I am trying to figure out is this a problem that is faced with these drugs one percent of the time, five percent of the time, fifty percent of the time. I just want a sense of it because my sense is that it "ain't" that common.

DR. JUSTICE: I would agree. I think the response rates generally are pretty low.

DR. MARTINO: Again, I would like to get to the issue--

DR. PAZDUR: There is literature--

DR. MARTINO: There is. So, can we all agree that it is an uncommon problem? Yet, my concern, Dr. Pazdur, is that I am trying to understand the manner in which we now write Phase 1 Phase/2 trials. My experience is that they tend to become Phase 1/Phase 2 or we label them that way or we cover them that way but, basically, what I am

seeing is that patients have the expectation from the beginning. Do you understand the point I am trying to get at? Am I correct or am I wrong on this?

DR. PAZDUR: I think you are correct, but let me kind of amplify one area. When we are talking about Phase 1 and Phase 2 trials, generally that represents a sequence where one has gone through an escalation and one achieves recommended Phase 2 dosing and then expands the cohort there to get further experience. That is not the situation we are talking about here. What we are generally talking about here is people that are at a dose that we have not extended and we don't know if this is the MTD or the recommended Phase 2 dose, and what to do with those patients that have stable disease. I think that is the issue here.

The issue that you are bringing forward is when do patients get clinical benefit or some type of benefit that is derived from that. I think most of the patients--you know, I am sure the other Phase 1 investigators may want to chime in here,

but people go on these studies not to determine toxicity but in the belief that they will get some benefit from these studies, and that is a fact here. These are relatively low response rates we see, but definitely they are seen in Phase 1 studies in a given population that generally has very few therapeutic alternatives open to them. So, that is I think the reality of the situation.

Usually the second criteria is to determine some anti-tumor responses and in general that information will help us, the investigators, whether to further extend those studies; whether to further study the drugs so, you know, there are some advantages in getting that response rate evaluation not only for the patients, which is most important, but also in the clinical development of the drug.

DR. MARTINO: Dr. Sausville, do you want to answer that for me?

DR. SAUSVILLE: I wanted to both agree with Dr. Pazdur and amplify on a few points. First of all, as most Phase 1 investigators will convey,

although you can state that the scientific goal is as stated--safety and pharmacology, when you ask the patients why they are participating it is because, yes, they know about that but the hope is that there may actually be benefit. That is point one.

Point two, I think that if you look over a variety of Phase 1 studies, the vast majority of patients come off between two and four months of treatment. A properly conducted Phase 1 will actually assess whether or not there is evidence of clinical deterioration. So, by definition, you have a response indicator. It is actually a very common scenario to agonize in that period of time whether the patient is really having progression of disease because, as we all know, the radiographic tools that we have are sometimes ambiguous on this point.

I think the key thing is that in constructing the informed consent for these activities our goals are scientific ones but we are going to follow you and we don't know actually what

the longer-term effects might be. I think the act of an informed consent process is a dynamic one. It needs to continue with the course of the study. I think those are the principles round which we might begin to see answers to some of the questions that the FDA asked.

DR. MARTINO: Dr. Cheson, I think you are next.

DR. CHESON: I have a question that I guess is best answered by Dr. Green of Biogen Idec. We are faced very frequently with these Phase 1 trials of monoclonal antibodies and I am still trying to get at what is the sense of doing these studies in the absence of just identifying the optimal biologic dose, as has been mentioned here a few times. Companies escalate, escalate and escalate but I don't see them looking at issues of receptor saturation and pharmacodynamics. They are just pushing and finally they say, well, we have got to a really high dose, which may be an overly expensive dose, and we are just going to stop here. If they looked instead at biological dosing

parameters, they could finish these studies a whole lot quicker I would think. Am I missing something?

DR. J. GREEN: No, absolutely not, you have no disagreement from me. In fact, I think the concept that was stated by the chairperson of biologically effective dose, minimally effective dose, whatever you call it, is attempted to get at by some of the dosimetry considerations that I raised. For biologics in particular the concept of MTD, in my experience or my perspective, is one that is best left with a small molecule. In fact, it might even be revisited with some of the small molecule testing paradigms because the issue here with some of these therapies is understanding the pharmacology, bracketing the biologically effective dose and delivering in that first patient cohort an optimal dose that you believe is pharmacologically active, and I think what you are struggling here with, with respect to stable disease--my perspective on that, because outside of the objective response indicators that you all deal with routinely, I think with some of these agents

stable disease may be, in fact, just binding to the receptor, lighting up the expected pathway. The patient essentially is showing no signs of toxicity and there is a potential of benefit, a hope of benefit. These are the patients that are in these trials.

And, I think it is a fair statement that there is an expectation, both on the patient's part and the investigator's part, as to what they can do with a patient that enters this trial. If I am diagnosed with stable disease or I don't have any side effects, can I continue to receive treatment? That is a very practical issue, and we are seeing investigators and patients declining to participate in trials because they are saying, no, if you don't respond we can't treat you beyond three or four doses. I think that is a significant issue.

DR. CHESON: But I think we have to come to some sort of definition of what is acceptable stable disease. As has come up in these meetings in the past, there are patients who enter trials with very large tumor masses, very symptomatic from

their disease and, if that doesn't change, that is still stable disease by the current response criteria but that is not somebody I would want to continue treating with a particular agent.

DR. J. GREEN: I don't disagree with that either, and I think that echoes one important point, that somehow this distills down to a discussion between the informed investigator and the patient around their condition.

DR. MARTINO: Dr. Perry?

DR. PERRY: Thank you. My remarks are in part addressed to the FDA. First about MTD, and I have to say that it would have been helpful for us if we had a glossary of the jargon used by the Phase 1 and pharmacology people. I speak several languages but I guess none of them are FDA.

[Laughter]

Virtually every slide had an abbreviation that was not defined, and I don't think I am the only one who is stupid enough not to recognize all these things. So, next time a one-page glossary or at lease definitions on the slides, would be

helpful.

Let's talk about maximum tolerated dose, and let's talk about our old friend Iressa. As I recall the Iressa data, the 500 mg dose of Iressa was not chosen, even though it was the MTD, because they had the same efficacy at the 250 mg dose. Is that correct?

DR. PAZDUR: I really can't answer the question.

DR. PERRY: For the moment you can just nod.

DR. PAZDUR: Yes.

[Laughter]

DR. PERRY: My point is that MTD for some of these agents is one of several endpoints. You don't have to go to a toxic dose to saturate a receptor or to get an effect. So, I think we need to acknowledge that there are endpoints other than MTD that allow for an effective dose, particularly with small molecules.

The second point, stable disease is very difficult at times to define. If we define it as

less than a 50 percent decrease or 25 percent decrease in size, we have a fair number of patients. Yet, some of these patients are clearly in a sort of homeostasis with their tumor and derive some clear benefit. Picking on Iressa again or Tarsiva, 8-month average survival is clearly better than 6-month survival that we would have predicted for somebody with stage 4 non-small cell lung cancer.

So, I don't think we can throw out stable disease because our radiographic techniques are simply not as effective. Sometimes what we see on a CT scan in lung cancer is the same size mass but it is really a necrotic tumor if we did the PET scan, or went to surgery, removed the lesion and found that it is mostly necrotic tissue. So, I don't understand the rationale for requiring complete or partial response when stable disease is becoming, I think, an acceptable endpoint for many of these non-cytotoxic drugs. I think that is a very good point.

Finally, a point that I am going to touch

on now because I may not get the microphone again is when you are talking about continuing dosing in the absence of supporting nonclinical data about signing a new consent form, that statement really rankles, particularly coming from a government agency. Those of us who have to deal with the IRB know that signing a consent form is not the same as obtaining consent, which is an ongoing process and it is not a simple legal document. If we want to perpetuate the culture of informed consent as a process, as an ongoing dialogue, as verbal and not just simply signing a form that is stuck under your face, I think we need to do it and get it right here and pass it on, rather than have somebody walk out of this meeting thinking that signing a consent form actually made a difference and the patient actually understood a 14-page legal document that they had two minutes to read. End of editorial.

DR. MARTINO: I tend to agree with you to a reasonable degree on that, but it does occur to me that some of these things really could be incorporated into the original consent. So, if

they are well defined in there, perhaps as a separate entry--you know, you may be one of the lucky ones who is treated for some length of time--we may get to a point where we have very little knowledge of whether that is good, better, indifferent or what side effects are pursuant to that. Yes, you would still inform the patient, perhaps in a legal way in that you have their initial or their name on some piece of paper that makes you happy, yet you have at least made them aware that this is a piece of what could happen to them. Because it sounds like though it is uncommon, it is not so uncommon as to be, you know, just a once in a blue moon kind of event.

So, I am also leery of having additional consent forms. It is not so much a problem with the patient because I am hoping doctors actually do talk to their patients, but it is the IRB and all of the other things that could easily delay you from even being able to continue therapy for a patient until they are able to sign that consent form. Dr. Kodish next, please.

DR. KODISH: So, there is a difference between what people say and what people hear, and that is very important in the context of informed consent. I think the Phase 1 investigators around the table know what they say to their patient or subject but we don't know--we don't have data to know what patients hear and those studies have not been done yet. So, I wanted to start with a plea for more data about the informed consent process, as Dr. Perry says, and not just a document.

We know that in the Phase 3 context in children with leukemia 50 percent of parents understand randomization despite the fact that they are all told about randomization. If that paradigm applies to the Phase 1 context, then that is an important piece of information to have.

In terms of the ethics, I think there is a phrase called therapeutic misconception that people write about and, actually, there is a helpful dissection of those concepts. One is therapeutic optimism and the other is therapeutic mis-estimation. I think that, although we don't

have the data, therapeutic optimism is ubiquitous. As people have said, that is what folks hope for. I am not sure that therapeutic mis-estimation is so common. I think subjects may be able to say what the numbers would be but in their mind at the same time hold this therapeutic optimism.

Having said that, it is important that the FDA have a policy that never allows us to subjugate the needs of an individual subject to the needs of science, and I think we are at risk for that already. I don't think that Phase 1 studies do that, but I think a scenario where someone has stable disease and the patient wanted to stay on the drug and we say, no, you can't do that, risks at least compounding a perception that we are subjugating the needs of patients to the needs of science. So, I would urge us to be very careful not to be in a situation where we pull a drug away from someone who wants it and has stable disease.

I also think that the natural history of the underlying disease is an important factor here, and there are some diseases where stable disease

means a different thing than in other diseases. So, I would want to think about which disease we are talking about. I share the chairwoman's concerns about the Phase 1/Phase 2 ambiguity that has crept into things. So, I think ethical clarity requires us to sort of be as clear with the paradigms as we can be.

DR. MARTINO: Dr. Fojo?

DR. FOJO: I have a question for Dr. Pilaro, and the second part of that also goes to Dr. James Green. Dr. Pilaro, I wasn't sure--in your presentation I was trying to read between the lines and I am not quite sure what you were trying to tell us with those two examples that you showed. But it seemed to me that in both of those examples the more long-term toxicity, if you will, became evident in the short-term studies. I wondered if there is evidence that that does happen frequently, that in a 28-day study you get an inkling that you should go further.

Then, related to that, it wasn't clear to me what you think of the more frequent dosing as a

surrogate, if you will, or substitute for the more prolonged studies. Related to that question, I was just wondering if Dr. Green's negative outlook, if you will, on more prolonged studies is also extended to shorter studies that use more frequent dosing or higher dosing, if you will, as a substitute for that.

DR. PILARO: Let me try and address all those issues, starting with the case examples. In the first case example where the T-cell toxicity wasn't really evident until 13 weeks, we had an inkling that there was going to be a problem just based on the thymic atrophy and the lymphoid depletion. That class of products hits a growth factor receptor that is known to be involved in T-cell maturation. It is also known to be involved in T-cell function. So, one of the concerns we had there was longer duration.

To address Dr. Martino's issue, I would say about 50 percent of those INDs that have come in for that particular class of product wanted to have blanket approval to continue treatment,

regardless of whether it was stable disease or objective response. So, with that particular example there was a hint at four weeks that there could be toxicity. There was other data available that suggested that if you are hitting this particular receptor you could run into problems and it wasn't until 13 weeks that you actually did see the effects.

The second example where they actually did the more frequent dosing to address it, that has been a mechanism that we have used before. I think that for that particular product that was a bad choice, but it doesn't apply to all products across the board. If you can increase the frequency of dosing and not run into these kinds of problems with either immunogenicity or enhanced toxicity then, yes, that is a mechanism by which you can get data to support continuation of dosing.

This is one of the questions that we have for the committee, which is should it be the number of doses that you match or should it be the duration of dosing in the animal studies that

supports what you want to do for the clinical? Let me turn it over to Dr. Green though to address the frequency issue.

DR. J. GREEN: Thank you. If I understand your question correctly, I think I would agree with that strategy as being an option for providing dose intensification to assess potential effects that might be observed within, let's say, a two- to four-week high dose intensification regimen. That experience then is perhaps extrapolatable to longer term depending upon the nature of the findings that are seen.

Let me give you an example, and this is purely hypothetical but this would be a case that might raise some concern in my mind. If you saw evidence of progression of effect over a short period of time with respect to number of treatments, then that would raise in my mind dose-time phenomena. There may very well be concern with respect to longer treatment periods. I think you have to ask yourself the question about, well, what does that signal mean? Can I

measure it? How clinically evaluable is it? What is the significance of that particular concern? So, I think that is a strategy that can be used.

On the other hand, if we get back to the concept of biologically effective dose, that goes against the concept of biologically effective dose where I think we should be mirroring both in the short-term studies that we do initially to support the preclinical development and early phase clinical studies. I think they are both manageable but they require an approach that sometimes is different than has been done in the past. So, I wouldn't rule it out but I don't think that all cases essentially would provide useful information but in some it might.

DR. PILARO: I just want to add one last caveat to the increased frequency of dosing. You saw Dr. Green present the curve that was basically the inverted U where the response tends to go down. The risk you can run with increased frequency of dosing is that you may down-modulate your target receptor and actually lose both your pharmacologic

and your pharmacotoxic effects.

DR. FOJO: Thank you.

DR. MARTINO: Dr. Bates?

DR. BATES: I guess I just wanted to amplify some of the things that were said previously. I agree also that the observed biologic effects ought to be included as one of the goals of testing rather than trying to look merely at toxicity. I think that is critical because more and more often in studies we do see patient populations who have indolent disease. Then, the definition of progression to take them off study is fairly lenient, and a patient can stay on a clinical trial for four months without really having impacted the biology of their disease. To me, that is a major concern. I know that if you look at some of the data presented with cerafinib [?] you can see patients who did have clinical benefit when they didn't achieve a PR. So, there is a group of patients who have minimum response in whom you are impacting the biology of their disease. But I think if you are going to give an

agent that is essentially inactive to an indolent disease population, you do run the risk of a publication coming out later saying, yes, we had stable disease in 40 percent of our patient population when you, in fact, had no impact on the biology of their disease. So, I think that if you are going to allow people with stable disease to stay on these studies and continue getting treatment you have to build in that you are at least hitting the target, if not having an impact on the disease's biology itself.

DR. MARTINO: Dr. Rodriguez?

DR. RODRIGUEZ: Actually, I probably have just a comment rather than a question. My experience in many Phase 1 trials is exactly the opposite of what is being discussed here, that is, the pharmaceutical companies are unwilling or unable, for technical or financial reasons, to provide ongoing treatment to patients who are having a slow response in their disease. That, from my point of view, brings in the opposite end of the ethical discussion here, which is in

patients who maybe are still having ongoing benefit from the treatment is there an ethical obligation to assist them or to help them to optimize their response, realizing that the benefit wasn't the endpoint of the study but that they are, in fact, deriving benefit and they may not yet have been given the optimum dose or treatment duration?

DR. MARTINO: Dr. Harrington?

DR. HARRINGTON: Thank you. I want to try to focus on the real intent of the Phase 1 studies. I mean, we know that they often extend clinical hope for patients and we know that we can use them sometimes as surrogates for larger studies to assess response. But for me the conundrum here is that when these schedules extend beyond the period where there was preclinical testing, clinicians are wandering a bit into the unknown in terms of side effects for patients.

So, for objective response I can understand the benefit and for stable disease I can as well. I think the distinction is often more apparent than real there because we don't always

know what the durability of those objective responses are. So, for me, I think one of the key questions is if we are willing to wander into that area of the unknown, exactly what is the process between the agency, industry and the trialists when the schedule begins to extend beyond the preclinical testing? So, what kicks in? Is industry required now, as rapidly as possible, to do extended dosing schedules? How quickly does information get back to the clinical sites conducting those Phase 1 trials about the results of those preclinical--they are not really preclinical anymore but animal testing being done concurrently? How quickly cam we mitigate the possible damage of wandering into an unknown zone where we don't know the real side effects?

DR. MARTINO: Please?

DR. M. GREEN: This is Dave Green. I think that we make a distinction between those patients who started on dose and exceed the amount of nonclinical testing versus those patients who have not been dosed but may in the future have

longer periods of time. We basically will communicate with the sponsor, in writing almost always, that longer-term studies are necessary for large clinical studies, beginning often in our minds formal efficacy studies, and then basically look to see what clinical picture is emerging, and use some of the decision criteria that I mentioned about whether there are acceptable toxicities and can they be managed, to basically decide on those patients who are already getting dosing whether they should continue.

So, for future clinical trials we suggest that they should perform those studies. We try to promote the paradigms. Since many of these patients will continue to have dosing beyond what is initially established nonclinically, the sponsors should plan for that and we encourage them to have longer-term studies with interim data available to us in a way that we think does not impact on continued dosing of patients.

DR. HARRINGTON: Just a follow-up question, and I think I know the answer to this,

how feasible is it to do that additional testing so that patients on the same Phase 1 clinical trial, who may go on at either the same or higher doses--for those patients there is extended toxicology or toxicity data from the preclinical studies. Or, is the timing such that for practical purposes once one observes in a Phase 1 trial that they are probably going to go beyond the preclinical dosing schedule that there will be no animal data available for the patients in those trials but only for subsequent trials?

DR. M. GREEN: We make our advice to the sponsor regarding the adequacy of duration usually at the time of the initial IND. So, at the time they are allowed to go forward where they have other communications, that is, 30 days after the initiation of the IND, we attempt to give them our best estimate of when those longer-term studies would be necessary.

DR. MARTINO: Dr. Pazdur, do you want to add to that?

DR. KEEGAN: Actually, I would say that I

think it is a rarity that we receive information on interim reports in a timely fashion, sufficient to make sure that it is incorporated into the informed consent document. The exception would be if there was a serious finding that would result in a 15-day report, as in the case that I think was alluded to of non-human primates that died of sepsis due to sloughing of the integument that was a drug-related phenomenon, and we received that as a 15-day report. But more minor findings I think we would not expect to see as a 15-day report and would not be rapidly turned around and available to patients in Phase 1 studies.

DR. HARRINGTON: Just one follow-up question then, can someone be more specific about what was meant by the rolling studies that were mentioned on a couple of slides?

DR. M. GREEN: The rolling studies--let's take a hypothetical example that a sponsor submitted a four-week study, nonclinical toxicology study, but were going to continue to dose patients. At a pre-IND--let me just back up. Let's say we

had a pre-IND and they wanted to dose patients indefinitely but the original study period would be four weeks. We would suggest to them that if their intention is to progress with clinical trials and they were confident, or sufficiently confident that this was something that where thought that not a large number of patients would continue to be dosed, we would suggest a three-month study. We feel that a three-month study is basically the study in which we get all the adequate information necessary to continuously dose patients. There are some exceptions, and there have been requests in rare instances for longer-term studies but, basically, we believe that a three-month study is typically adequate to assess all the toxicity information that we need to continuously dose patients all the way up to the time of approval. At the pre-IND, we would suggest to sponsors that they might consider a longer-term study as a means of providing continuous information, so if they had ten animals, five animals would be made available for toxicity assessment at one month and the

remaining animals would be made available at three months.

DR. MARTINO: It strikes me personally that with practically any agent that you are looking at you have at least a possibility that Mrs. Jones will be treated longer than the expected brief period. So, since you assume that there is going to be at least one person, don't you sort of have to anticipate all of this beforehand? That really is where you are leading me here. So, it gets me to this question of in the studies that have been done, how often is it that you truly don't have a Mrs. Jones?

DR. KEEGAN: I would have to say that it is difficult to track. Assuming all of you put in your reports to INDs which only summarize data on an annual basis, it is very hard to distinguish patients and what is going on, get that data in real time and to summarize until the end of final study reports. I can't say that we have final study reports, nor have we done that exercise.

DR. MARTINO: But I am dealing with a

possibility here that with any study there is likely to be one person where you are struggling. You know, do they have stable disease or are they responding and are going to be, you know, treated beyond a certain limited point? So, unless I am hearing here that this happens once out of a hundred times, in which case I would say, well, in that case why are we having this discussion, but if it happens often enough that there is at least one person, then the problem becomes, to me, one that is constant and, therefore, one that needs to be addressed earlier than once they tell you that Mrs. Jones was on longer. Am I not understanding the problem here?

DR. PAZDUR: The alternative to that, Silvana, would be that the FDA would not let any study go forward, until there were three-month tox. data. I don't know how reasonable people would feel to support that because that could mean significant delays in the development of therapeutics if it came down to you must have three and you cannot start because of that. Here again,

we are always in this arena of what is optimal versus what is absolutely required.

Yes, if I was living in a perfect world we would want the total pharm. tox. package done and then we would allow the first person on this. Unfortunately, there are demands to get these studies started and there are patients out there that would feel, and many companies that would feel, as well as investigators and the oncology community that we would be overly restrictive in that. That is point one.

Point two, getting back to the basics here, I think one of the things that we have been arguing about is what is clinical benefit to an individual patient, and that is very difficult. We have tried to ascribe that to a response rate here, and I would like to have everybody remember that in the good old days when we were developing response rates, etc., this had nothing to do with any linkage to clinical benefit or to benefit to a patient. They were basically looking at what would be reproducible from a radiographic point of view.

When the full criteria came out it was a 50 percent reduction due to inaccuracies of measurements and physical examination and plain radiography.

So, you know, I think that is one of the essential questions. How do you measure clinical benefit? Obviously, if somebody had developed symptoms and had symptom improvement on a therapy or if they had stable disease, everybody would agree that that patient should continue. But the question is what should be that determination of clinical benefit for an individual patient.

DR. MARTINO: Yes?

DR. KEEGAN: I am sorry, it came to me that your real question is how often does that happen, and I tried to answer to you that we don't know. However, based on the feedback we get from companies, investigators perceive that it happens a lot because they complain about it. So, I don't know what the reality is but I know what the perception is.

DR. MARTINO: Dr. Bates, do you have something to add to that topic right now?

DR. BATES: Basically I agree that it happens a fair amount depending on the patient population. That wasn't my question but I agree that it happens, and you do have to address it from this perspective.

DR. MARTINO: I will get to your question in a bit. I am getting back to this issue that if it happens quite a bit maybe one ought to think about it quite a bit, and it doesn't have to be necessarily something that is ready when you put the first patient on, but perhaps it is something that should be ongoing. Dr. Cheson, I think you are next.

DR. CHESON: Yes, but it is off the topic; it is back to a different topic. If you want to keep this theme I can wait, or are ready to entertain other things?

DR. MARTINO: No, proceed any way you want.

DR. CHESON: Okay. Getting back to Tito's question and Dr. Green's answer, I personally think it is not a good idea to do this high dose, short

course thing for a number of reasons, particularly with antibodies. One of the goals of the Phase 1 trials is to do pharmacokinetics, and if you are doing that you are going to lose your ability to determine what the optimal dosing is of this antibody. For example, you will never know how to dose in a Phase 2 trial if you are just looking at escalating the dose.

The other problem you run into, particularly in antibodies and particularly in effective antibodies, is that over time you will be depleting something, and if you just look at the toxicity in the short course you are going to miss that. Look at rituximab. We don't know very well the long-term consequences of chronic B-cell depletion from the antibody. We are starting to learn this based on maintenance studies, but with all the interest in maintenance of antibodies we wouldn't be able to get that information if we just looked at the short-term toxicity.

So, I think, as the comment came out several times, this does have to be somewhat

case-by-case dependent on the type of compound. I would think for the small molecules that might be quite different because, as we heard, they go in and they go out. But for antibodies that last a long time it might have long-lasting complications that--based on cumulative blood levels, etc.--it is probably not a good idea in that context.

DR. MARTINO: Dr. Sausville?

DR. SAUSVILLE: This is a question for Dr. Pilaro that might get at this a little bit. In your presentation of the examples I guess there was a T-cell example and there was the example that had some, as I interpreted it, renal findings. Do you have preclinically a way of grading, so to speak, the significance of these phenomena? Because, again, from a clinical perspective, if you have someone who has the perception of benefit, be it stable disease or response, an asymptomatic grade 2-something or other is something that probably the patient and the physician would accept. On the other hand, you can imagine other toxicities that, depending on their grade, would be far less

acceptable. So, when you think about this in the preclinical extended study context, how would you approach that if you were to put that into practice?

DR. PILARO: Well, for the preclinical studies we don't have anything like the NCI common toxicity criteria so I couldn't say that that T-cell response was actually a grade 2 toxicity, which is what I think that it would be if I was looking at it clinically. However, what we do look for are things that cause death or irreversible toxicity, or toxicities that cannot be clinically monitored.

In the second example with the renal pathology, it is a potentially irreversible toxicity. Even after completion of the treatment in the recovery period that toxicity was still present. That raises a significant flag for a clinical study.

DR. SAUSVILLE: And in that case did the renal toxicity progress to renal failure in the animals or was it, again, an abnormality?

DR. PILARO: Without going into the actual data from the IND, all I can say is that there was significant proteinuria and it did not resolve. It was still at the same level at the end of the four-week treatment-free period as it was at the end of the treatment. Then you sacrifice the animals so I don't know if they progress.

DR. SAUSVILLE: Well, thank you for that perspective, but I do think that that is going to be an important consideration as this goes forward because the grade and nature of the toxicity really has a lot to do with ultimate clinical acceptance.

DR. MARTINO: Dr. Grillo-Lopez?

DR. GRILLO-LOPEZ: I would like to go back to stable disease and the decision-making process around that patient continuing therapy or not. Stable disease 30 years ago was not the issue that it is today because 30 years ago we were primarily dealing with small molecule chemotherapeutic agents and if a patient achieved only stable disease that was rapidly followed by progression usually. Whereas, in the last 30 years and with the advent

of biologic therapies, what we have learned slowly is that with these new therapies you do see an increasing number of patients developing stable disease and then you are in that quandary, that situation where you have to make a decision. Clearly it is not easy, and that is why the FDA has us here today discussing this problem.

I would say that there are a number of considerations in such patients. Dr. Cheson brought up one example of the patient who, yes, has stable disease but is symptomatic and probably has bulky tumor and, therefore, is there any real clinical benefit to this patient. I think one also has to consider what therapeutic options are available to the patient after the experimental study is concluded. Patients who enter that Phase 1 trial, simply because they were relapsed after a few or perhaps just one prior therapy, may have a lot more options than a patient who enters that Phase 1 trial being refractory to several different therapies and, therefore, there are no options left for that patient. If he is just stable with

symptomatic bulky disease, maybe that is the best that we can therapeutically do so that has to be considered.

Also, one has to consider the patient who enters a study after progressing on a therapy and, yet, maybe that patient, after progression, was stable for months before entering the Phase 1 trial. If in the Phase 1 trial the patient just remains stable, you have not really changed the natural course of that patient's disease, as opposed to the patient who enters the study and has clear, documented progression, rapidly progressive disease over the course of a few weeks before entering the study. If we achieve stable disease in that patient, that means something entirely different.

So, I guess we have to look at stable disease and consider all of these different factors. One of the things that I think is important--particularly with Dr. Cheson who is the author of many of the response criteria that we have today--is that maybe we need to look at those

criteria again and more clearly and more amply define stable disease, taking into consideration all of these different factors.

Likewise, I think that it is important, as we write protocols for Phase 1 trials involving these biologic agents, that we again clearly define the significance of achieving stable disease, in what kinds of patients, and that that be communicated to the patient via the informed consent and also verbally as you discuss the study with the patient so that they, as clearly as possible, understand the consequences in terms of their continuing or not continuing treatment.

DR. MARTINO: Dr. Pazdur, did you want to make a comment?

DR. PAZDUR: Yes. One of the issues here that I think we really have to understand is that when we talk about response rate and stable disease, etc., those are criteria that were developed to describe a drug effect in a population of patients. What we are talking about here, as Dr. Grillo-Lopez referred to, is benefit to an

individual patient. That is a very complicated area because one could assume what was the growth pattern before the patient went on; did the patient have rapidly progressive disease; was the response a 10 percent response but you are really confident as an investigator about what that is.

So, you know, I think we really have to understand that we are not talking about response rates here. We are talking about a benefit that a physician must determine about an individual patient. Here, again, that brings us into a very complicated analysis because we are trying to put criteria on that and I don't know if that can be done even.

As I said before, all of these response criteria are dealing with not any relationship to clinical benefit, but to measurement of tumor so one could feel comfortable that they really had some tumor shrinkage. They have nothing to do with clinical benefit or somebody improving. So, we really need to focus on an individual patient. That is what is here; not a group of patients.

DR. MARTINO: Dr. Hussain?

DR. HUSSAIN: I had a question for Dr. Green again. You made reference in your presentation with regard to what you felt was optimal and then on a case-by-case extended evaluation may be necessary. Could you give me an example of what you feel is the justification to put the burden back on the sponsor for what drugs or what type of situations or what observations would warrant, in your opinion, that that sponsor go back and do more evaluations?

DR. M. GREEN: I will try to address that. Could I just make one comment about Dr. Cheson's comment and about the dose intensification issue because I think it is important? I agree, and I think my answer was in two parts. In some cases it may apply; in other cases it might not. Usually single dose pharmacokinetic studies are also conducted to address the dosimetry issues that are important, the biologically effective dose. The dose intensification is really toxicity. So, I think those are two separate issues.

But to your point and question, I think an example might be, and this may be very well observed within the context of some repeat-dose study of some arbitrary length, and let's pick four weeks for example, that these animals essentially are monitored very carefully from the first day of dosing through the duration and you see essentially evidence at week one versus week four differences.

Why might that be? Well, one example might be related to accumulation that occurs over that period of time because, as has been pointed out in many examples, these antibodies have long half-lives essentially so weekly dosing does build to large levels over a period of time and you may see, essentially, some evidence of progressive effects hitting the target versus off-target effects that are then manifested by some clinical symptomatology. I think if that kind of profile is manifest, then that is a signal that there are time-delayed, time-dependent effects that are going on and, therefore, if the clinical picture is one of worsening then, by all means, longer-term

studies are appropriate to support that.

A situation where it might not be, in my view, is if you have enough research discovery data at the molecular or receptor level that you are seeing stability of response, for example, from first course, second course, fourth course and you match that essentially with a safety profile in a pharmacologically responsive specie that shows it to be well tolerated and benign, I think in that particular kind of circumstance the concern might be a little bit different. In particular also, if it is within a biology that might be somewhat better understood and where there is some prior experience, there I think you could come to a different conclusion.

The other point which I feel compelled to make as a non-clinician is a statement about stable disease just from a purely scientific, common sense perspective. We are bringing so many tools to bear in the discovery arena right now, trying to identify responders, relevant biologies from animal systems to human systems, different patient

populations; we have tools that are at our disposal that allow us to essentially monitor at new levels effect doses. This gets to the point about biologically effective dose, minimally effective dose. I would think it is incumbent upon us to be incorporating some of those parameters into these early studies. Therefore, when we have a patient that has perhaps a given profile like what was described previously we also have information that this is a true biologic response to this agent that is now on board and how could we, in the absence or limiting side effects, deny treatment?

DR. MARTINO: Dr. Bates?

DR. BATES: I have a question following the remarks of Dr. Martin Green. You showed the data with your current database where you showed that 41 percent of the nonclinical tox. that comes to you in the first place is one to four weeks, which I gather is what is acceptable to you for going forward. But it wasn't clear to me for what fraction of studies you require the three-month period. Before they start or currently, what the

current practice is?

I guess another way to look at the question is how often you are missing toxicities that you then find in the clinic. Do you have any sense for that? In other words, how often are people actually doing the three-month studies currently and then, if you are now requiring them all of the time, at least in some point during the life of these studies how often are those identifying or failing to identify toxicities that emerge in the clinic?

DR. M. GREEN: The number that was cited is the observed duration of studies for four weeks being about 40-some percent were those that were submitted by the sponsor in support of their proposed clinical study. So, the relationship of that to clinical holds I don't know exactly, but if I were to hazard a guess I would suggest that almost none of those, if any of those, went on clinical hold for duration. Usually clinical holds for duration involve continuous dosing way beyond proposed clinical dosing by the sponsor, or

durations in excess of four months.

We basically use the guidance that was proposed in M3, with the proviso that if it is feasible to continue to dose nonclinically to support the proposed duration of the clinical study, we think that is a good standard. I think, as Dr. Pazdur indicated, there is a distinction to be made between the formal development plans versus those which are occurring in patients as they receive dosing. So, oftentimes our recommendations are based upon the formal proposal of the sponsor, but we also are concerned about those patients who receive continued dosing. But oftentimes the recommendations are based upon the proposed duration of the clinical study.

As I noted, we think that three-month studies nonclinically suffice to tell us everything we need to know all the way through Phase 3 and perhaps to approval, depending upon the particular toxicities that we observe clinically and the reliability of what the animal data tell us. So, we also try to make it a conscious decision as to

whether any more reliable data is likely to emerge from the nonclinical testing paradigm or whether we need to change that paradigm based upon clinical findings. So, if we are asked formally what we recommend, it is different than using the real-time experience to guide our recommendations. So, if we were to see emergence of clinical toxicities which formal toxicology studies cannot address, we would probably place greater reliance on specialized pharmacology studies to look at those particular types of toxicities. But in absence of that kind of knowledge we try to go by the general rule of duration for up to, as I mentioned, three months.

DR. BATES: So, the majority of studies eventually do have the three-month duration before you would go into chronic testing. So, that is the answer, that the majority do have it at the present time. But then how often is it your sense that people develop toxicities that are not picked up by the studies at all?

DR. M. GREEN: Well, I think that we need to think carefully about toxicities. Because we do

rely on relevant an animal model we often observe the types of toxicities which are clinically important, such as change in cell counts or other aspects. For some of the ones that, for example, we have learned are not predictable, such as cardiomyopathy for Herceptin, it wouldn't have made any difference how long we would have tested those and nonclinically we wouldn't have seen those. We, hopefully, become better at what we do and try to address those toxicity studies to answer the relevant questions, but we do place primary relevance on the standard toxicity study that is commonly performed.

DR. MARTINO: Dr. Pazdur, would you like to add something to that?

DR. PAZDUR: I just wanted John Leighton to comment on drugs. How often do we have three-month tox. studies before we allow sponsors to start their trials?

DR. LEIGHTON: Very rarely. Usually those are foreign sources, perhaps Japanese companies, but it is very rare that we have studies beyond 28

days to support an initial Phase 1 trial and end of Phase 2.

DR. MARTINO: I think that was the answer you were looking for.

DR. BATES: What I was driving at was what is your current practice. I thought I understood you to say that eventually during the Phase 1 development you are requiring or asking for the three-month tox. at some point in time of the development.

DR. LEIGHTON: Yes, at some point in development. This is addressed by the article that I alluded to in my presentation, by De George et al. It does not specify specifically when the long-term chronic studies are necessary in relation to clinical development.

DR. PAZDUR: Frequently they can be done after the Phase 1 studies are completed. Here again, I wanted to come back to your point, Silvana, about being adamant in a perfect world that everybody have three-month tox. studies done. That would be great. However, that would represent

a major change in drug development.

DR. MARTINO: Dr. Reaman?

DR. REAMAN: My question actually relates to that issue. Dr. Pazdur mentioned earlier that there really was no alternative with the abbreviated preclinical testing, but why wouldn't an alternative actually be a change in the standard requiring the three-month testing of all sponsors, not requiring it prior to the development or implementing of a Phase 1 study, but during the Phase 1 study so that if there is information that becomes available it could actually result in changing that study or future studies?

DR. PAZDUR: I think many people would look at this as very negative, trying to slow down drug development, and if we made the recommendation that we would not allow any studies to go forward, even to start without three-month data, we would have to have a significant amount of discussion.

DR. MARTINO: I think that is what he said though.

DR. REAMAN: No, I said to start with the

28-day toxicity data, but to continue the three-month testing in the event that new information may change in an ongoing trial.

DR. MARTINO: We would then almost request that it be ongoing simultaneous to the clinical Phase 1. Dr. Reaman, is that fair?

DR. REAMAN: Right.

DR. MARTINO: That, to me, makes the most sense but that is me. Dr. Fojo?

DR. FOJO: I just wanted to clarify one thing from Dr. Green because I think I have heard you say it twice. You seem to think that three months or 13 weeks is enough to predict any significant toxicity that is going to occur. Is that what I am hearing you say? And how does that contrast with the "rolling toxicology" study that was proposed by Dr. Pilaro where you end up going out to six months?

DR. M. GREEN: I think that our experience to date has demonstrated to us that a three-month toxicity study in general will be the point of diminishing return for the amount of information

that we observe nonclinically that is clinically relevant. In some rare instances we have recommended that sponsors go longer. So, they may conduct a six-month study or they may conduct and even longer-term study. That is their decision. As I mentioned, in some cases we encourage them to do so. But in terms of proceeding to a Phase 3 study, we believe that a three-month nonclinical toxicity study is adequate to stage that Phase 3 study.

DR. FOJO: So, in the end what we have been talking about is the patient who would start on a study, and that would be a one-month study based on one-month data, would have stable disease or PR or CR and then would continue beyond that without having three-month data available. Right?

DR. M. GREEN: But the rolling toxicity concept is that we would be getting information from the nonclinical study as that patient was continued to be dosed, such that the nonclinical study would proceed by 30 days in reporting to us information that we would think would be important

as to whether that patient should continue to be dosed or not.

DR. FOJO: Could I just ask Dr. James Green what he thinks of that concept?

DR. J. GREEN: Somehow that question was very predictable to me. I think on face value it has merit in the sense that it does get away from this conundrum about how long to treat. There are some practical issues which I think have to be dealt with. They are not insurmountable. One of the advantages I think is that once we are in the clinic most companies have obtained some way of maintaining clinical trials or using clinical grade material. That is not an insignificant issue. I think the panelists should keep that in mind because we would like to be testing the clinical material for all the reasons that I talked about--about some of the complexities--because sometimes the activities of a molecule can be affected by how you make it, and sometimes inadvertently when you go between the preclinical setting and the clinical setting there are changes.

So, that does increase our confidence in the value of these studies that we do.

One point I would make, however, to the proposal that is on the table is that, if I hear Dr. Green correctly, in some cases three-month studies may, in fact, be adequate to support registration. That would be, in fact, a benefit if that is the conclusion essentially of the survey because currently we do studies that are six months and sometimes 12 months. We do those for reasons which are outside the purview of this committee because many of these drugs are developed in other indications where the risk/benefit may be somewhat different, and there are international considerations with respect to European acceptance, Japanese acceptance et., And, for all the reasons that we stated regarding animal use and cost, we only want to do these studies once.

So, I think, yes is the answer to that question. Practically, it is easier said than done. Just the information flow--it is easy to say we want to be 30 days ahead of that patient but

with respect to the information we get, for example, if the histopathology information is of great importance that is what comes in late. So, we can certainly say that the noses are alive, there are no deaths, etc., and no major effects but until we look at that level we can see major changes going on that were manifested in earlier studies. So, I think that is a consideration but I think that may be a step forward.

DR. MARTINO: Thank you. At this point I think I would like to turn you all to the questions--okay, you get a chance.

DR. TAKIMOTO: Thank you. I wanted to ask Dr. Leighton a question about small molecules. I have worked with a number. There have been cases of Phase 1 studies with agents that have much longer half-lives when we actually test them in humans than we predicted in animals, sometimes as long as 10 or 15 days. So, that would put them in the same ballpark as a monoclonal antibody. If we knew that in advance before the Phase 1 started would you require three-month tox. there? Is the

major difference here a pharmacokinetic one?

Then, the other comment that I want to make is that, as Dr. Sausville pointed out, the number of patients that actually are on Phase 1 studies beyond three months or so is very small, and the number that may be on as long as six months with either response or stable disease is even smaller. One of the things that I have actually deplored is the fact that a number of Phase 1 studies are being done at multiple sites with three, five or six different centers. One of the issues in terms of keeping the patients on long term with stable disease and I think the risk/benefit ratio provided they are tolerating treatments well, does support that. So, there are going to be a few patients that are going to go beyond any type of toxicity data that you have. As long as you are watching these patients closely with experienced investigators and the safeguards that are built into Phase 1 studies, I think that is an acceptable risk/benefit ratio. But as an investigator, if I am putting one patient on every

three months and even a smaller percentage of these patients are going to be observed long term, it is going to be much harder for me to have a sense of this. The same is true for all the other investigators and it is really only the sponsor that is going to have a sense of what is going on with these longer-term patients because they are spread out at so many places.

DR. MARTINO: Thank you. At this point we will turn to the first question--

DR. TAKIMOTO: Excuse me, can we hear the answer?

DR. MARTINO: Oh, I am sorry.

DR. LEIGHTON: In terms of a drug that has a particularly long half-life, say 15 days, or for example a drug administered by depot formulation, what would be expected? Well, the first thing I would say is that these drugs aren't likely to be administered by continuous daily administration so some intermittent schedule of a few doses would be important and we would expect an evaluation of some toxicities. If the toxicities are observed within

a few doses, not of an unexpected duration, then that should be sufficient. But I think a pre-IND meeting in this particular case would be of particular help to make sure that the data that are submitted to support the IND are sufficient to support the intended clinical schedule.

Questions to the Committee and Committee Discussion

DR. MARTINO: Now I will turn to the questions. As often, they are redundant and long and wordy.

Number one, for most drug development programs, FDA recommends that the duration of nonclinical studies match the duration proposed for the clinic, an approach supported by the ICH M3 guidance document. However, an abbreviated duration of nonclinical testing is generally acceptable for small molecule drugs under development as anti-tumor therapies. An abbreviated dosing duration has also been proposed for selected biological products intended as anti-tumor treatments.

Please discuss scenarios where the

duration of nonclinical studies may be abbreviated relative to the clinical duration; should match the duration of the proposed clinical study. In your response, please address the anticipated nonclinical parameters, such as PK/PD, toxicity profiles, that should be considered in determining the minimum duration of toxicity testing. Who wants to begin? Dr. Cheson, I want to call on you, please.

DR. CHESON: Swell!

DR. MARTINO: My pleasure!

DR. CHESON: I am not sure I have adequate information actually to answer some of these questions. You know, we were shown a lot of summary statements without a lot of data and it would seem to me that it is a case-by-case thing dependent on the drug and that, in general, it would be nice to be able to abbreviate the preclinical testing so that we can get drugs to the clinic as quickly as possible. But I think it is a case-by-case. Some, based on their toxicity profile and pharmacokinetics, are going to require

longer duration of preclinical study than others.

So, I don't think you can make a generalization. I think it will depend on all these things listed below, the PK/PD and toxicity profile. I think those are absolutely critical, and we talked about the optimal biological dose which I think may help us expedite the entrance of some of these drugs into the clinic, but I think it is really case-dependent, drug-dependent, and it is going to vary based on the PK/PD and toxicity as to whether it can be shortened or whether that is not safe.

DR. MARTINO: Who wants to speak to this? Dr. Kodish?

DR. KODISH: I guess I would draw the distinction between--you know, this question is about the initiation of a trial versus the other questions we have been talking about which are the continuation of the trial, and I think there is ample reason to try to think of those differently and think about our commitment to subjects once they enter a trial as being ethically different

from the determination that we are going to open a study.

DR. MARTINO: Doctor?

DR. SAUSVILLE: Yes, I would take the position that if the relevant species has been studied at the anticipated concentration, a value based on scientific information, that the exposure of patients should in some way mirror the requirement for initiation of the study. So, in that regard, I would feel a relatively abbreviated exposure would be suitable in the two- to four-week range. I think that beyond that, the question really should not focus on animal testing but should be guided by clinical experience.

DR. MARTINO: Dr. Perry?

DR. PERRY: I would like to amend what my senior colleague, Dr. Cheson, said, on a case-by-case to study the drug but also the disease. In the diseases Bruce sees stable disease may not be significant at all and you may have an option. In the patients I see, if you are treating someone with stage 4 non-small lung cancer, third

line, they have no other options. So, I think we need to look at the disease; we need to look at the drug; and we need to look at the line of therapy we are talking about.

Since we are talking mostly about Phase 1 studies here, it seems to me that there are generally not going to be too many other options. There may be another Phase 1 study, but I think that I agree with the comments on the right that they ought to be as short and as consistent with getting the drug out and looked at in human studies. And, I am glad somebody already made the analogy about Herceptin. This is a very significant potential clinical toxicity, unnoted in animal studies and only picked up when we had long-term human studies, and basically best picked up in the adjuvant breast cancer setting for patients who didn't have lots of previous treatment and had a long enough prognosis that this becomes a real issue.

DR. MARTINO: Dr. Fojo?

DR. FOJO: Bruce, I wasn't sure, were you

saying that even for, say, a six-month study three-month data would not be adequate in your opinion?

DR. CHESON: No, I think three-month data is probably adequate for most things. You know, if you try to equate the life span of one of these little critters, three months in them is 40 years in us.

DR. FOJO: And, Ed, were you suggesting that two to four weeks was enough and that that can be guided by the clinical data?

DR. SAUSVILLE: Yes, that is exactly what I was suggesting.

DR. MARTINO: Dr. Takimoto, did I see your hand up?

DR. TAKIMOTO: No, but I certainly agree with Dr. Sausville's comment about what is satisfactory for initiating a clinical trial.

DR. BATES: But, Ed, are you saying then to abandon practice of requiring three-month testing in order to do continuous dosing? Is that your proposal?

DR. SAUSVILLE: My understanding was that the longer period of testing was for continuation for the infrequent patients who have achieved benefit, and then for the inception of later phase studies. Again, I think that those are separate questions. If the commitment from a sponsor has been made to do a full-phase development, then I think on a case-by-case basis the desirability of filling in with longer-term data may or may not be desirable depending on the nature of the substance. But to narrowly focus the question before us for treatment of patients on the Phase 1 and for initiation of Phase 2, I think that relatively abbreviated testing is reasonable.

DR. MARTINO: Dr. Harrington?

DR. HARRINGTON: I guess I am not really sure how to separate this question from the requirements that the agency would have for sponsors about beginning these studies in settings where you might expect a small proportion of patients might go on longer than the specified dosing. I mean, the question, as phrased, sort of

pushes the decision down into the clinic once someone has been responding and ignores the fact that there might have been negotiations at the start of the study that said, you know, this is one where, in this disease, we might expect some percentage of at least stable and objective responders so this is one where you should start your extended toxicity testing even though the majority of patients may not need it.

So, I don't know if the chair or the FDA is willing to entertain a suggestion that we should couple this to a clearer statement to the way in which these trials get started and the implicit contract between the Food and Drug Administration and the sponsors on how to approach this. There was a suggestion earlier, for instance, that there will always be the requirement that longer-term toxicities be started at the time the patient is initiated. That, to me, is as important for this committee as deciding what happens in the context of a particularly difficult clinical decision.

DR. MARTINO: Well, the chair completely

agrees with you. I really don't see these questions as being very distinct questions. They really are related to each other because it still strikes me that, yes, inherent in starting a Phase 1/Phase 2 there are things you want before you put the first patient on. I don't have the impression that what is being done to this point really is something that the FDA wants to alter. The only real question that I am getting out of all of this is this issue of do we want that three-month longer-term toxicity trial in every one, and when do we want it. Does it have to be there before we put the very first patient on? I think that is the question you are asking us. We can dance around other issues, but guide me if that isn't what your point is here, people. Yes, doctor?

DR. SAUSVILLE: I think that is a very succinct phrasing of the question. Again, my interpretation of the data presented to us is that it is hard to show with the data that we have in hand that at a high frequency there are things that are going to be discovered on the three-month level

that are going to have a serious impact on making the decision to either dose more patients, in the unlikely case that they are responding in Phase 1, or start the Phase 2. That is with all other clinical factors being equal.

So, I think to have the requirement for the three-month could potentially, for the reasons that were alluded to, ultimately be a barrier to getting a broader number of products out into clinical testing and I think this would be a bad thing.

DR. MARTINO: Can I just hear a few more thoughts on that very, very point, whether in fact we should require the three-month evaluation as a standard prior to starting anything? Are there additional comments on that? Because, yes, I do see that that would then become a standard which has certain complications inherent in it. Dr. Harrington, did you have a question?

DR. HARRINGTON: No, but I would certainly agree with Dr. Fojo that there is no intent to delay new agents from being out in testing. So,

the suggestion about requiring the three-month testing wasn't to have those data prior to opening a Phase 1 study but to implement the Phase 1 studies and continue the testing throughout if there was, in fact, going to be a complete development plan for a drug. DR. MARTINO: Would it serve the FDA if we actually took a vote to that very specific question? Would that be of use to you? Okay.

The question I believe is should we require three-month toxicology data to be available before a patient is placed on a Phase 1 or Phase 1/2 trial? Should that be a requirement in all situations? That is the question on which I would like a vote. Before it starts, before the very first patient is placed on the trial. We will start on my left, Dr. Cheson?

DR. CHESON: No.

DR. REAMAN: No.

MS. HAYLOCK: No.

DR. HUSSAIN: No.

MS. SOLANCHE: No.

DR. MARTINO: No.

DR. RODRIGUEZ: No.

DR. PERRY: Perry, no.

DR. HARRINGTON: No.

DR. D'AGOSTINO: No.

DR. FOJO: No.

DR. BATES: No.

DR. TAKIMOTO: No.

DR. KODISH: No.

DR. MARTINO: It was not a vote required by the FDA but we hope that it has been of use to you, therefore, names, as you realize were not taken. It is for your information primarily.

With that, shall we then move on to perhaps this issue of do we need this information as routine after a study has begun, realizing that there are likely to be patients who will derive clinical benefit, however you define that, which then will mean that they will be treated beyond the original time frame for which we do have data? Yes, doctor?

DR. SAUSVILLE: So, here again I make the

distinction between the decision to go to a full Phase 3 development, in which case certain aspects of end product may call for extended evaluation. I do think that is important when it comes to the point. This question of the three months is now being focused on the admittedly infrequent, but clinically very useful to the patient and hopeful to the investigator, or vice versa, situation where a patient is deriving clinical benefit on a Phase 1, or where there is the potential for rapidly transitioning, whether in the same trial or into a subsequently defined Phase 2 trial.

So, the reason for dancing around that state of affairs is that I actually think that to require the three months as somehow being acquired while the initial Phase 1 is going would functionally still be perceived as a barrier to getting things out, because when you got into the Phase 1 you would have to be doing the three-month anyway and, there the decision to go forward into initial clinical testing would reflect some calculus as to whether or not there was going to be

likely value of the agent based on the need to conduct the three-month studies.

So, my own view is that if we take the position that we already did, again in the spirit of getting as many new things out, it would not be a good thing to require the rolling acquisition of three-month data because the clinical scenarios that you are going to impact are going to be ultimately quite limited, and those are going be very small numbers of patients who are going to have some perception of benefit.

DR. MARTINO: Yes?

DR. FOJO: Just so that I am clear about what you are saying, because I think there would be a concern that if you don't require it for starting, as we have already sort of voted on, and then a study started you could foresee a situation where there would be multiple studies, something that was tried in several centers, and that you could accumulate enough data in people with stable disease that then you would say, well, in fact in stable disease I have been able to treat actual

patients for three, four, five, six months or longer. So, you are not alluding to that becoming a possibility for any study that would be longer would require animal data.

DR. SAUSVILLE: But that is exactly the point. If I have patients that have bee exposed to several months of the drug, what am I going to see in animals treated for three months that is going to influence me as to the value of that phenomenon?

DR. MARTINO: Yes, Dr. Bates?

DR. BATES: To follow-up on that, as I understand it, that would be a complete departure from the current practice in the monoclonal antibody development, and that is what you are proposing though, a complete departure from that practice.

DR. SAUSVILLE: I don't know. I heard that three months is usually the norm but I didn't get the impression that that wasn't necessary.

DR. KEEGAN: It is not a complete departure. It would be that for patients who were perceived to be deriving clinical benefit, which we

have defined as tumor shrinkage, continued exposure beyond the knowledge of the risks might be justified. The departure is that for patients who are not apparently deriving drug benefit because their disease is not changing, is that also a justifiable risk that they should take--and it may all hang around how you define clinical benefit? But we have asked that we have more knowledge about the risk such patients are accepting if it is not clear that they are deriving a benefit. So, the distinction has been primarily around patients with stable disease, how much risk they should assume when they are moving into an unknown; when they are moving into renal toxicity which may or may not be reversible, nor diagnosable prior to substantial damage, is that an acceptable risk?

DR. SAUSVILLE: Thank you for that clarification, but then we already alluded to the distinction between the diseases that we see. I mean, three months for one of Dr. Cheson's indolent lymphoma patients is a very different matter from three months for Dr. Perry's lung cancer patients.

DR. KEEGAN: And we have those studies. I mean, there are examples of studies in follicular lymphoma patients as the first study.

DR. MARTINO: But I would argue that even a patient who is having a radiological response, and in all fairness when you get to a point where they are going into Phase 1 trials, most of the time what you see is a radiological response, and with that means anything is a question that I am not sure that even in that setting I am comfortable allowing them to bear the unknownness of serious toxicity without some data to give me a sense of what might come down the road. I mean, I see the potential to actually harm such a person even when the x-ray looks better.

So, I appreciate this distinction between "the responding" patient versus "a stable" patient but, to me, they are only slight degrees of each other. I am not sure that my mind separates them as clearly as some of the rest of you seem to separate them. Yes?

DR. KODISH: Well, I think that is an

important point. The ethical balance changes when you are in that area of unknown and that, to me, lends justification to the idea of continuing on with the three-month study--at least the contemporaneous effort to learn something that may not be the best, but I think in the area of uncertainty, which is where we live here, the best we can do maybe is an ongoing effort to get data.

DR. MARTINO: Dr. Harrington?

DR. HARRINGTON: I think from what we hard earlier that, practically speaking, if we don't require the extended toxicology testing before the trial starts there will almost certainly be patients on Phase 1 trials who will get out beyond the available tox. data. So, for me as a non-clinician, that sounds to be primarily a clinical decision unless these early phase testing protocols specify that in the absence of animal toxicology data a patient should be taken off drug, either regardless of response or according to certain responses, and that seems to wander into an area that is extraordinarily difficult to specify

given the nature of these patients and how they might respond.

So, I guess I would certainly be willing to live with the requirement that toxicology testing begin when the Phase 1 trial begins; that it is, hopefully, available for patients who are among the first enrolled but unlikely, and that those decisions have to be made between the clinician and the patient consistent with what is known in the clinical picture of the way the patient has responded to the drug and the side effects, but that it may well be that future patients on that trial, if the extended testing gets done rapidly enough, may have the benefit of that side effect. So, it may mean that patients are handled somewhat differently at the same dose level depending upon the information available.

DR. MARTINO: Dr. Hussain?

DR. HUSSAIN: Just a comment, and that has to do with the distinction on response issue. I think that every day we counsel patients on risks and benefits, and there are times when we stop

chemotherapy, for example, because the side effects of the treatment outweigh the fact that the measurable disease has shrunken a bit, and patients do make that decision.

What I have not heard yet is that three-month testing is worthless. Has anybody suggested that this slightly extended period testing is worthless? Because if it is worthless then we shouldn't be doing it but, in fact, if we gain information that is helpful to our patients, and I think that is important to be done. I voted no on reading it beforehand because I think it is important to get this to patients, but unless someone thinks it is worthless I think if you have stable disease or a partial response, and in some of these solid tumors a partial response is really a minimal change in tumor size, it is important to be done. But if you think it is worthless, if the FDA thinks it is worthless because there are no examples whatsoever that that extended testing has resulted in identification of issues that are relevant in humans, then it seems to me it ought to

be done but I would like to hear about that. Is it worthless or is it not?

DR. MARTINO: Yes?

DR. M. GREEN: We believe that those findings are worthwhile and we believe that it is because we choose a relevant animal model and we are guided by the clinical experience relative to the nonclinical findings, and we are very comfortable with not requiring initial animal testing should those nonclinical studies be uninformative of future clinical events. And, we have made those decisions in the past so we believe that when we request those studies or recommend those studies that they will be informative to a reasonable degree.

DR. MARTINO: Dr. Fojo?

DR. FOJO: I am sorry, but when I voted not, as we all did, inherent in that was the understanding that some of these patients that were going to go on the study would face this decision, or the clinician would. So, I think that we were thinking, yes, one month is enough and we are

willing and prepared to know that that will be a risk that will be taken by the clinician and the patient.

I do think that now what is being brought up comes to what Ed was saying that you are, in effect, tying the two together and then it is sort of window dressing because what you are really saying is one month is enough but we really want you to go and get the three-month anyway, and there is no point then in setting up the division between one and three months in that situation.

I would also say that I am not quite sure why we need to discriminate partial and complete from stable disease. The FDA currently doesn't do that in Phase 3 studies. Stable disease is being lumped in with partial and complete responses but if you look at time to progression in the cerafinib study, then stable disease did count.

DR. PAZDUR: Yes, definitely. That is a time to event analysis that has to be demonstrated in a randomized trial.

DR. FOJO: Right, I understand. But it is

from all of these patients with stable disease, adding to that, of course, that applies to the population, not to a single person.

DR. PAZDUR: The problem you get into, as Pat alluded to, with stable disease in an individual patient is, is that the drug effect or is that the natural history of the disease?

DR. FOJO: Correct. So, then we are saying in a Phase 1 study it is a different definition, if you will, in some ways, stable disease is. But I think where it is heading now and what you were just mentioning, Dr. Hussain, impacts somewhat on what Ed was saying which is that we are, in effect, just tying them both together. So, in some ways, that original vote was not all that meaningful.

DR. MARTINO: Dr. Sausville?

DR. SAUSVILLE: Thank you. I actually agree from a scientific standpoint that three-month studies would have information, to Dr. Hussain's point. Well conducted three-month studies would be valuable and certainly, as you have stated, if they

were negative in the sense of removing any concerns, I guess they can be valuable in that regard.

Again, I am more concerned in this scenario where a patient group is already started. You have people who are at that four-, five-, six-month window. I really want to avoid the situation where a low grade--hence my question to Dr. Pilaro earlier--finding in an animal would prevent a patient from getting a drug that is benefiting them in that particular case. That is where I see a problem in mandating that the three-month thing be going when you start a Phase 1 trial.

DR. MARTINO: Does the FDA want to comment?

DR. M. GREEN: Yes. I don't think the discussion should be concerned with low grade findings. These are not the findings that we would consider important to making decisions about continued dosing. What we are talking about are very significant findings that either cannot be

managed clinically, are irreversible or present significant danger to the patient such as gout. Those are the toxicities we are talking about, not low grade findings.

DR. SAUSVILLE: Oh, I agree with that philosophically. As Dr. Pilaro stated, there is no grading system for what you see in the animals so it is more or less an impression and I think care would need to be evolved in applying those.

DR. MARTINO: Dr. Cheson?

DR. CHESON: And that is why we have informed consent and a comment in all informed consent documents that says as new information is obtained it will be presented to you, and it becomes a decision between the patient and the physician as to whether the risk/benefit is in favor of continuing or not based on a rat having some unspecified toxicity, and if the two feel that they should continue on study, then that would be just fine.

DR. SAUSVILLE: So, to pursue that issue, and I think you are right, ultimately the informed

consent governs a lot of what goes on in discussion between doctor and patient. If we have agent X that causes dire toxicity in an animal that you would have justification for a concern about, yet, the clinical experience at the point when that becomes available is at stark variance with that, I think there needs to be leeway in interpreting the clinical experience heretofore. If such a decision to do testing of that nature is undertaken, there should be a true flexibility in the application of those results based on the clinical experience. That is what I was trying to say.

DR. MARTINO: To the FDA, I will give this group five more minutes. Is there a burning question of a specific nature that you want an answer to or a vote to?

DR. PAZDUR: [Not at microphone; inaudible]

DR. MARTINO: We are sort of into question number two which deals with this issue.

DR. PAZDUR: The area I think of 2(b) is something that we wanted to concentrate on.

DR. MARTINO: Then I will read that question and we will spend the remaining time on that. Where extended nonclinical safety data are unavailable for long-acting biological therapeutics, for example, monoclonal antibodies, the FDA believes that continued dosing in the Phase 1 study is appropriate only in patients who have demonstrated an acceptable benefit, for example, objective tumor response or symptomatic improvement. Should extended nonclinical testing be available prior to allowing continued dosing in patients who have not had clear evidence of benefit? Please discuss this following scenario: the patient with stable disease; the patient with progressive disease. How do you want to handle this?

DR. PAZDUR: We would like to go around the table and have a discussion from each individual and a vote. This is a real-life situation that we face. Okay? Irrespective of whether we have the three-month data ongoing, as was stated, we will have people that will face this

situation. They will have stable disease, for example, and we will have to make a determination whether these people go on. We have generally decided that if people have symptomatic improvement or experience some anti-tumor response that this was fine, that we would allow them to proceed. Okay? But this is a real-life situation that we have to face and there has been some discrepancy about how different divisions and different reviewers have handled this. We realize that there are different situations here and people can discuss this as they go around the room.

DR. MARTINO: So, then the question is continuing therapy prior to having data, prior to having data in a patient with stable disease?

DR. PAZDUR: Correct.

DR. MARTINO: Versus a patient with progressive disease?

DR. PAZDUR: Correct.

DR. MARTINO: Do you actually want that second one in there?

DR. PAZDUR: Well, we really are trying to

concentrate on the stable disease situation, not versus anything. I think most people would consider that if they are having progressive disease they would take that patient off study.

DR. MARTINO: That is why I am asking the question. Yes, Dr. Perry?

DR. PERRY: I would suggest that patients be allowed to continue on treatment until they had evidence of progressive disease or unacceptable toxicity.

DR. PAZDUR: Let's go around the room.

DR. PERRY: That seems to me to cover both possibilities. I see no rationale for continuing somebody who has progressive disease.

DR. PAZDUR: Why don't we go around the room?

DR. MARTINO: So, then the question is limited to continuing administration of drug in the absence of animal long-term toxicity in a patient with stable disease, however your gut defines that. Okay, that is the question. We will start on my left. Dr. Cheson?

DR. CHESON: Yes, getting back to that stable disease, I think if you call it stable disease with clinical benefit versus stable disease without clinical benefit, then a patient who is having stable disease with clinical benefit should be allowed to continue the drug, whatever the status of the preclinical data. If it is the patient I presented before who is on morphine, has a big mass and unstable disease, then that is not clinical benefit and that patient shouldn't continue on that but should move on to something else.

DR. PAZDUR: But what we are usually talking about--we would all agree with that if somebody is having some clinical symptom improvement. Usually what we are faced with is a situation where somebody has stable disease and on x-ray has no evidence of improvement or symptoms, etc., or is asymptomatic even.

DR. MARTINO: But now we are having to break this down into definitions that clinicians may not agree with, Rick. So, if you want our

opinion, I think it has to be somewhat general in the sense of whatever any one of us defines as clinical benefit because ultimately it is going to be the patient and their individual doctor in Podunk who will label that patient as stable or otherwise.

DR. PAZDUR: If that is one of the recommendations, that is fine because, as I alluded to, you know, it is very difficult to ascertain what is clinical benefit in an individual patient. The scenario that we are faced with that brought this forward--

DR. MARTINO: Yes?

DR. PAZDUR: --is a situation where an individual going on the study is asked to continue on the study without adequate preclinical data, nonclinical data, to support that continuation. The patient has stable disease. They are not having any symptom improvement. It is a radiographic stable disease.

DR. MARTINO: So, it is a radiographic parameter only?

DR. PAZDUR: Usually, yes. Here, again, if people had clinical benefit, if they had, as Bruce was saying a large mass with shortness of breath, obviously, we would let them continue with the therapy.

DR. MARTINO: So, stable disease without clinically apparent improvement? Without clinically apparent improvement, that is the patient you want us to vote on?

DR. PAZDUR: Correct.

DR. MARTINO: Without clinical apparent improvement, simply an x-ray getting better?

DR. PAZDUR: Correct.

DR. MARTINO: Okay, ladies and gentlemen--

DR. SAUSVILLE: What is the basal state?

DR. MARTINO: Staying the same or slightly bigger, again, whatever you think stable is but no clinical improvement. That is the point I want to make here. Dr. Cheson, you may vote. State your names, please.

DR. CHESON: Cheson, I think if there is no evidence of clinical benefit then it would be

sort of irrelevant with the preclinical data where I would not be in favor of continuing. But, again, it is a decision between the physician and the patient.

DR. MARTINO: Is that a yes or a no?

DR. SAUSVILLE: Madam chairman--but, Dr. Pazdur, what is the basal state? Where are you starting from? If you are starting from what I would say is grade 2 shortness of breath that Dr. Cheson--but if it is an asymptomatic situation where a patient has stable mass, I have a different feeling about it.

DR. PAZDUR: Well, I mean you can dissect this as much as you want here, but the clinical situation or the situation that we face is the following: We don't have the preclinical data to support the dosing. The patient is on study. There is no change in any symptoms or the patient is asymptomatic. There is no evidence that we have that can say that there is symptomatic improvement of the patient. We just don't have that information if the patient does not experience any

symptom improvement. However, we are asked that that patient should continue.

DR. SAUSVILLE: Well, you can't improve on being asymptomatic. So, if that is the basal state then this is a different scenario. If they are asymptomatic, that would be fine for me. But if they have a grade 2 dyspnea, then no.

DR. CHESON: If I might clarify my position, I don't think that the patient with stable disease who is characterized by a huge mass and is on morphine should continue on the drug. They should move on to either hospice or some other form of therapy. I agree with Dr. Sausville, if a patient and physician feel that it is in the patient's best interest to stay on the study drug, then that--

DR. PAZDUR: So, it should be an individual patient and physician decision?

DR. CHESON: Yes.

DR. PAZDUR: Which is fine. We would like to hear that also.

DR. MARTINO: Then that is a different

question. Is that the question you want an answer to? I mean, we can discuss this in the next minute and a half, but if you want a vote, then you cannot change the question.

DR. PAZDUR: Go ahead, Pat.

DR. KEEGAN: I just want to clarify that the milieu and the concern is that, unlike the typical cytotoxic therapy toxicities which are nausea, vomiting and hair loss that we see quickly, what we are worried about is against a background of slowly accumulating toxicities that are silent--myocardial, renal, the impairment of wound healing, discus perforation, things like that. Against that milieu, is there a way to weigh this or not? If you are saying that it is an individual patient judgment and physician judgment, that is helpful but we wanted to clarify why we consider this--

DR. CHESON: These are Phase 1 studies where patient median survival is probably in the range of two months--okay, two and a half months, fine. Things won't have a chance to develop

because the patients aren't going to live that long.

DR. KEEGAN: I think if that was the case we wouldn't be pushed by people to treat these patients. I think, in fact, that may not be the case.

DR. SAUSVILLE: Dr. Keegan, these adverse events are in the informed consent, I take it?

DR. KEEGAN: Not all of them because some of them we are not sure about yet.

DR. SAUSVILLE: Well--

DR. MARTINO: I am taking the floor back. Thank you, ladies and gentlemen. Dr. Kodish, you may speak.

DR. KODISH: I will briefly. Respect for persons is a real important part of the Belmont report and it seems to me that the FDA should not prohibit patients who have already become subjects and, in some sense they have served a humanitarian need to learn something. The FDA should not be overly paternalistic in prohibiting them for continued access to the medication.

DR. MARTINO: Your feeling then is that patient and physician for that individual make decisions. That is what I am hearing from you. Okay.

DR. PAZDUR: This is what we are after, the issue here is should we say that the patient must have a response to continue, or would stable disease or a benefit that the patient and the physician determine really override that?

DR. MARTINO: I am going to take a vote to the following question, that the patient and their respective physician make the judgment of what constitutes clinical benefit, which is really what the issue is here. That is the question, that we leave that autonomy to patient and doctor. Dr. Cheson, I will start with you.

DR. CHESON: I already said that that is what I would do.

DR. MARTINO: Okay. Proceed, please, Dr. Reaman.

DR. REAMAN: If there is a clinical benefit, then yes.

DR. MARTINO: Remember, as judged by patient and physician, whatever they think it is.

MS. HAYLOCK: Haylock, yes.

DR. HUSSAIN: No one will answer no to that question so it is a silly question really. I don't mean it in a bad way, but I think the FDA is being a bit schizophrenic about it in that you are concerned but you are really not concerned enough to be standing up to say I want the three-month data. So, you are trying to dump it on ODAC to say, well, but if there are any clinical benefits as judged by you, Dr. Hussain, then I am going to let you do it and then the burden is on you, and I think that is unfair. I think if you think a drug has the possibility of toxicities, it seems to me it is your job to require that the safety be provided. And, I think to go back and say with stable disease, I would argue that the patient who is responding may be the person who is living the longest and may be the subject of a horrible side effect. So, I think that this is an impossible question and it is impossible to answer, and you

might want to think about what you really are asking us to do. The answer is yes.

DR. MARTINO: Continue.

MS. SOLANCHE: Martha Solanche, patient rep. I don't think there is an answer to this question.

DR. MARTINO: Silvana Martino, to the question as stated my answer is yes, I do think patients and doctors make the final decision even a Phase 1 trial.

DR. RODRIGUEZ: Maria Rodriguez, yes.

DR. PERRY: Perry, yes.

DR. HARRINGTON: Harrington, yes because I believe that once a patient has started on a trial it is difficult for the government to impose, but I think it should be yes consistent with the protocol having a pretty clear specification of what clinical benefit means in a given situation along with stable disease.

DR. D'AGOSTINO: D'Agostino, yes, but clinical benefit in or stable.

DR. FOJO: Fojo, yes, tied in to the

previous though because I think they both go together. I was voting no before knowing that I would vote yes to a question such as this.

DR. BATES: I would vote yes, provided that we, at some point in the guidance, state that clinical benefit, when we talk about stable disease, should indicate a difference in the biology of the disease compared to what the patient experienced before. So, if you had a patient who had disease progression over the space of two months before and now they have two months or four months of stable disease, that could be construed by the patient, and I think reasonably so, that that is clinical benefit. But I think if someone has stable disease for a year before going on study and now has stable disease for two months, that is not clinical benefit. So, I just believe that the guidance should be a little bit clear about what you think clinical benefit is.

DR. TAKIMOTO: Takimoto, yes, provided that the patient and the physician decision that there is a benefit doesn't violate any preexisting

rules in the protocol, so the patient is progressing but if they have some symptomatic or psychological benefit they can continue.

DR. KODISH: Kodish, yes.

DR. MARTINO: That is 13 yes apparently here. Now, do you have any other burning needs?

DR. PAZDUR: None that I have.

DR. MARTINO: FDA, I hope you got some of what you needed out of this.

DR. PAZDUR: Yes, we have, believe it or not.

DR. MARTINO: Thank you, ladies and gentlemen. You are dismissed, and the afternoon session will begin promptly at 1:00 for the committee.

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

Call to Order and Introduction of Committee

DR. MARTINO: I would like to call the meeting to order. The topic for this afternoon discussion us Gemzar for injection, proposed indication for use in combination with carboplatin for the treatment of patients with advanced ovarian cancer that has relapsed at least six months after completion of a platinum-based therapy.

The first portion of our meeting, as usual, will be that the pharmaceutical company will have the opportunity to present the data from their studies, and Dr. Richard Gaynor will introduce himself as well as the members of his panel, please.

I am sorry, I have been reminded--I didn't have coffee and therefore I am confused--that is the topic and that is the person who will do the introductions of the pharmaceutical representatives, however, you need to know who we are before that. So, with that, we will start on my left and I would like the members of the

committee and the FDA to introduce themselves, please.

DR. WEISS: I am Karen Weiss. I am the Deputy Director of the Office of Oncology Drug Products. Dr. Pazdur had an appointment and isn't going to be here for this afternoon.

DR. JUSTICE: Robert Justice, Acting Director, Division of Drug Oncology Products.

DR. JOHNSON: John Johnson, Clinical Team Leader, FDA.

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

DR. CHESON: Bruce Cheson, hematologist/ oncologist, Georgetown University Hospital.

DR. REAMAN: Gregory Reaman, pediatric oncologist, George Washington University.

MS. HAYLOCK: Pamela Haylock, oncology nurse and consumer representative.

DR. HUSSAIN: Maha Hussain, University of Michigan.

MS. SOLANCHE: Martha Solanche, patient representative, 11-year survivor of stage 3-C

ovarian cancer.

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

DR. MARTINO: Silvana Martino, medical oncology from the Angeles Clinic.

DR. RODRIGUEZ: Maria Rodriguez, medical oncologist from M.D. Anderson Cancer Center in Houston, Texas.

DR. PERRY: Michael Perry, hematology and oncology, University of Missouri, Ellis Fischel Cancer Center, Columbia, Missouri.

DR. HARRINGTON: Dave Harrington, statistician, Dana-Farber Cancer Institute.

DR. D'AGOSTINO: Ralph D'Agostino, statistician from Boston University.

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

DR. LONG: Harry Long, medical oncologist, Mayo Clinic, Rochester, Minnesota.

DR. GRILLO-LOPEZ: Antonio Grillo-Lopez, hematologist/oncologist, and the industry representative on ODAC. However, I do not receive

any compensation from industry for my participation in these meetings.

DR. MARTINO: Thank you. Next Ms. Clifford will read the conflict of interest statements for the group.

Conflict of Interest Statement

MS. CLIFFORD: The following announcement addresses the issue of conflict of interest and is made part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting with the following exceptions.

In accordance with 18 USC, Section 208,(b)(3), full waivers have been granted to the following participants: Ralph D'Agostino for being a member of a competitor's advisory board on unrelated matters, for which he receives less than

$10,001 per year; Maha Hussain for ownership in stock in two competitors, valued from $25,001 to $50,000; Silvana Martino for consulting for a competitor on unrelated matters, for which her employer receives less than $10,001 per year.

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

Dr. Harry Long is permitted to participate in the committee's discussion on Gemzar. He is, however, excluded from voting.

We would also like to note that Dr. Antonio Grillo-Lopez is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Grillo-Lopez is employed by Neoplastic and Autoimmune Diseases research.

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

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

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

DR. MARTINO: I need to correct something. My conflict of interest is specifically with this company, not with its competitors. I have served as a PI for one of their hormonal agents in a breast cancer prevention trial, for which my employer received less than $10,000 per year. But it is specifically for Eli Lilly.

Does the FDA have any introductory comments they wish to make at this time?

DR. WEISS: No.

DR. MARTINO: Dr. Hussain?

DR. HUSSAIN: I had declared a conflict of interest potentially consulting with the company last year for an unrelated matter.

DR. MARTINO: Any other members of the

committee have anything they need to add to the conflict of interest statement at this point?

[No response]

Thank you. We will proceed then with Dr. Richard Gaynor, who will introduce himself as well as the members of his panel, please.

Eli Lilly Presentation

Introduction

DR. GAYNOR: Thank you.

[Slide]

First I would like to thank the members of the Oncologic Drugs Advisory Committee and the members of the FDA for allowing Eli Lilly today to present this sNDA application for Gemzar in combination with carboplatin as treatment for women with recurrent ovarian cancer.

[Slide]

The agenda is shown here. It differs somewhat from the printed agenda and we will just go through the order of these presentations, and the speakers are listed on the right side, here.

[Slide]

The participants today are listed on this slide. They consist of participants from Eli Lilly, shown here, and our external consultants who will be involved in the presentation and be available to answer questions.

[Slide]

Today we are here to discuss a supplemental NDA, and this involved the indication of submissions based on a 356-patient randomized Phase 3 study, conducted by a well-known cooperative group, the AGO-OVAR, that met a primary endpoint of statistically significant improvement in progression-free survival. This is in women with recurrent ovarian cancer that have relapsed at least 6 months following platinum-based therapy.

[Slide]

Established chemotherapeutic agents are frequently used off-label. Gemzar is used in the treatment of recurrent ovarian cancer and is listed in the NCCN guidelines for 2006 as potential treatment for women with recurrent ovarian cancer.

The FDA guidance on new treatment

indications encourages the submission of data for supplemental indications to label all indications where there is established safety and efficacy, and recognizes alternative data from high quality cancer cooperative groups to meet some of these requirements.

The current study was performed by a well-known EU cooperative group. It is consistent with the FDA guidance and demonstrates the efficacy of Gemzar with carboplatin in recurrent ovarian cancer.

[Slide]

Historically, overall response has been primarily used for the approval of drugs in recurrent ovarian cancer. Lilly requested a meeting with the FDA to discuss the trial we are going to discuss today for potential submission. The FDA agreed that the package met criteria for submission and that the PFS, which was the primary endpoint, is acknowledged as a measure of clinical benefit in lung and colorectal cancers. Lilly will discuss today the totality of the data including

effects on progression-free survival, overall response rate, trends in patient-reported outcomes, and the time of subsequent chemotherapy supports full approval for the Gemzar/carboplatin regimen for the treatment of women with recurrent ovarian cancer.

[Slide]

As most of you are aware, Gemzar is a widely used chemotherapeutic agent. It is an anti-metabolite with broad activity across numerous tumors. Over 1.3 million patients have been treated globally with this agent and it has had FDA regular approvals for pancreatic, non-small cell lung and metastatic breast cancer indications. The Gemzar/ carboplatin combination is widely used in a variety of tumors and Gemzar, both as a single agent and in combination with carboplatin, has been extensively studied in ovarian cancer. The safety profile is well-characterized and it has relatively low, manageable toxicities.

[Slide]

The objectives of the presentation today

are to discuss the activity of Gemzar in ovarian cancer; to also discuss the results of our trial of Gemzar plus carboplatin and to demonstrate that it provides a clinical benefit for women with recurrent ovarian cancer based on superior PFS, overall and complete response rates, improved patient-reported outcomes and time off chemotherapy; with no new safety issues and a lot incidence of neurotoxicity. In summary, we will present data that Gemzar plus carboplatin is an effective, less neurotoxic treatment option for women with recurrent ovarian cancer.

At this time, let me introduce Dr. Robert Ozols, of Fox Chase, to discuss the management of ovarian cancer.

Management of Ovarian Cancer

DR. OZOLS: Thank you.

[Slide]

It is a pleasure to be back with ODAC again after so many years. What I would like to do today is put into context the results of the gemcitabine/carboplatin data in the overall

management of patients with ovarian cancer.

[Slide]

This remains a major health problem in the United States. There have been about 15,000 deaths estimated in 2006. The current standard therapy for this disease consists of debulking surgery, followed by combination chemotherapy with carboplatin and paclitaxel. Although this is a very effective regimen, 75 percent of patients achieve a clinical complete remission, but the big problem is that most of those patients, about 75 percent, will ultimately relapse and, more importantly, the median disease interval before relapse is less than 2 years. Perhaps most distressing of all, the median survival after relapse is only 18-24 months. So, we are talking about treatments that impact on the quality of life for the effective treatment of these patients for 3 months or so. This represents a substantial amount of time in the overall history of this disease.

One of the other aspects of treatment that is very important is that while paclitaxel and

carboplatin is effective treatment, the major toxicity is neurotoxicity. The vast majority of patients, in fact, develop some degree of neurotoxicity and, in fact, 30 percent of the patients develop at least grade 2 neurosensory toxicity.

For those of you who don't treat ovarian cancer patients, I want to just point out a little bit about the neurosensory toxicity. This is a life-altering toxicity. Women have difficulty putting in earrings. They have difficulty writing checks. They have difficulty buttoning their clothes and, even worse, at times they have difficulty walking and there are gait disturbances. This toxicity can persist for extended periods of time during the course of the entire life span of their disease. Some people have neuromotor toxicity which, of course, is even greater.

[Slide]

When we treat patients for recurrent ovarian cancer, our primary modality of treatment is, in fact, treatment with chemotherapy and we

categorize patients primarily on the basis of whether they are platinum-sensitive or platinum-resistant. In addition, when we make our decisions about treatment for this group of patients we also take into account the residual toxicity, the performance status and co-morbid conditions.

So, the platinum-resistant patients are the patients in whom platinum chemotherapy has stopped working because they had less than a 6-month interval between treatment and progressive disease with the current treatment options that we use very frequently in the United States and most frequently, we use liposomal doxorubicin, topotecan, paclitaxel and gemcitabine. The first three drugs, of course, are FDA approved but gemcitabine has also been used, as I will show you. But in this group of patients with platinum-resistant disease the response rates are relatively low, about 10 percent, and the time to progression for platinum-resistant patients is, again, right around 3 months.

[Slide]

This shows you the efficacy results of single-agent chemotherapies in patients with platinum-resistant ovarian cancer. The response rates are reported in the package inserts for the drugs that are, in fact, FDA approved: liposomal doxorubicin, topotecan and paclitaxel. I will mention again that the response rates have quite a bit of variability between the different clinical trials, but they all cluster somewhere around 10-15 percent, and the median time to progression is, again, low, somewhere around 3-4 months.

[Slide]

Now, compare that with what we see with the single agent Gemzar in the same group of patients. On the basis of several Phase 2 trials, you can see that the overall response rate for gemcitabine is very similar to the response rates reported for the other FDA approved drugs in this situation and, in fact, there are a few complete response rates in this group of patients. Again, you can see that the median time to progression

seems very similar to what is reported for the FDA approved drugs and, in fact, the toxicity profile of Gemzar is very favorable in this group of patients and it is an important aspect of our overall management of patients with platinum-resistant ovarian cancer.

[Slide]

Taking the most important aspect of the presentation today, dealing with platinum-sensitive disease, this is a group of patients in whom prognosis is, in fact, better. By platinum-sensitive, we mean after initial chemotherapy a greater than 6-month interval between treatment and progressive disease. Over the years, the traditional treatment for that group of patients has been singe-agent carboplatin. This has been the most active drug in this disease and patients with platinum-sensitive disease were treated primarily with single-agent carboplatin. However, some Phase 2 trials show that the combination of carboplatin together with a drug such as paclitaxel and ultimately Gemzar produced

higher response rates than one would have predicted with single-agent gemcitabine in that group of patients and that, in turn, led to the prospective randomized trials comparing combination chemotherapy with single-agent carboplatin.

The first of these trials was ICON4. This was an important proof-of-concept for use of combination chemotherapy. This trial was primarily done in England so there are very different implications as far as how we treat patients in the United States. It did report an improvement in overall survival and progression-free survival, and there was a very high degree of neurotoxicity in this study, greater than 20 percent for patients who were retreated with the combination of paclitaxel and carboplatin. Again, this may underestimate the degree of neurotoxicity that we would see in the United States of these patients who would be treated with this combination because, in contrast to the ICON study where only about 45 percent of patients received prior taxane before they progressed and had a disease-free interval and

then were treated with taxane, in the United States almost everybody gets taxane-carboplatin-based chemotherapy, so when they would be retreated with this neurotoxic regimen one would, in fact, expect a higher degree of neurotoxicity than was reported in the study. I think also the fact that these patients did not receive prior treatment with taxane impacts upon the overall survival and progression-free survival results that were reported in this trial which may, again, affect secondary effects of platinum drugs, particularly paclitaxel which, again, is not used as initial therapy in almost half of the patients.

[Slide]

Now, the AGO developed a neurotoxic regimen that was needed in this disease because, as you saw in the ICON study where they were randomizing patients to single-agent platinum versus a combination of carboplatin and paclitaxel there was this high degree of neurotoxicity. The AGO group participated in this trial. It was clear that they needed a less [sic] effective neurotoxic

regimen for recurrent disease. Gemcitabine and carboplatin are both active agents. The AGO is a very well established trials group and they backed out of the ICON study, which they initially participated in, because of the unacceptable degree of neurotoxicity that they were seeing in that trial. In fact, this group developed the combination of gemcitabine and carboplatin in Phase 1 and Phase 2 trials, and in their Phase 1 and Phase 2 trials they demonstrated a lower incidence of neurotoxicity and a very high overall response rate, higher than one would have predicted with single-agent carboplatin but, again, that was Phase 2 trials and they felt that they had to design a prospective randomized trial to see if they could, in fact, have decreased neurotoxicity and increased efficacy with gemcitabine and carboplatin compared to carboplatin.

[Slide]

So, they designed this study to try to determine that the combination was an effective regimen in the patients treated with recurrent

disease. The endpoint that they chose in this trial was PFS. This was the primary endpoint for this particular randomized trial. PFS is recognized as an important endpoint for first- and second-line treatment of ovarian cancer patients. In fact, there was a large ovarian cancer consensus conference which we will be talking about a little today. Both Tate Thigpen and I were members of that ovarian cancer consensus conference about a year and a half ago and, again, we recognize this to be an important endpoint.

The reason we think PFS is an important endpoint is because it is not confounded by post discontinuation therapies. Survival, in fact, may be confounded with multiple lines of therapy. It is very common in the United States for patients with platinum-sensitive disease to go through a series of different drugs, and often patients wind up getting six and eight different chemotherapies during the course of their management for recurrent ovarian cancer. So, there may be confounding effects of those multiple different treatments upon

the ultimate survival of these patients.

PFS represents the efficacy of the only study drug, and we certainly all agree to the fact that we need better agents for this disease. Most patients with recurrent disease invariably die of their disease. So, we need to develop better treatments and PFS has allowed earlier identification of active agent.

But the most important aspect about PFS is that in conjunction with other efficacy parameters such as overall response rate, complete response rate, and quality of life, we feel that this entire constellation is a very important measure of clinical benefit for patients with recurrent ovarian cancer. In fact, the AGO trial met the primary endpoint of a statistically significant improvement in PFS.

[Slide]

Dr. Allen Melemed will give you the details of this particular study.

Clinical Efficacy of Gemzar/Carboplatin

DR. MELEMED: Thank you.

[Slide]

The submission for Gemzar plus carboplatin in recurrent ovarian cancer is based on these following three trials: the pivotal trial JHQJ, OVAR 2.4, which is a Phase 1/2 trial which was performed by the AGO, and JHRW, a supportive trial.

As you can see on this slide, the response rate is around 50-60 percent, which is approximately two times the response rates seen in active agents that Dr. Ozols has previously mentioned in monotherapy. In addition, we included three Phase 2 studies of Gemzar plus carboplatin and ten Phase 2 studies of Gemzar plus monotherapy, again showing efficacy in these studies.

[Slide]

The study design is as follows: The control arm was carboplatin AUC 5 administered every 3 weeks for 6 cycles total. The experimental arm was Gemzar administered at doses of 1000 mg/m

2

on days 1 and 8, and carboplatin AUC 4 on day 1 for 6 cycles again. Patients were stratified at the AGO office according to three main factors,

platinum-free interval; type of platinum therapy, prior taxane or no prior taxane of bidimentionally measurable disease.

[Slide]

This was a randomized Phase 3 study which included the following three cooperative groups, the AGO, the NCIC-CTG and EORTC, overall encompassing 12 countries and 105 investigators. The primary endpoint for this study was progression-free survival, which was defined as time from randomization to disease progression or death. Patients who were alive without progression were censored at their last visit. The study was designed specifically to have 85 percent power to detect 41 percent improvement in this endpoint, requiring approximately 300 events. The secondary endpoints are listed right here.

[Slide]

Patients on studies were assessed symmetrically in both arms of the study throughout the study. While patients were receiving therapy they were evaluated every 6 weeks using the same

methods as baseline. Once patients discontinued the chemotherapy they were again followed every 2-3 months, again using the same methods as baseline. The determination of the events for our primary event endpoint of progression-free survival were either death, objective progression and clinical progression. Again, the majority of the progressions were objective progressions.

[Slide]

Overall, the patient characteristics were well balanced in the study. A few important characteristics that I need to mention are that most patients had very advanced disease. Over 70 percent had stage 3b or greater at their initial diagnosis. Around 70 percent of patients had been previously treated with paclitaxel and carboplatin and around 40 percent had a short platinum freedom of 6-12 months.

[Slide]

The primary endpoint of the study was progression-free survival which was met and was statistically significant showing a 28 percent

reduction of progression or death. You can see that at the first evaluation there was a clear separation which lasted approximately to 12 months. The median improvement was at 8.6 months, which represented a 50 percent improvement over the control arm at 5.8 months. Adjusted hazard ratio and unadjusted hazard ratio were statistically in favor of this combination.

[Slide]

Overall survival in this study was similar between treatment arms. The median was 18.0 months for patients on the Gemzar and 17.3 in the control arm. The unadjusted hazard ratio was 0.98. This was not statistically significant. The adjusted hazard ratio did show numeric improvements with an adjusted hazard ratio of 0.92.

[Slide]

Post-discontinuation therapy was frequent on this study. Approximately 75 percent received at least one line of subsequent third-line therapy and some patients received two or three more regimens. Patients could have also received

hormonal therapy, radiation therapy and other therapies.

[Slide]

Patients treated with this combination of Gemzar plus carboplatin also had statistical improvements of overall response rates, around a 50 percent improvement, 47 percent for patients who had Gemzar plus carboplatin compared to 31 percent. Again, this was statistically significant. Patients also had a doubling of the complete response rate, from 6 percent to 14.5 percent, again highly statistically significant.

[Slide]

In conclusion of these efficacy results, the trial was a well conducted Phase 3 cooperative group study. The patient characteristics were well balanced and well characterized, and did have a high percent of patients with high risk therapy. The primary endpoint of the study was improved and highly statistically significant in favor of the Gemzar plus carboplatin arm, and there was a statistical improvement of both overall and

complete response rates in patients treated with Gemzar plus carboplatin. In conclusion, Gemzar plus carboplatin demonstrated clinically meaningful benefit for women with recurrent ovarian cancer.

[Slide]

Dr. Gralla, former past president of the Multinational Association of Supportive Care, will now discuss the safety results and patient benefit.

Safety Results and Patient Benefit

DR. GRALLA: Thank you and good afternoon. Clearly, it is important to review the safety results as seen in this study and to examine the experiences as reported by the patients who took part in this randomized trial.

[Slide]

Patient benefit will be discussed in terms of PRO or patient-reported outcomes. Using these data, I will relate them to the other primary endpoint, PFS as presented by Dr. Melemed, and other secondary endpoints such as response rates. I will also review how PFS resulted in an additional patient benefit seen with the

gemcitabine plus carboplatin arm, that is, an improved time off all chemotherapy. In that gemcitabine is a widely used anti-cancer agent with a well characterized toxicity profile, I will focus on major side effect areas and will outline how the toxicities of the two regimens in this trial resulted in clinically relevant effects for these patients. Clearly, a two-agent regimen composed of full doses of gemcitabine with the addition of carboplatin will have more side effects than just carboplatin alone. The key issue is whether the combination resulted in a side effect profile with significantly more meaningful negative consequences for patients or if this profile abrogated potential PRO benefits from the addition of gemcitabine.

[Slide]

This slide outlines common hematologic and GI toxicities observed with the regimens. The results indicated with an asterisk are those in which significant differences were found between the two treatment arms. As fully expected and consistent with the broad experience with

gemcitabine, the laboratory blood test values showed more hematologic effects on the combination arm. In reviewing the important GI side effects such as nausea and vomiting no significant differences are seen between the arms. Fortunately, the side effect profile is very modest for these agents, with only 3 percent differences seen in the combination arm.

To manage the minor differences with the combination regimen and the significant effects seen in the hematologic toxicities, appropriately the physicians used more supportive care interventions for patients on the gemcitabine plus carboplatin arm, such as the use of preventive anti-emetics and growth factors or red cell transfusions.

[Slide]

As Dr. Ozols discussed, most patients in this setting are currently treated with taxane in first line, leading to neuropathy in many patients. In this study 67 of the 350 patients had preexisting neuropathy at baseline using the CTC

criteria. Thus, peripheral neuropathy in a second-line regimen is highly undesirable and can limit the use of an agent or combination. We were pleased to see that even such highly susceptible patients as those who presented with peripheral neuropathy had a low incidence of neuropathy while on trial, and that this side effect was very similar for both the gemcitabine combination arm and the carboplatin arm, indicating that the gemcitabine combination is an option with a very low potential for neurotoxicity.

[Slide]

As expected, there were numerically more SAEs reported in the gemcitabine combination arm, but this 7 percent difference was not statistically significant in this 350 patient trial. As can be seen in the table, there was no difference in treatment discontinuations due to adverse events between the two study arms, and this rate of discontinuation is quite low for both regimens.

[Slide]

Again, it was not surprising that the

addition of the active chemotherapeutic agent, gemcitabine, was associated with more hematologic toxicity. What is key to patients and physicians is whether this toxicity results in major consequences, such as febrile neutropenia or hemorrhage. Importantly, these clinically meaningful toxicities are remarkably low in both study arms and are very similar with both regimens.

Also presented in this table are the peripheral neuropathy rates for all patients on the study, not just those with preexisting neuropathy as shown on the prior slide. The low rates of peripheral neuropathy as well support the finding that the gemcitabine/carboplatin regimen has a very low toxicity profile in terms of the consequences important for patients, and these safety results establish this regimen as a quite acceptable combination option for appropriate patients.

[Slide]

Continuing with major toxicities, as seen on this slide, the number of deaths occurring during this trial in the 30-day post-study period

was identical for both arms and was low. About 7 percent more patients on the gemcitabine arm were hospitalized due to AEs during this trial. However, this difference is not significant in this 350 patient trial.

[Slide]

In summary, the side effect and AE results were not unexpected and were consistent with the known gemcitabine safety profile. The addition of gemcitabine resulted in few clinically relevant consequences and the occurrences of such major factors as hemorrhage, febrile neutropenia and death on study were similar between the treatment arms. Importantly, the neurotoxicity rate was very low and there was no evidence of exacerbation due to gemcitabine. No new safety issues were observed when considering the long history of the use of gemcitabine.

[Slide]

It is useful to explore possible patient benefits resulting from higher response rates in PFS with the gemcitabine and carboplatin regimen.

As such, these analyses are exploratory and of themselves are not meant to meet standards for regulatory claims. The patient-reported outcomes, or PROs, were elicited using the validated EORTC general instrument and the validated ovarian specific instrument as seen on the slide. By their nature, PROs are subjective outcomes. We also explored the patient benefit associated with improved PFS and response rates with an objective time-to-event endpoint that allows an evaluation of the duration of time when patients were able to be off all chemotherapy after completing the planned 6 cycles of treatment as specified by the study.

[Slide]

The two PRO instruments included in the JHQJ study resulted in 22 scales that include symptoms, functional and global measures. Several publications have identified symptoms that are particularly relevant for patients with ovarian cancer and these include those that are listed on the slide. We report results including all 22 scales, but I will focus on these 7 key symptoms

which I believe are clearly of significance for these women.

Again, this study was designed for patients to receive treatment for 6 cycles unless disease progression was evident before that time. Nearly 90 percent of the patients had baseline and follow-up PRO evaluations. This completion rate is high and is essentially equal in both arms, thus, providing an excellent and representative data set to examine.

[Slide]

Were the women on this study symptomatic and were there similar symptom profiles on each arm of the study? About 75 percent of the patients reported 3 or more of the 7 key symptoms discussed earlier and listed on this slide. Virtually all patients reported symptoms, with more than 70 percent having pain and over 80 percent having abdominal bloating. This shows a highly symptomatic profile and is similar for patients on both randomization arms. This symptom profile is based on the actual patient reporting from the

baseline evaluation as recorded in the validated EORTC PRO instruments rather than an observer-reported preexisting condition list. I requested this analysis in that abundant research has shown that healthcare professionals underestimate both the prevalence of symptoms and their magnitude. Under-reporting by healthcare professionals occurred again in this study in which the preexisting condition list would have indicated one-third fewer symptoms than the patients themselves reported.

Given how symptomatic these patients are, is there actual value in palliation by achieving a response? We looked at whether women having a major response reported better symptom control independent of which treatment arm they were randomized to. In fact, responding patients reported more symptom relief than those with less than a major response. With the significantly higher response rate for the women randomized to gemcitabine plus carboplatin, one would then expect better symptom improvement for patients on that

treatment arm.

[Slide]

Indeed, that is just what was found. This slide shows the results of the PRO analysis focusing on the 7 key symptoms by randomized arm. Again, you can see the gemcitabine/carboplatin arm being in yellow, the carboplatin in blue. As can be seen, in each of the key symptoms patients on the gemcitabine/carboplatin consistently rated improvement greater than those on the single agent. In analyzing all 22 scales, patients rated better symptom improvement with the gemcitabine arm in 21 of the 22 scales, a highly significant difference.

This consistent result favoring the gemcitabine arm reflects the reported higher response rate as discussed by Dr. Melemed. While this reporting of consistently greater symptom control is welcomed, it must be realized that difference in benefit in any particular symptom is modest and not statistically significant. It is the consistent results seen with the total analysis of all symptoms that yields the highly significant

difference.

Similarly, we see that patients rated global quality of life higher with the gemcitabine regimen. Thus, the modestly greater toxicity, as expected with the combination, did not abrogate an overall numerically better rating for quality of life on the gemcitabine regimen.

[Slide]

When this consistency of benefit in patients randomized to the gemcitabine regimen is seen, it is indeed modest but we explored the question of the magnitude and duration of benefit further. Several well-respected experts in this area have published evidence that differences of 10 percent in PRO outcomes are meaningful to patients. We then explored the differences between the treatment arms of those patients who experienced changes of this magnitude.

As seen in these bars showing quality of life results, more patients on the gemcitabine regimen experienced this 10 percent or greater benefit. Additionally, the same result occurred in

5 of the 7 key symptom scales continuing to show consistent results.

[Slide]

An analysis of the duration of patient-reported quality of life is seen in this graph. Patients on the gemcitabine arm maintained a higher quality of life longer than those on the comparator. Overall, there was a median 2-month advantage favoring the gemcitabine regimen before patients reported a 10 percent or greater worsening.

[Slide]

We then wished to see if the PFS and response advantages indicated an additional tangible benefit, that is, time off all chemotherapy after completing the treatment regimen specified by the JHQJ study protocol.

This graph displays patient outcomes after discontinuing study chemotherapy. Please recall that 75 percent of patients received further chemotherapy after the JHQJ trial. As can be seen, patients randomized to the gemcitabine plus

carboplatin arm had 3 months longer without restarting any chemotherapy. This is a significant time off chemotherapy interval. We believe that this is a reflection of the greater PFS, and that this can be easily appreciated by patients and their families.

[Slide]

The gemcitabine plus carboplatin regimen has an acceptable toxicity profile, as discussed previously. The expected moderately higher side effect rate for the combination regimen gave no indication of a decrease in quality of life. In fact, patients reported modest benefit in quality of life with consistently reported improvements in symptoms and in nearly all the PRO parameters using a validated instrument.

Perhaps of greatest value was the significantly longer period off all chemotherapy, 5.6 versus 2.6 months favoring the gemcitabine plus carboplatin arm. We feel that this benefit is related to the significantly improved progression-free survival result. These results

reflect how patients perceive the benefits related to the primary efficacy endpoint and are supportive of the efficacy measures, as presented by Dr. Melemed.

[Slide]

Dr. Dan Sargent, from the Mayo Clinic, will now present data concerning the efficacy endpoints.

Robustness of Efficacy Results

DR. SARGENT: Thank you.

[Slide]

As this was an open-label, unblinded study we have performed a number of analyses to confirm the robustness of the primary endpoint results for progression-free survival, the primary endpoint. As well, we have performed analyses to assess any possible impact of investigator bias on the endpoints of progression-free survival and response rates.

[Slide]

Before I begin these analyses, I should point out that the analyses I will be presenting

represent in no way multiplicity analyses. We have here a positive outcome on our primary endpoint. We are conducting, as part of due diligence, a number of sensitivity analyses to see if we can so-called break that analysis based on any activities of the investigators that may not have followed per protocol.

I will present two sensitivity analyses today. I should point out that the sponsor has presented additional sensitivity analyses that are present as part of the briefing document. At my request, a number of additional sensitivity analyses have been conducted, and these include three sensitivity analyses that are part of your briefing document, two that I will present today.

[Slide]

The first analysis, SA1, is a sensitivity analysis that includes only objective progressions, that is, clinical progressions were ignored. A more restrictive analytical, labeled SA3, includes only documented objective progressions. Clinical progressions are ignored. Objective progressions

without lesion measurements to verify them are ignored. If a scan was missed and progression occured at the next scan, we back-dated the date of that progression to the scan that was missed. In addition, in SA3 we have trimmed this to only the 7-month period where patients were on therapy, being followed every 6 weeks. I will point out that for each of these analyses we have also conducted them where we censor events, as opposed to ignoring those events, and the results are the same.

[Slide]

In the first sensitivity analysis to be presented today, SA1, where only objective progressions are included we see a consistent result with the primary analysis, hazard ratio 0.76, significant p value in favor of the combination therapy arm; approximately 3-month improvement in median survival; a slightly higher censoring percentage, as would be expected.

[Slide]

SA3, which is the very restrictive

analysis where only documented objective progressions are included, where back-dating was being used, and where we were only using the 7-month period where the patient was on treatment and the 1-month follow-up visit, again shows a highly significant advantage in favor of the combination arm, hazard ratio 0.45. We do note here a very high censoring proportion. So, this should really be considered a sensitivity and robustness analysis but, due to this high censoring proportion, I personally have less confidence in these medians that are reported on this slide.

[Slide]

In conclusion for these analyses, we have sensitivity analyses that support the primary endpoint of progression-free survival defined per protocol. Each of the analyses represents a hazard ratio in favor of the combination therapy arm with a significant advantage.

[Slide]

This is supported by looking at the internal consistency of the progression-free

survival endpoint within protocol defined subgroups. In each of these subgroups we see a hazard ratio for progression-free survival in favor of the combination therapy arm and we have no significant p values for test of interaction, indicating no evidence of differential improvement in progression-free survival by baseline characteristics.

[Slide]

Second, I will comment on the independent assessment of response rate that was performed. Again, this was an open-label trial. At the sponsor's request an independent review of response rate was conducted where imaging films were submitted by the investigator. Patients needed to have at least one subsequent radiologic image in addition to their baseline to be included. And, some patients who were followed by ultrasound or physical exam were not able to be independently reviewed.

This independent review board was blinded to treatment arm, investigator assessment and,

importantly, were blinded to the target lesions that the investigator was following. So, it is very possible that the independent radiologists were looking at a different subset of lesions than the investigator was following. This independent assessment was available in 222 of the 356 patients, therefore, there is some reduced power for this comparison.

[Slide]

Importantly, what we found in looking at the concordance between the independent review and the investigator assessment was that an equal number of patients who were considered responders by the investigator were considered non-responders by the independent review, as were the converse, non-responder by investigator but responder by independent review. So, we have no evidence of bias from the investigator perspective in calling these tumor responses.

[Slide]

Looking at the response rate then in that subset of patients who were independently reviewed,

we see very similar results, almost identical results in terms of the response rate with respect to independent review and investigator assessment in that subset of patients who were able to be independently assessed.

[Slide]

In conclusion, we feel that based on these analyses the primary endpoint, progression-free survival, these results are statistically convincing and internal. Consistent multiple sensitivity analyses have confirmed the robustness of this endpoint, and significant benefit was reproduced in each of the patient subgroups.

In addition, we have no evidence of investigator bias. The results from the independent review were consistent. The concordance analysis showed no bias, and there were very similar overall response rates among the patients who were able to be independently reviewed.

[Slide]

I would like now to introduce Dr. Tate

Thigpen, from the University of Mississippi, who will offer concluding remarks.

Risk/Benefit Overview

DR. THIGPEN: For the final part of our presentation I would like first to discuss potential benefit on the one hand, and the potential risks of the treatment on the other.

[Slide]

First, I would direct your attention to the assessment of benefit. OVAR 2.5 adopted progression-free survival as its primary endpoint. There are several reasons for this. First of all, as Dr. Ozols has indicated, progression-free survival was recognized as an important valid endpoint by the results of the third consensus conference on ovarian carcinoma held in Baden-Baden, Germany in September of 2004. This conference was sponsored by the Gynecologic Cancer Group which is a coalition of now 15 major cooperative groups internationally, and was hosted by the AGO OVAR.

[Slide]

The conference unanimously adopted two statements regarding progression-free survival in ovarian carcinoma. The first statement concerns patients who have newly diagnosed ovarian carcinoma: Although overall survival is an important endpoint, progression-free survival may be the preferred primary endpoint for trials assessing the impact of first-line therapy because of the confounding effect of the post-recurrence/progression therapy on overall survival. When progression-free survival is the primary endpoint, measures should be taken to protect the validity of analysis of overall survival.

A second unanimous statement adopted concerned the use of progression-free survival in post-recurrence/ progression trials. The choice of the primary endpoint needs to be fully justified with appropriate power calculations. Symptom control or quality of life for early relapsers and overall survival for late relapsers may be the preferred primary endpoints, although

progression-free survival should still be used in the assessment of new treatments. Whatever the primary endpoint, the ability of the study design to detect important differences in survival should be formally addressed.

Any other statements taken from manuscripts that were associated with this conference represent the opinion of the first author of that paper and not the unanimous consent of the consensus conference. Thus, the adoption of progression-free survival as the primary endpoint of OVAR 2.5 was both rational and reasonable.

[Slide]

A second reason for the adoption of progression-free survival is the fact that progression-free survival is not confounded by post-discontinuation therapies. As you have seen indicated several times during this presentation, survival may be confounded with multiple lines of additional effective therapy. But progression-free survival represents the efficacy only of the regimens under study in that particular trial.

Thirdly, progression-free survival differences can alter practice patterns. The best example of this goes back to 1993 when the Gynecologic Oncology Group presented the results of a trial comparing paclitaxel/cisplatin to cyclophosphamide/cisplatin. The presentation in 1993 at ASCO concerned only progression-free survival. We did not have sufficient data at that time to present a survival analysis. Despite that, within 18 months of that conference, based on a survey done by Bristol-Myers Squibb, 82 percent of all ovarian cancer patients in the United States were being treated with paclitaxel plus a platinum compound. It wasn't until 12 months after that survey that the GOG was able to present survival data showing that the Taxol/cisplatin combination, indeed, resulted in a survival improvement as well. So, progression-free survival can, in fact, alter treatment practices.

[Slide]

Finally, progression-free survival in conjunction with other efficacy parameters can be a

measure of clinical benefit as we see on OVAR 2.5. The primary endpoint of progression-free survival showed a statistically significant improvement favoring the doublet, so did the overall response rate, the complete response rate and, as Dr. Gralla has shown you patient-reported outcomes where we saw a consistent trend for improvement in 21 of 22 symptom scales, a circumstance that is highly unlikely to be due to chance alone.

[Slide]

In contrast, survival can be a very murky endpoint in ovarian cancer trials. Two quick examples: The GOG conducted a trial in the early 1990s of cyclophosphamide/ cisplatin versus paclitaxel/cisplatin. While that trial was maturing we ran a second trial, cisplatin versus paclitaxel versus paclitaxel plus cisplatin. The first study showed a striking advantage for paclitaxel/cisplatin in terms of survival, a 13-month difference at the median. The second trial showed no difference among the 3 arms.

We spent a great deal of time re-analyzing

these two trials and finally concluded that the only rational explanation for the difference in the two trials was the fact that effective second-line therapy was available at the time of the second trial for both of the single-agent arms. Whereas, at the time the first trial was run Taxol was not available for salvage for the cyclophosphamide/cisplatin group of patients.

Then, if you go back to the mid 1980s, when cisplatin was approved for ovarian carcinoma, the GOG ran a trial of doxorubicin/cyclophosphamide versus cisplatin/ doxorubicin/cyclophosphamide. This trial showed a striking advantage in progression-free survival but absolutely no difference in overall survival. Reason? Based on our re-looking at the data a number of times, this group of patients had available a very effective salvage regimen, cisplatin, and that blurred the survival differences that we feel otherwise would have been seen.

We see the same situation with regard to the trial that has been presented today. The OVAR

2.5 trial was run at a time when multiple lines of effective salvage therapy were available, and 75 percent of the patients on this trial received subsequent therapy with drugs that have been identified and approved as effective agents in ovarian cancer.

In contrast, ICON4 was run in the United Kingdom where practice patterns dictate that very little post- progression therapy is used. Hence, it was a pure comparison between Taxol/carboplatin and carboplatin and was able to identify the survival advantage.

[Slide]

The other side of the equation is risk. We have shown you evidence that the standard of care in front-line ovarian cancer is carboplatin plus paclitaxel. In fact, the conclusion of the consensus conference was unanimous that this represented the standard against which other measures would have to be compared. Neurotoxicity is a frequent complication of this treatment.

We have also shown you that standard of

care in recurrent platinum-sensitive ovarian cancer is platinum-based therapy, and we have shown you two trials, ICON4 and OVAR 2.4, which suggest that combination therapy is superior to single agent carboplatin. If that is true, then 20 percent of the patients in that group are not going to be able to receive paclitaxel/carboplatin because of residual neuropathy. So, an effective and less neurotoxic regimen is needed, at the very least for that group of patients.

[Slide]

So, to sum up, gemcitabine/carboplatin showed an advantage over carboplatin in terms of a clinically meaning importance in progression-free survival. These improvements were robust, internally consistent and statistically significant.

Secondly, in terms of a significantly greater overall and complete response rate, the combination demonstrated a manageable and well characterized safety profile with infrequent neurotoxicity and infrequent alopecia. The

combination also demonstrated a longer period without a decline in quality of life and, as Dr. Gralla has shown you, a longer time without need for further chemotherapy.

So, the bottom line, OVAR 2.5 is a positive study with regard not only to its primary endpoint of progression-free survival but at least three additional supporting endpoints of overall response rate, complete response rate and trends toward improvement in 21 of 22 symptom scales. This total package of 4 major parameters, we think, speaks for the efficacy of the combination. So, our conclusion is that gemcitabine plus carboplatin is an effective, less neurotoxic treatment option for women with recurrent ovarian cancer and may, in fact, be the treatment of choice for those who have significant neurotoxicity or major concerns about alopecia.

The bottom line is we believe that these data justify full approval of gemcitabine and carboplatin for the treatment of patients with platinum-sensitive ovarian carcinoma. Thank you.

DR. MARTINO: Thank you. At this time I would like to ask the FDA to proceed with their presentation.

FDA Prescription

Gemzar plus Carboplatin Treatment of Late Relapsing Ovarian Cancer

DR. COHEN: Good afternoon.

[Slide]

My name is Martin Cohen and I will summarize the FDA review of supplemental NDA S20-509 evaluating gemcitabine plus carboplatin treatment of late relapsing ovarian cancer. The sponsor is Eli Lilly.

[Slide]

The proposed indication is that Gemzar in combination with carboplatin is indicated for the treatment of patients with advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy.

[Slide]

A single randomized, open-label pivotal Phase 3 trial was submitted that enrolled a total

of 356 patients with advanced epithelial ovarian carcinoma with failed first-line platinum-based therapy, but who were platinum-sensitive. That is, relapse had occurred greater than or equal to 6 months after completion of treatment. Study treatments were gemcitabine plus carboplatin versus carboplatin alone. In addition, several Phase 2 and 3 supporting trials using the same treatment regimen in relatively identical doses and schedules was summarized.

[Slide]

Patients randomized to the combination therapy arm received Gemzar at 1000 mg/m 2 on days 1 and 8 and carboplatin AUC 4 administered after Gemzar on day 1 of each cycle. Patients randomized to single-agent treatment received carboplatin AUC 5 administered on day 1 of each 21-day cycle as the control arm.

[Slide]

Regarding regulatory background, the study was not conducted under an IND. Neither the protocol nor the case report forms had been

reviewed by the FDA. Lilly had an initial pre-IND meeting with the FDA on December 21, 2004 to discuss the submission. The major question at that meeting was whether progression-free survival was acceptable as an endpoint to support approval. Based on those discussions, the FDA agreed to accept the application for review, noting the need for further discussion of endpoints.

Lilly subsequently held a teleconference with the FDA on March 23, 2005. The purpose of this meeting was to agree on the content and format of the Gemzar sNDA. At this meeting, FDA advised that Lilly provide both a primary statistical analysis plan and a sensitivity analysis plan for the endpoint of progression-free survival. This was subsequently provided.

[Slide]

Submitted studies included the previously described Phase 3 pivotal clinical trial. Also submitted was a multicenter Phase 2 trial in an identical patient population who received the same doses and schedules of gemcitabine plus carboplatin

as was used in the pivotal trial. Forty patients were enrolled in this trial. The investigator-determined response rate was 62.5 percent.

The third submitted study was a Phase 1/2 trial in an identical patient population receiving varying doses of gemcitabine and carboplatin and 25 patients were enrolled. The response rate for all dose levels was 40 percent.

[Slide]

Participating groups in the Phase 3 trial included three cooperative groups, the AGO which is a German gynecological oncology group, the EORTC and the NCIC Canada clinical trials group. I addition, there were 14 independent sites. In total there were 101 participating sites and no U.S. institutions participated.

[Slide]

The major inclusion criteria were women greater than or equal to 18 years of age with histologically proven ovarian cancer, with evidence of recurrence or progression that was not amenable

to curative surgery or radiotherapy. Patients must have relapsed 6 or more months after discontinuation of first-line platinum-containing therapy. Patients had to have ambulatory performance status, adequate marrow reserve and measurable or evaluable disease.

[Slide]

The study plan called for 6 cycles of chemotherapy unless there was a valid reason to prematurely discontinue treatment. Disease was evaluated by radiologic studies, physical exam and/or ultrasound as appropriate every other treatment cycle. A final diagnostic evaluation was performed 30 days post study. In addition, one additional diagnostic evaluation could be performed on select patients to confirm a tumor response. There were no scheduled post study diagnostic evaluations. During this period assessment of progression was per clinical practice. There was independent review of CT and MRI lesions for response to treatment but not for progression. There was no review of physical exam or ultrasound

findings for either response or progression.

[Slide]

The primary objective of this study was to compare progression-free survival in patients treated with gemcitabine plus carboplatin versus those receiving carboplatin monotherapy. Secondary objectives included overall survival, response rate, response duration and quality of life measured by the EORTC-QLQ C-30 and OV-28 patient-reported outcome questionnaires. These health-reported outcome assessments cannot be used as a basis for Gemzar approval, however, because the study was not blinded and the effect of concurrent medications was not assessed. On some items the carboplatin alone group did better and the effect on global quality of life, although statistically significant, is not thought to be clinically meaningful. Therefore, the quality of life endpoint will not be further discussed my presentation.

[Slide]

Patient and disease characteristics of

study patients are reviewed on this slide. Gemzar plus carboplatin-treated patients and patients receiving carboplatin alone were comparable for age, ethnicity, pre-treatment performance status, platinum-free interval, with 40 percent of each group having a free interval of 6-12 months and 60 percent of each group having an interval greater than 12 months. They were also comparable for ovarian cancer histology, grade of tumor differentiation, stage at diagnosis and pretreatment tumor burden.

[Slide]

This slide summarizes prior chemotherapy received by study participants. As indicated, there were 178 patients in each treatment arm. As seen on line one, approximately two-thirds of patients in both groups received prior platinum and paclitaxel with or without other drugs. A small percent of patients received platinum plus docetaxel, as seen on line two. The remaining patients received platinum combined with non-taxane drugs or they received carboplatin alone.

[Slide]

This slide summarizes the sponsor's primary analysis of progression-free survival. Because diagnostic studies were not routinely performed after the post study period in the sponsor's primary PFS analysis, the timing of progression assessment was determined by the investigator. Censoring rules for the primary progression-free survival analysis are s follows: Non-progressive patients were censored on their last visit date. For patients who received new therapy post discontinuation but prior to documented progression, their progression date was the progression date after the new therapy. Patients with missing scans pre-progression who later progressed were considered to have progressed on the day that progression was declared.

[Slide]

Results of this analysis are shown on this slide. This slide shows the sponsor's primary analysis. Using the censoring rules described earlier, 13 percent of patients in each group had

not progressed as of their last physician visits. Patients receiving Gemzar plus carboplatin had significantly longer time to progression than the carboplatin-treated patients. The medians were 8.6 months versus 5.8 months. The hazard ratio was 0.72 and the p value was 0.0038.

[Slide]

This slide shows the Kaplan-Meier curve of progression-free survival for Gemzar plus carboplatin treatment, shown as the light survival curve and carboplatin alone treatment shown as the darker line.

[Slide]

In the progression-free survival sensitivity analysis, conducted both by the sponsor and the FDA, non-progressing patients were censored on the last date of complete diagnostic evaluation of baseline disease signs. Similarly, patients with missing scans prior to progression and patients who died after an extended loss to follow-up time were also censored on the last date of complete diagnostic evaluation of baseline

signs. Patients who began a new therapy prior to progression were censored on the day that therapy was initiated.

[Slide]

This slide shows the sponsor's sensitivity analysis results. It should be noted that in this analysis 74 percent of GC patients were censored versus 57 percent of carboplatin-treated patients. Again, patients receiving Gemzar plus carboplatin had a significantly longer time to documented progressive disease than did carboplatin alone treated patients. The medians were 6.9 months versus 5.6 months. The hazard ratio was 0.47 and the p value was 0.001.

[Slide]

This slide shows the FDA sensitivity analysis of progression-free survival. The top curve is the combination of Gemzar/carboplatin, the bottom is the carboplatin monotherapy arm. As is evident in the above curves, patients receiving combined Gemzar/carboplatin had a significantly longer time to progressive disease than the

carboplatin-treated patients and the p value is less than 0.001.

[Slide]

This slide summarizes objective response rate as determined by investigator assessment, and confirmed by the FDA. The overall response rate was 47.2 percent for the Gemzar/carboplatin arm versus 30.9 percent for carboplatin alone. This difference was significantly different, with a chi square p value of 0.0016. The CR rate, as you see, was also significantly better for GC treatment compared to carboplatin alone. Response duration analysis was conducted with responders censored at the date of last progression-free survival assessment. The median duration of response was 8.2 months for Gemzar/carboplatin treatment versus 6.7 months for carboplatin alone.

[Slide]

Post study chemotherapy is summarized on this slide. Altogether, about three-quarters of patients in each treatment arm received post study chemotherapy. Knowledge of specific drugs that

patients received is incomplete. Specific drug information is available for about 40 percent of patients on each treatment arm. Among all patients receiving chemotherapy, it is known that there were a minimum of 13 carboplatin-treated patients or 10.1 percent who received gemcitabine post study versus zero percent for gemcitabine/carboplatin patients. Other drugs administered to patients included topotecan, VP-16, Doxil, taxanes, platins, cyclophosphamide or anthracyclines. Available data suggests that there were no important differences in post study chemotherapy between the two groups.

Therefore, regarding post study chemotherapy, we know that about 25 percent of patients in each arm did not receive post study chemotherapy and about 40 percent of patients in each arm received specific drugs. This leaves about a third of patients in each treatment arm who received chemotherapy but the specific drugs are not known.

[Slide]

This slide shows survival by treatment.

Approximately 20 percent of the patients are censored for survival. The red curve is gemcitabine/carboplatin and the green is carboplatin alone. Median survival was 18 months for GC-treated patients and 17.3 months for carboplatin-treated patients. The hazard ratio was 0.98 and the log rank p value was 0.898.

[Slide]

Turning now to safety, as indicated on this slide, treatment was generally well tolerated. Patients treated with gemcitabine plus carboplatin received 93 percent of the planned mean day 1 gemcitabine dose; 63 percent of the planned mean day 8 gemcitabine dose; and 96 percent of the planned carboplatin dose. Patients receiving single-agent carboplatin received 98 percent of the planned dose. The median number of cycles of treatment received on each arm was 6, with a range of 0-10.

[Slide]

This slide shows grade 3/4 hematologic toxicity. As expected, there was more hematologic

toxicity, including anemia, neutropenia and thrombocytopenia and more red blood cell and platelet transfusions with gemcitabine plus carboplatin treatment than with carboplatin alone.

[Slide]

This slide shows non-laboratory grade 3/4 toxicities. As seen, grade 3/4 toxicity was infrequent in both study arms but generally slightly more common in the gemcitabine plus carboplatin arm.

[Slide]

In conclusion regarding efficacy, gemcitabine plus carboplatin treatment resulted in significantly prolonged progression-free survival and significantly increased response rate compared to carboplatin alone. The median progression-free survival was prolonged approximately 1.5 to 3 months depending on which analysis is considered. In addition, the response rate increased from 31 percent for carboplatin alone to 47 percent for the combination.

A caveat is that progression was not

independently reviewed. Also, response was based on physical exam and ultrasound findings in 32 percent of GC patients and 43 percent of carboplatin patients and those studies could not be independently reviewed.

There was no significant survival increase. Median survival for the gemcitabine/carboplatin arm was 18 months versus 17.3 months for carboplatin alone. A caveat is that many study patients received post study chemotherapy with drugs that have demonstrated activity in ovarian cancer. It should be emphasized, however, that available data suggest that there was no important difference in post study chemotherapy between the two treatment groups.

[Slide]

Regarding safety conclusions, grade 3 and 4 toxicities were primarily hematologic and were more frequent with gemcitabine/carboplatin treatment compared to carboplatin alone. Toxicities were consistent with the single agent

toxicity of each drug, and no new safety concerns were raised.

[Slide]

The main issue of this sNDA is whether significant improvement in progression-free survival and response rate, with no increase in overall survival, is an adequate basis for drug approval for patients with advanced ovarian cancer who have relapsed at least 6 months after completion of platinum-based therapy. Dr. John Johnson will further discuss this issue.

Basis for Drug Approval

[Slide]

DR. JOHNSON: I am going to summarize the four issues that the FDA would like the committee's advice on, but first I will briefly summarize the results of the Gemzar randomized trial in ovarian cancer. Gemzar increased median progression-free survival by 2.8 months, with no apparent survival increase. The hazard ratio for death was 0.985. An independently assessed tumor rate was Gemzar/carboplatin 46 percent and carboplatin alone

36 percent. This was achieved at a cost of increased toxicity, mainly hematologic, requiring increased red because cell and platelet transfusions and use of growth factors.

[Slide]

In 2004 there was an international consensus conference on ovarian cancer. Because we are going go be citing the consensus conference, I will tell you a little about it.

[Slide]

This slide shows the organizations participating in the consensus conference. Organization from the United States included the GOG, RTOG and the NCI. Also participating were the NCIC Canada, organizations from most West European countries, the U.K., Australia and New Zealand and Japan. There were three publications on this consensus conference on the same issue in The Annals of Oncology in 2005. There was a consensus conference statement with recommendations and two companion articles elaborating on and explaining the rationale for the recommendations and

conference statement.

[Slide]

The first issue is are there chemotherapy regimens that increase survival in randomized trials in the setting of patients in the Gemzar trial, that is, patients with advanced ovarian cancer that recur 6 months or more after platinum-based chemotherapy? This is important because if there is already chemotherapy that prolongs survival it would be difficult for the FDA to approve new therapies for this condition that do not prolong survival. It appears that there is one, and probably two, chemotherapy regimens that have been shown in randomized trials to increase survival in this setting.

[Slide]

The ICON4 study was a randomized trial comparing the combination of Taxol and carboplatin with conventional platinum-based chemotherapy without a taxane. All patients had recurrent advanced ovarian cancer after platinum-based chemotherapy and were still platinum sensitive. In

802 patients the hazard ratio for death was 0.82, p equal 0.02 favoring the Taxol/carboplatin group.

[Slide]

A second randomized trial compared pegylated liposomal doxorubicin to topotecan in 474 patients with recurrent advanced ovarian cancer. Both platinum-sensitive and platinum-insensitive patients were included in this trial. Patients were stratified prior to randomization by platinum sensitivity. In the study overall survival was better in the pegylated liposomal doxorubicin group. The hazard ratio for death, 0.82, p equal 0.05.

The FDA was confident that the nominal p value was 0.05 or less, but the p value needed to claim superiority was uncertain because the survival analysis was repeated without p value adjustment. Also, lipo. dox. did not win on progression-free survival, the primary study endpoint. In the platinum-sensitive subgroup there was an impressive survival advantage for lipo. dox., hazard ratio for death 0.7, p equal 0.017.

[Slide]

The 2004 consensus conference addressed this issue of whether there is second-line chemotherapy that prolongs survival if given after progression on first-line therapy. Quote: There is an impact of post recurrence/progression therapy on overall survival. End quote.

[Slide]

This slide shows a quote from one of the two companion consensus conference articles: The unanimous answer was that second-line chemotherapy does impact overall survival. The ICON 4 trial and the liposomal doxorubicin versus topotecan trial were cited as examples.

[Slide]

The second issue is are there regiments that have been shown in randomized trials to increase survival in the patient population in the Gemzar randomized trial setting, if given post progression?

This is probably of interest only if there is imbalance in both study treatment between

treatment groups. The FDA knows of no such regimens and the FDA found no imbalance in post study chemotherapy between the treatment groups that is likely to obscure a Gemzar survival effect.

[Slide]

This slide provides more information on post study chemotherapy. Whether post study chemotherapy was administered is known for all 356 study patients, 76 percent of Gemzar and 73 percent of carboplatin alone patients received post study chemotherapy. The case report form required recording the names of all post study chemotherapy drugs, but this information is not available for 34 percent of study patients. There is complete information for 66 percent of study patients. These patients are described on the slide as post study chemotherapy status known. Either they received drugs and the drugs are known, or they received no drugs. Seventy-three Gemzar patients and 71 carboplatin alone patients got post study chemotherapy and the drugs are known; 43 Gemzar and 49 carboplatin alone patients got no post study

chemotherapy. In the 66 percent of study patients with complete information on post study chemotherapy, 13, or 10.8 percent, of carboplatin alone patients received Gemzar after progression. No Gemzar patients received Gemzar after progression.

[Slide]

This slide shows the post study chemotherapy drugs administered to patients for whom complete information is known. More patients in the Gemzar group received topotecan and etoposide, and more patients in the carbo. alone group received alkylating agents.

[Slide]

The third issue is that although the Gemzar study was not adequately powered to detect a realistic survival effect, we have quite a lot of information on survival in the Gemzar trial. A favorable Gemzar survival effect, if this trial were enlarged, appears improbable. The hazard ratio for death in this trial is 0.985. Eighty percent of patients have died; 283 of 356 patients

are dead.

The following analysis indicates the improbability of showing a statistically significant Gemzar survival effect if the trial were enlarged. To have had a power of 0.8 to detect a 30 percent survival effect, about 460 deaths would be needed. If we added additional patients to the Gemzar trial to have an additional 177 deaths, for a total of 460 deaths, and during this additional follow-up, using a prior distribution for the two hazard ratios based on the survival results in the first 283 events, the probability of finding a statistically significant Gemzar survival effect of any size is 0.01 using the Cox unstratified hazard ratio for death. The probability is 0.15 using the Cox stratified hazard ratio for death.

[Slide]

The fourth issue is whether a 2.8-month median progression-free survival improvement, with no apparent survival improvement and at a cost of increased toxicity, is an adequate basis for drug

approval in this setting.

[Slide]

The 2004 international consensus conference on ovarian cancer addressed this issue. Today, we are interested in the second-line platinum-sensitive setting but for completeness we will first show the consensus conference recommendation of the primary endpoint for first-line chemotherapy trials in advanced disease. This slide and the following slides are verbatim quotes, but the added emphases are the FDA's. Quote: Advanced first-line: Both progression-free survival and overall survival are important endpoints to understand the full impact of any new treatment. Thus, either may be designated as the primary endpoint. Regardless of which is selected, the study should be powered so both progression-free survival and overall survival can be appropriately evaluated.

[Slide]

Now we will show the consensus conference recommendation for the primary endpoint in trials

of second-line chemotherapy. This quote is from the consensus conference statement. The vote on this answer was unanimous. Quote: Post-recurrence/progression trials: The choice of the primary endpoint needs to be fully justified with appropriate power calculations. Symptom control/quality of life (for early relapse) and overall survival (for late relapse) may be the preferred primary endpoints, although progression-free survival should still be used in the assessment of new treatments. Whatever the primary endpoint, the ability of the study design to detect important differences in survival should be formally addressed.

[Slide]

Now we will show the answer to this question from one of the two companion articles describing the consensus conference recommendation on whether progression-free survival is an acceptable primary endpoint in this setting and the rationale for it. Quote: For Phase 3 trials in the second-line setting progression-free survival

does not seem to be a good surrogate for survival. There are several examples where progression-free survival was significantly improved, with no survival impact. It can be argued that some of these studies were underpowered to detect survival improvements. However, the weight of evidence to consider progression-free survival a surrogate for survival, and thus a primary endpoint in the second-line setting, is not strong as yet.

[Slide]

In the recurrent disease setting, overall survival remains an important primary endpoint, particularly if more costly or toxic therapy is being offered). Progression-free survival data remain of interest but are unlikely to be sufficiently persuasive to shift practice patterns. Furthermore, since the rationale for treating patients with relapsed disease is a desire to improve symptoms and thus quality of life, an adequate measure of these factors would also be an appropriate primary endpoint to randomized trials. However, no universally and acknowledge and

standardized system of symptom measurement analysis is readily available. GCIC will continue, through its working groups, to build a consensus on how meaningful improvements in disease-related symptoms can be quantified.

That completes the presentation. Thank you for your attention.

DR. MARTINO: Thank you. Next, Dr. D'Agostino will address sensitivity analysis.

The Role of Covariates in Clinical Trial Analyses

[Slide]

DR. D'AGOSTINO: The agenda has me listed as talking about sensitivity analyses. I was actually not asked to talk about sensitivity analyses but, rather, about the analyses that were done for the primary endpoint and for overall mortality. I feel like a student who says, I don't really know how to answer that question but I am going to answer some other question that I feel comfortable answering.

[Slide]

What I want to do is talk about the

analyses that were done in this study with the progression-free survival and the overall survival, and try to give you my view in terms of how we might be able to interpret it. I am going to talk about the randomized, controlled trials; the general issue of what I am going to call covariates and you will see how that fits in. Covariates are basically measures you take on an individual's age, gender, severity and how that will fit into what has been presented by the sponsor and what the FDA is dealing with. Then I am going to talk about some clinical trial scenarios that include covariate analysis dealing with primary analysis and secondary and third level analyses; and I will talk about what I think are good procedures and what are not such good practices. Then I will try and put it all in context of the present submission.

[Slide]

I am dealing with two treatments to be compared. Subjects are randomized, open-label, and it is desired to test the differences in the

primary endpoint. For example, it could be progression-free survival or time to death. As we take the individual into the study, we have a set of covariates that we measure on the individuals--again, age, gender, severity, location of the cancers, clinical sites.

[Slide]

For the general issues for use of covariates, for use of variables, in the analysis there are three different basic scenarios. Randomization is assumed to be adequate to balance the treatment groups, and we are not going to use any covariates. Basically, this is what was done for the progression-free survival. A straight survival analysis was done.

Then there is a second possible way of using covariates. This is where you say at the beginning of your analysis, in your protocol development, that you think that you need to take into account some covariates. Now, the issue why I am raising it is that the first analysis plan of the sponsor for dealing with overall survival was

basically mode number one and then later shifted to mode number two, and I want to try and put context for the two different modes that were done. Hopefully, it will become clear as we move along.

The third reason for using covariate type analysis is to balance treatment groups. That is not the major issue of the present submission.

[Slide]

In the following scenarios I am going to talk about good practices. The following scenarios have the feature of a careful analysis plan stated clearly in the protocol or in a statistical analysis plan that was developed before the data sets were locked before people started looking at the data. So, I am going to give a number of what I call good practices.

[Slide]

The first one, the primary analysis is where you think the randomization is assumed adequate to balance the treatment groups and the covariates are not used in the primary analysis. A statistical test is performed comparing directly

the two treatments with a statistical test that does not include covariates, such as a log rank test or time to death in the survival analysis. This is the primary analysis.

[Slide]

Basically this is a time-to-event. It is basically the analysis we saw with progression-free. You had two groups. You didn't bring in any covariates in your analysis. You did a straight log rank test and you got a significant result, very significant.

[Slide]

Then you ask the question, and this is where the sensitivity analysis comes in, well, would I, and do I get the same results if I start perturbating the system? Do I get the same results if I look at individuals and control, say, for initial survival? Do I get the same results if I control for the age of the subjects? This is what I mean by the covariates. You have a primary analysis, progression-free survival, that says you have significant differences. Now you want to push

it, and this is what we saw in Dr. Sargent's presentation. You want to push it and see does that hold as I start bringing in different variables and control for different variables.

Also, you look at subsets. Do I get the same effect in males/females? Do I get an effect in those who have had the disease for a while versus those who haven't? Quite often this type of analysis is done with the covariates in a Cox regression where you have lots of variables and you are trying to see if I add lots of variables to the analysis does the treatment difference still hold. In a similar fashion, you look at the overall analysis then you look at males, females; you look at age; you look at years with the condition and location of the condition, so forth and so on.

[Slide]

Now, the presentation that Dr. Sargent gave was basically this type of presentation. You look at the progression-free survival, its significant differences, and then you start dealing with subgroups. You start dealing with the

introduction of other variables. He even took it further and started changing definitions and looking at some refined subgroups and found the results still hold. That is the first and second level.

[Slide]

The third level is that sometimes you take the analysis one bit further. After you have done the subgroup analyses and after you have done all the covariate analyses you build a big multivariate model to see whether if you throw in everything all at the same time you would get significance. They didn't carry it to this level but they could have and I am sure they would have gotten that the progression-free survival holds up.

[Slide]

The second type of primary analysis--and this is where the FDA's briefing document to us and the sponsor's briefing document to us tend to differ. In the analysis that was presented on the mortality, the sponsor said that they were going to use covariates in their primary analysis, that they

weren't going to look at mortality pure and simple as the only analysis. They were going to look at mortality adjusted for covariates. I will come to some more details of that in a second. But this is the framework they had.

Here what you do, you take an endpoint like overall survival and you understand and have spent some time understanding how some of your covariates, some of your initial variables may impact on the survival. Then you do an analysis that controls for these other variables and see what happens to the treatment analysis, the treatment group analysis.

[Slide]

As a simple example just to put it in context, if you are doing a study looking at diets and effectiveness of diets, the initial weight is such an important component--people who are very obese tend to have a lot of weight that they can lose, and doing the covariance analysis, your primary analysis is really a very key and important way of doing the analysis. In the type of examples

we are talking about there is some stratification that is done right at the very beginning of the analysis or beginning of the study, and those stratification variables are thought to be important and an analysis that incorporates them might be a much more efficient analysis than one that just does the overall survival analysis.

[Slide]

The second and third level analysis after you have done that primary is pretty much the same, except that you have to worry about the a priori selection of covariates.

[Slide]

A third analysis is one that tries to handle imbalances. This was not at all the case in the submission that we have. The submission we have focused mainly on the first and second type analysis and used the treatment group alone or used the treatment group with adjustment for covariates.

[Slide]

But just to be complete here, a possible use of covariates is to adjust for balance or

imbalance in your original data.

[Slide]

A bad practice that we want to put on the board here is to have a primary analysis done in your protocol. It fails and then you go searching for covariates and you try to do an analysis that salvages your data.

[Slide]

This analysis is quite impossible to interpret. Once your primary analysis fails you can't do anything with the alpha value and also, as I said, the variability that is associated with this is usually impossible to deal with.
Again, if the overall test is not significant you can't really go beyond that.

[Slide]

So, how do we get to our particular case? What do we have in our particular case? Well, with the progression-free survival the simple log rank test worked. The subgroup covariates at definition were quite fine, and I think the results are quite clear in terms of what was presented.

When you come to survival, the survival curves wrap around each other and if you took the primary analysis. It is a secondary variable but if you took the primary analysis and the secondary variable as overall survival, you have no statistical significance so, in some sense, you stop there.

[Slide]

The sponsor took a different tack. The sponsor said that what they were going to do was to look at some variables before they did their primary analysis, or part of their primary analysis was to look at some particular variables.

[Slide]

Here are some examples. One of their variables was the ECOG variable and they found that the ECOG variable, if you dichotomized it, was significantly related to treatment. They said that they should include it in the analysis. Well, what they did is they identified--and they said it was a priori laid out--they identified a number of important types of variables. They tested them

each individually against the outcome of survival and they identified significant variables. Then they built a multivariate model. This is why I mentioned the multivariate model before. Then, in the multivariate model they looked at the difference between the two treatments.

[Slide]

They get this type of result. Here is sort of one way of presenting it. The primary analysis, if it was just a simple log rank test, failed. However, if you do the analysis that brings in the covariates first and then adjusts for the significant covariates, then you get a hazard ratio of 0.86.

Now, in the FDA document this is presented as the primary analysis. In the sponsor's document this is basically the primary analysis on overall survival. I notice that the sponsor didn't even mention this but it will come up when we talk about the third question.

What I want to point out is very important I think to point out. No matter how you interpret

the results, if you say that this was the primary analysis or this was the primary analysis because you can look at those covariates, you get different hazard ratios numerically but neither is significant and the confidence intervals are quite wide.

The sponsor did something else which was quite nice. They looked at imputation, how do you take into account missing values on the covariates, and they ended up getting 0.92. I think the important thing that we need to keep in mind as we do our discussion is that when it comes to overall survival there is no significant difference. These numbers are quite far away from statistical significance. We basically have no statement we can make about overall survival.

[Slide]

I wanted to just give you this slide to amuse you. What I usually find in these types of analyses, I will get the overall analysis not being significant. I will get one set that is not significant, but then I will get a third set that

is significant and we spend all our time arguing over the covariates that we have. In our present submission that is not the case. No matter what they did, there was no significance in survival.

I have a couple of other slides to basically round off the presentation of covariate analysis but this is pretty much what I was asked to talk about, the interpretation of the survival, the analysis plan that was put forth for the survival. I don't have the history of who was right in terms of who came up with an analysis plan. It is somewhat immaterial. Whichever analysis plan was followed, there are no survival results and, as was mentioned a moment ago, it is not a case of not having enough observations. If you multiply the number of events it isn't going to get you to statistical significance. Thank you for your attention.

DR. MARTINO: Thank you. Ladies and gentlemen, at this point we will take a 15-minute break and we will then start with the open public hearing at that time.

[Brief recess]

Open Public Hearing

DR. MARTINO: We will start now with the open public hearing. We have a microphone in the middle of the room and I believe that one speaker is going to be in a seated position, which is acceptable to us.

Before we move on to that, I need to let the group know that Dr. Sandy Levine, whom the committee knows and who is one of our members is not available here physically but she is available to us by phone.

DR. LEVINE: Thanks so much. Hello, thanks very much.

DR. MARTINO: We wish you the best. Apparently she has had a mishap.

DR. LEVINE: Can you hear me?

DR. MARTINO: Yes, we can. Thank you. As the fist speaker approaches the podium, I need to read a statement from the FDA to the group: Both the Food and Drug Administration and the public believe in a transparent process for information

gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationship. If you choose not to address this issue of financial relationship at the beginning of your statement, it will not preclude you from speaking. Please announce our speakers.

MS. CLIFFORD: Our first speaker is Zena

Itani.

MS. ITANI: Hi. My name is Zena Itani. I am actually giving this statement on behalf of Debby Bitticks who was not able to be here today due to travel complications, and whether she was meant to give the statement on behalf of her sister, Selma Schimmel who is the founder and CEO of Vital Options International, as you can see up there. I will also be giving a statement separately, representing my organization, the Wellness Community. Again, I am giving this statement on behalf of two other individuals, Debby Bitticks and Selma Schimmel.

Hello and thank you for the opportunity to be heard. My name is Debby Bitticks. I am the sister of Selma Schimmel, who is the CEO and founder of Vital Options International, the not-for-profit cancer communications and advocacy organization that produces "The Group Room" cancer talk radio show. Many of you know my sister. She had hoped to be here personally to deliver this statement to you, but is unable to do so as she,

herself, is undergoing treatment for ovarian cancer.

Neither I nor my sister have any financial interest, investment or gain associated with my presence here today, and neither Eli Lilly nor any other company has paid for my transportation or lodging.

I am here to represent my sister's voice and her testimony because she has dedicated her life to patient advocacy and meaningful cancer communications. She is a long-time breast cancer survivor and a hopeful ovarian cancer survivor as well. Like my sister, I am also BRCA positive and understand the agony of ovarian cancer, having watched our mother and grandmother succumb to this insidious disease which will claim another 16,000 lives this year.

I read you Selma Schimmel's statement: How many options are there for women with recurrent ovarian cancer? I may be among the luckier ones, but I am no less cognizant of the cycle that may rear its threat again.

Clearly, the design of the Gemzar Phase 3 trial identified time to disease progression as the primary endpoint. It was not powered to look at survival and the company met its objectives.

Recently I read an article in the "Pittsburgh Post-Gazette" by an ovarian cancer survivor where she poetically and metaphorically described the dance with NED, no evidence of disease. For the first time I know that dance. Many ovarian cancer patients do and they will receive additional treatments each time their disease recurs. So, time to disease progression as an endpoint is a meaningful measurement because it is a way to determine the true benefit of a therapy without the crossover effect from sequential therapy often seen when survival is the endpoint.

But the basis for deciding the true value or meaning of time to disease progression as the primary endpoint must also consider the human element. This is a subjective gift. Choice is our greatest option. Informed decisions are made between patients and their doctors when there is a

clear understanding of clinical benefits and risks, as well as toxicities. Women have already been receiving Gemzar off-label for some time now, and physicians will continue to do so, especially as there is growing evidence supporting combination therapy with Gemzar and carboplatin. Approved labeling will ensure proper prescribing information and informed choice.

American women facing ovarian cancer know that several European countries have already approved Gemzar in combination with carboplatin for the treatment of recurrent disease, and they expect no less here.

Time to disease progression from 5.8 months in the carboplatin arm to 8.6 months in the Gemzar plus carboplatin arm, while meaningful in clinical terms, may bear immeasurable meaning in human terms. I recall my young niece saying to my mother in the last weeks of her life with ovarian cancer, "if you die, grandma, then I don't want to have my Bat Mitzvah anymore." My mother died shortly thereafter and my niece did have her Bat

Mitzvah. But as the discussion of Gemzar approval takes place today, I cannot help but think about my mother and what three months would have meant for her, for her grandchild, for all of us. And, I cannot help to think what three months might mean to me.

Noting that there are toxicities associated with this regimen, the randomized clinical trial demonstrated that the safety profile of Gemzar plus carboplatin is very similar to that of carboplatin alone, thus, providing additional benefit without added toxicity.

Perhaps one day we will have the ability to see a significant increase in the cure of ovarian cancer, but today we must hope to at least increase time to progression and prolong survival. Gemcitabine is amongst the limited arsenal to offer such hope.

I respectfully appeal to the distinguished members of ODAC to consider the ethical responsibility to vote for a positive decision to approve this additional treatment option for women

with recurrent disease. And, I thank you for allowing my sister to represent me so my voice could be heard today. Copies of this statement from Selma Schimmel and Debby Bitticks are available to anybody who might want it. Thank you.

Again, I am Zena Itani. I am the director of patient education at the Wellness Community, and the following statement is made by myself for the Wellness Community.

Good afternoon and thank you for allowing me to be here today. My name is Zena Itani and I am the director of patient education and outreach for the Wellness Community, an international non-profit organization that provides support, education and hope to people affected by cancer. For the record, the Wellness Community receives unrestricted educational funding from Eli Lilly. However, we received no funding or compensation for my presence here today.

The Wellness Community offers free programs, including professionally-led support groups, educational seminars, nutrition workshops,

and mind-body programs among others. Our mission is to help people living with cancer regain a sense of control over their lives, feel less isolated, and restore their sense of hope for the future, regardless of the stage of their disease.

Last year, we reached more than 150,000 people with cancer and their caregivers, including numerous women with ovarian cancer. Through the Virtual Wellness Community online, we were able to connect with even more women fighting ovarian cancer.

At the Wellness Community we have learned a great deal from those we support, and we believe in the importance and value of an educated and empowered patient. People with cancer often feel stigmatized, alone, and overwhelmed with grief. They feel stronger and more hopeful when they have more treatment options available to them and are empowered with knowledge about those options to then manage their cancer with their healthcare team.

Women with ovarian cancer usually deal

with multiple recurrences of the disease over the course of their lives. Knowing that there are multiple treatment options for them to try with each cancer recurrence gives ovarian cancer survivors hope for the future. With an estimated 22,000 women newly diagnosed with ovarian cancer in 2005, we need an array of treatment options more than ever, as well as access to those treatments and clear information about possible side effects and toxicities.

We have the opportunity here to expand treatment options for women with advanced ovarian cancer, prolong their survival, and increase their quality of life. Today I ask you to consider the circumstances of women battling advanced disease and realize the power of providing all possible treatments and, thus, hope to these women and their loved ones. The Wellness community feels strongly about supporting ovarian cancer survivors and their families in their quest to live well with the disease. Please take a leadership role in providing that support by approving a broader range

of treatments for advanced ovarian cancer and encouraging patients to be informed, empowered and optimistic about the possibility of longer and healthier lives. Thank you.

DR. ASHKAR: Good afternoon, everybody. My name is George E. Ashkar, retired research physicist. First, I find out that cancer research and development is upside down. When I finished my doctorate degree in chemical physics I decided to start research in cancer. First I wanted professional advice so I asked a doctor, do you know what is cancer? He said no. I asked do you have cure for cancer? He said no. I thought I was asking the wrong person. Then I asked what kind of specialist you are? He said expert oncologist--difficult to believe what he said.

I have no medical education, no medical background, no medical experience. But I have knowledge in physics, common sense and correct judgment. So, I decided to start from ABC of medical science. What is disease? Disease starts when bacteria or virus invade human body and start

to damage human body cells. Damaged cells give us symptoms of the disease. To cure the disease we have to eliminate the causation, what is causing the disease. In this case bacteria or virus. When we eliminate the bacteria or virus, actually we eliminate causation and disease will be cured--very simple judgment.

Expert oncologists, instead of destroying the causation, carcinogen which causes cancer disease, decided to go the easy way, destroy cancer cells which are the victim of the carcinogen. That is not the reason. After a hundred years there is no cure and we are still continuing treatment in the wrong way. How you can cure disease by leaving carcinogen inside the body and destroy cancer cells which are the victim of the carcinogen, not the problem? By destroying cancer cells you can eliminate the symptoms, not disease.

I do not understand what kind of education expert oncologists are getting from medical schools. What expert oncologists are doing is 100 percent wrong. What expert oncologists are saying

is 100 percent lie. How long can this continue this way? When politicians lie it is normal because they are born to lie. When President George Bush lied about Sadam Hussain and invaded Iraq, the result was 2000 young American soldiers died, 15,000 became invalid, 10,000 Iraqi people died. But when expert oncologists are lying millions of people are dying.

Drug treatment must be stopped. Enough is enough. Let's correct the problem. I would recommend to the Oncology Drugs Advisory Committee to stop approval of any drugs intended to be used to cure cancer and recall all the drugs approved before.

The National Caner Institute has the duty, responsibility and obligation to find cure for cancer, but from the first day of establishment of the Institute in 1937 I heard lie, lie, and they are still lying. They never even tried to find a cure for cancer. In 1973 President Nixon gave the National Cancer Institute 35 billion dollars and said in 25 years you have to find a cure for cancer

and eradicate it from the surface of the earth. Management of the Institute misunderstood what President means. So, they eradicated 35 billion dollars from the surface of the earth and at the end of 25 years, in 1998, the result of the research was this: cause of illness with no known cures.

I like to compare my research. I needed one week or seven days, which is shorter time, and a one dollar budget to develop natural infection absorption method to cure cancer 100 percent. United States is becoming liars country, lying about cigarettes causing lung cancer, which never has happened. My father started to smoke since 12 years old and died 80 years old; never had cancer in his lung and nobody can prove that cigarette is causing lung cancer. Amount of cholesterol causing heart attacks, which is a big lie also. Even they do not know why HDL is good, LDL is not good. Statistics show that 80 percent of dying from heart attack because of cholesterol, they had normal, 125 or less cholesterol in their body. But people

having 400 and more never died from cholesterol-related heart attack.

If the Oncology Drugs Advisory Committee needs or wants--or National Cancer Institute or any institution involved in cancer research, needs explanation I am willing and ready to participate, to visit their institution and explain what is cancer and how to cure it 100 percent. I can give you my web site address to get more information.

To understand what National Cancer Institute is doing, I want to tell you Russian joke which describes exactly their work: A Russian young man is walking in the streets of Moscow at night, at bus stop he notices an old lady looking for something. He wanted to help her. He approached and asked what you are looking for, lady? She said I dropped my bus token; I cannot find it. He said just a minute, I find it for you. He looked around, could not find. Then, asked again, where exactly you dropped the token? She said over there. Then he asked why are you looking here, not there? She said because over there it is

dark, I cannot see. Here I have spotlight, I can look, I can see because there is spotlight.

No matter how many people are employed, they will never find any cure since they are looking in the wrong place. I tried for 25 years to tell them to correct the direction of the research. Nobody wanted to talk to me or meet me. I treated with my treatment method, natural infection absorption, about two dozen people, 100 percent. And, as today, 200 people being treated all over the world, in Europe, in Russia, in Armenia, in Canada, mostly in Los Angeles area.

Myself, in September, 2003 I had pancreatic cancer. After five and a half hour surgery, five doctors participating in surgery, they gave up hope to save my life. They asked my wife to prepare funeral for me. So, my wife come to me and said, George, what are we going to do? We have not enough cash in the bank for funeral. I said what for? They are recommending me to prepare funeral. Ah, very simple, I said, if we don't have money I will not die and I didn't and now I am

here. Thank you very much.

Questions from the Committee

DR. MARTINO: Thank you. We will now have some time for the committee to ask questions of either the FDA or Eli Lilly. Go ahead, doctor.

DR. CHESON: I am really kind of troubled by this. This is a study looking at progression-free survival as the primary endpoint. A study that meets its primary endpoint I think should be considered a positive study and approved. The problem here is, as we have been shown, that if you are going to look for an endpoint you have to look at the endpoint and you have to measure it, and it seems that this was not done in a sufficient number of patients to satisfy me and probably some of my colleagues.

My question is do we have any idea of the relative frequency of assessment, by whatever these means were, in the two arms? In other words, did everybody get measured every two months? Is there a substantial difference? Because, obviously, if one arm gets measured every three months and the

other arm gets measured every two months there is a full month difference in time to progression, not that it is going to make a lot of difference since optimal means of measuring response weren't used in an adequate number of patients, but I would at least like to have that question answered.

DR. MELEMED: I think you are looking at investigator bias and we can actually have Dr. Sargent address that. Dr. Sargent?

DR. SARGENT: We have examined the frequency of assessment both in the on-treatment period and in the off-treatment period.

[Slide]

While patients were on treatment patients were examined every six weeks, which was exactly per protocol. When they were off treatment they were examined every eight weeks which, again, was per protocol. And, this was well balanced between the two arms so we don't see any evidence that patients in one arm were assessed more frequently than the other.

With respect to how patients were assessed

and how they were deemed to have progression, we see that in the on-treatment period we have greater than 90 percent of patients who were assessed and progressed via objective measures, and in the post-study period we have 80 percent of patients assessed similarly. So, the great majority of progressions were, indeed, based on objective measurements which would be either new lesions or measurements of existing lesions.

DR. CHESON: Do you mean ultrasounds and CT scans or do you mean physical examination?

DR. SARGENT: I will have Dr. Melemed discuss the details of the assessments.

DR. MELEMED: To address this I will go to what was seen at measurements at baseline.

[Slide]

You can see that at baseline around 65-70 percent of patients had CT scans, and they were followed by the same methods throughout the study. We also had around 25 percent who had ultrasound, and then a small percentage had physical examination. We also had MRIs. The same methods

that were addressed at baseline they followed throughout the study. So, the majority of the progressions were by radiological imaging.

DR. MARTINO: Dr. Hussain?

DR. HUSSAIN: I have two questions, one for the sponsor and one for the FDA. I am going to ask the sponsor, so gemcitabine is out on the market. In real terms, what is the difference if we vote yes or no today to the patients because access is available to the drug? If I can follow-up afterwards with the FDA?

DR. MELEMED: The main reason for coming forward today is really to get better awareness of the drug, and we think it is important that patients have the appropriate information to know what their options are, and by actually having is as a label information can be available to these women to make that choice.

DR. HUSSAIN: To follow-up, you know, so I am a GO oncologist and I do bladder cancer as part of what I do. Gemcitabine has never had, to my knowledge, an indication of bladder cancer, yet the

information is out there and everybody is using it. How is this any different?

DR. MELEMED: Again, the more information we can give to women, the better we can actually have them address these issues. We can address it only by publications and, of course, by labeled indications, and by having a labeled indication I think we have a better chance of truly getting the information so women have the appropriate options and information.

DR. HUSSAIN: But there will not be an impact in terms of insurance reimbursements or insurance refusing to pay for patients? There would not. So, the issue is advertising, more so than actual real impact on the patients because the doctors, I would imagine, will see this information published and, as per usual, it is not the patient who is going to read the article but it is the doctor who will read the article.

DR. MELEMED: Again, I think information is a good thing to have for patients and I don't have anymore to add.

DR. HUSSAIN: Thank you. Can I follow-up on the FDA question? I wanted to ask the FDA members, in the last two years there was a lot of discussion back and forth on progression-free survival and its suitability for approvals. In this case, it sounds to me that you don't like what was being presented. You are not questioning that it is a positive study. So, it is clear there is a progression-free survival difference. It is clear that there is no survival advantage. No matter how you slice it, it is not there. And, I guess my question is what makes this different than another study where you would accept progression-free survival? Is it because it was not done with the rigor that you would like it to be done, or is it that in this setting this kind of endpoint is unacceptable? In all fairness, it sounds like the consensus criteria came after the study was designed I would imagine because it is not likely that they knew that information beforehand.

DR. WEISS: I am going to start but then I am going to ask my other FDA colleagues, who are

more intimately familiar with the trial, to also respond. In some settings PFS is an adequate outcome, and in itself is an outright endpoint for an approval. There are a number of factors to consider, including I think the magnitude of the effect; the toxicity of the therapies; the particular scenario that you are dealing with. In this case, the question that the committee is going to be addressing when you get to question three is really the heart of it, the finding of a persuasive effect on PFS in itself without evidence of overall survival which, of course, you would like to have seen. Oftentimes, it is because the data aren't mature enough. In this case, as has been shown, that isn't the issue. There is no effect on overall survival.

So, the question in this setting I think is what does this mean. Clearly, there are times when PFS is acceptable. Sometimes it is acceptable as an accelerated approval outcome. Sometimes it is acceptable in itself as an outright outcome. And, it is a real dilemma I think that, you know,

we are asking this committee for their thoughts on.

DR. HUSSAIN: But I don't understand how you make a distinction from one disease to the other. Why is it okay in one cancer to have a progression-free survival endpoint but not in ovarian cancer? That is my question. What is the criteria that you use? Because those criteria can't be shifting depending sort of on the mood of ODAC. It has to be some solid criteria.

DR. JOHNSON: Well, whether progression-free survival is an acceptable endpoint for approval is really specific to the disease setting. Specifically, FDA has accepted progression-free survival as an adequate basis for approval in lung cancer and in colon cancer, and the FDA did that because of a recommendation by this committee, and I think the main reason that the committee made that recommendation in those two specific settings was that progression-free survival in each of those settings was considered a surrogate for survival, and there was quite a lot of data and randomized trials were presented. Some

of them were presented by Dr. Sargent, who is here with us today, that indicated that in those conditions progression-free survival was a surrogate for survival. That is not the case in the second-line ovarian cancer setting, as far as we know.

DR. MARTINO: I would like to ask the next question to Dr. Ozols. Given a patient who has relapsed with ovarian cancer, and let's say they are a year beyond when they finished their chemo., what options do you feel you can offer them at this point? What do you say to these ladies?

DR. OZOLS: Well, I think for a woman who has relapsed a year after initial treatment what we are looking for is really trying to prolong her life. We would like to. We certainly would like to prevent any symptoms. And, in that group of patients the toxicities are also very important so when we are talking about treating that group of patients we want to prolong their lives if possible. We want to prevent the disease from progressing. We want to alleviate symptoms. These

women will frequently have some residual effects of their previous treatments, such as neuropathy. They also will have had their hair grow back. I think in that group of patients to offer them an option where neuropathy is not going to get worse; where their hair loss is not going to be a problem I think is an important consideration for the women to have.

In this group of women, again, with a disease interval that long the primary drug that we use is carboplatin. I think the data we have from today's presentation and from the ICON study is that adding something to the carboplatin is, in fact, better. The carboplatin/Taxol in the ICON study was a different group of patients. The survival issues there I think are somewhat blurred. It is a different population than we treated here. I think all of us in practice would offer patients a carboplatin-based regimen if they had a disease-free interval that long, and I think carboplatin/gemcitabine is a good option for those women to consider when hair loss and neuropathy are

particularly important issues for them.

DR. MARTINO: Be a little more specific for me. I appreciate the point that a carboplatin-based program is what you would tend to offer them at this point. I want to know what other options specifically you really would offer them.

DR. OZOLS: Well, outside of a clinical trial I think the consensus is that you would retreat them with carboplatin. Carboplatin is the most active drug in this disease and in the platinum-sensitive group of patients I think all of us would use carboplatin. I think there are some studies, as was mentioned, with Doxil but that was a subset analysis where it looked like there was some survival benefit in patients who were treated with Doxil. But that was compared to topotecan. It wasn't compared to carboplatin.

For example, in GOG we feel that in a group of patients who have a disease-free interval of that length the primary treatment for all clinical trials should be carboplatin-based because

we think the evidence supports that it should be carboplatin-based chemotherapy. I think these two trials that were talked about today support combination as being better than single-agent carboplatin. I think that is a paradigm shift and we are all using carboplatin combinations. Again, I think that carboplatin/gemcitabine is a good option for a significant group of patients for whom that may be a preferable option than carboplatin/paclitaxel.

DR. MARTINO: There are members of the committee that take care of these patients. Could I hear your answers to that same question, please?

DR. NERENSTONE: First I have a question for the sponsor. There was no mention made of what happened to patients who had carbo. allergies and, certainly, in clinical practice this is a significant problem. In either group, how were they dealt with? We don't see them as reflected in toxicity.

DR. MELEMED: Overall, the incidence of allergic reaction to either carboplatin or the

combination was minimal. That is we didn't need the slides. So, we did look at that but it was a very rare occurrence.

DR. NERENSTONE: Just to get back to what the chair has asked, my concern with this study is that without a survival advantage I would want to know what sequential treatment does. We are in a setting where patients are not cured. We are looking for long-term palliation. If you look at the carboplatin dose that was used, it is an AUC of 4, which is rather low. Gemzar, at 1000/m

2

is

certainly adequate and may be even more than many of us give. But I wonder about an AUC of 5-6 of carbo. followed by Gemzar at the time to progression.

We certainly know in breast cancer that increased response rate is often seen when you use combination chemotherapy and that very often it does not improve survival. So, I think there are a lot of us who treat a lot of patients with ovarian cancer and other cancers who tend to use sequential treatments until there is a clear survival

advantage using combination because it is more toxic.

DR. MARTINO: Dr. Long, do you want to respond as well?

DR. LONG: Yes, Madam Chairman. Specifically, what we do in practice is a sequence of single agents. We have the luxury in ovarian cancer of having six to eight single agents, each with activity. So, if the patient responds sequentially it may buy them, you know, two to three months with each drug and until you have run out of drugs you have improved survival. So, I think that creates the dilemma that FDA is looking at, that you have at least a half dozen drugs that may add two months to the median survival each, and if the patient responds to each of the drugs you will dilute survival advantage when you are looking at second-line therapy with a combination.

This is not unlike what you see with lymphoma and with breast cancer where you have multiple salvage agents that can prolong survival as well as response. So, you know, I think in this

particular population progression-free survival would be reasonable. In my personal practice we have many patients who get through six or eight different single agents. One of the problems that you run into with gemcitabine is that it is non-label and it took a while to convince our Medicare carrier to cover it. We have that same problem with several other agents that are used sequentially that are effective agents but are non-label. I think a single-agent label is important. Whether the combination is something that I would use in practice, that is a different story.

DR. MARTINO: Dr. D'Agostino?

DR. D'AGOSTINO: My question was already answered. I was concerned that where we have that progression-free survival, those are settings where it did show itself to be a surrogate and I just wanted that on the table, but it was already mentioned.

DR. MARTINO: Dr. Melemed, I realize you are up there. Is there something you want to say

or can I ask you a question?

DR. MELEMED: Yes, I was wondering if I could have Dr. Thigpen address the comment regarding sequential therapy and combination therapy.

DR. THIGPEN: First of all, I think that it would be fair to say that we all agree with Dr. Long in one respect, that sequential single agents probably would yield the same overall survival as combinations of drugs. However, our general philosophy at our institution is to try to get people into a response as quickly as possible, hopefully, a clinical complete response, which is distinctly possible in this patient population, particularly in those patients who have a longer treatment-free interval. If you can get them to a clinical complete response you can stop treatment and they get better time off all therapy.

What the GOG found out in the study I cited in the close of the core presentation, Taxol versus cisplatin versus Taxol/cisplatin, was that when you received the doublet you accomplished in 6

cycles in therapy what it took you 12 to 18 cycles of therapy to accomplish if you gave them sequential single agents. So, the patient had substantially longer period of time off all treatment and a complete remission even there was ultimately no difference in overall survival. So, I think we need to keep focused on the issue that a longer period of time off treatment is a clear benefit to these patients so they don't have to be subjected to the toxicities of treatment.

DR. MARTINO: I would like to ask a question of the sponsor related to the toxicity. It does appear that combination has more hematological toxicity, which one would expect, and that requires some additional assistance to these patients in terms of transfusions and growth factors.

If I remember the data correctly, I also had the impression that there were more hospitalizations that occurred in the combination arm. The question I would like answered is can someone give me a sense of the number of days

hospitalized on the two arms?

DR. MELEMED: Yes, Dr. Gralla will discuss the hospitalization by days.

DR. GRALLA: Again, I think there are several reasons to look at this important question. First of all, it is true that the rate of hemorrhage and febrile neutropenia was only two percent versus one percent so the really meaningful aspects were very low.

If we look at the total number of days of hospitalization for febrile neutropenia, it was 11 days total. For 178 patients only 11 days were spent in the hospital for febrile neutropenia.

The leading reasons for hospitalizations were drug administration. This shows a difference between European practice patterns and ours, and social reasons. You know, it takes about an hour to give the combination chemotherapy so this is not something that really would occur here. After that come study tests and then for other drugs.

Interestingly, transfusions were more common on this arm, although platelets were not

much more common, 8 percent versus 3 percent of patients got platelet transfusions But for RBC or whole blood transfusions there is 30-some odd percent versus about 15 percent. They also hospitalize for transfusions. The average patient got about one unit of blood. Therefore, these are also aspects of what we would do an outpatient basis.

So, for adverse reactions which were study drug related very, very few patients that were hospitalized. I think if you look at the fact that febrile neutropenia admissions were two patients our of 350 for the whole study, two out of 178, my guess is the average general oncologist, if he or she gave a fair amount of gem/carb would probably never hospitalize in their career more than one patient as far as this is concerned.

DR. MELEMED: If it is okay, I would like to have Dr. Pfisterer discuss some of the reasons for the transfusions since he is the PI of the study.

DR. PFISTERER: In 1999 until 2002 when

the enrollment of these patients was done, there were no transfusion guidelines in Germany. Usually German physicians and also the investigators of this trial are trained to give a transfusion at a hemoglobin level of 10 and less. So, this may be a difference to common practice in the U.S.

DR. MARTINO: Yes, Miss Haylock?

MS. HAYLOCK: I wanted to ask if Dr. Gralla would discuss the issue of neurotoxicity and specifically peripheral neuropathy? I know so many ovarian cancer patients or ovarian cancer survivors who have not just three or two go-arounds with chemotherapy but maybe have one every year and they are surviving for 11-plus years. But one of the problems with each subsequent time is that they get more neurotoxicity and, as far as I know, that is one of the major effects on their quality of life. It kind of distresses me that some of these patient benefits are sort of being dismissed. Could you talk about that just a little?

DR. GRALLA: Thank you for the question. I agree with you. The point about neurotoxicity is

that, unlike emesis where emesis has a terrible complication but goes away in a few days to a week, the neurotoxicity can stay with a patient for the rest of their life. So, this is a serious, serious issue that can have an effect.

As you saw, almost 20 percent of all the patients presenting for this protocol had preexisting peripheral neuropathy. Fortunately, it was not increased on the gemcitabine/carboplatin arm.

[Slide]

So, I think when Dr. Ozols mentions that the combination regimen is of great interest and that basically this would be something to see, you can see that there really is very little difference in the total amount of neuropathy that is seen on these two.

With carboplatin there is some risk of neurotoxicity and overall, as you saw, for all patients there was only about 1-2 percent neuropathy issue here. So, this is an important factor. To look at it overall, it is not going to

have all that much of an effect for one arm versus the other because there is very little neuropathy in here. But patients who have grade 3 neuropathy end up with a very poor quality of life. So, avoiding that in subsequent areas is important.

May I make one other comment based on the earlier issue of why get a supplemental NDA, why get a drug approved once you have it on the market? I think that the problem there is that if we ever get a drug on the market, say, for a rare tumor type, there is then no impetus to study it further. For those of who have been on guideline committees, to be able to have really evidence-based medicine I think it is so important to really have not only the studies out there, but also to have the drug go through a panel like this for approval when there is evidence to approve it when the primary endpoints are met.

I think it is interesting to look at the quality of life of all of these patients. The original design of this trial was not one that we might have used. It was within arm so they used

the patient as her own control. Those patients on the gemcitabine/carboplatin arm did have a significant improvement in their overall quality of life versus the comparator single agent arm.

This is not the way that we would design a study today, especially since we have a concurrent control arm as far as that is concerned. But there is something to say that this might be a reasonable way of looking at it. Thank you.

DR. MARTINO: Question from me to the FDA, I think I am asking the same question that you are asking us in your first question, which is are there alternatives in this setting that have shown a survival advantage? Now, the two things that have been placed up there were the Doxil trial and then the ICON trial. Can one of you re-describe the ICON trial to me because I am getting the impression, at least from what Dr. Ozols says, that when he is faced with such a patient, somehow that information doesn't impact on him, that he basically is using single-agent carbo. and now he is looking for something to add to that

single-agent carbo. I need to understand that.

DR. JOHNSON: I can describe the trial again. It was a randomized trial comparing combination of Taxol and carboplatin with conventional platinum-based chemotherapy without a taxane. These patients all had recurrent advanced ovarian cancer after platinum-based chemotherapy and were still platinum-sensitive. There were 802 patients. The hazard ratio for death was 0.82 and the p value was 0.02 favoring Taxol/carboplatin. What is it you don't get about it?

DR. MARTINO: You have given me the information I was interested in. Now I would like to ask Dr. Ozols if, in fact, we have shown a survival advantage to that combination why do you not use it routinely? What goes through your mind to make you not use it?

DR. OZOLS: I didn't say I don't use the combination. I wanted to point out that that trial is different than the OVAR study. In the ICON study more than half of those patients never had taxane as part of their initial treatment. In the

U.K. when that study was started, many of those patients never had combination chemotherapy with taxane. So, that is one big difference.

The second difference is that many more of these patients in the ICON study had more than 12-month of disease-free interval compared to the 6-month disease-free interval, and there is a continuum as far as the response goes in that group of patients for length of disease-free interval. They also had less volume of disease than we saw in the OVAR study. So, this was a more favorable group of patients, and I think a group where it was easier to show that, in fact, there was an improvement in survival because they had a very long disease-free interval and they had never receive prior taxane, and when they got the taxane together with the carboplatin there was certainly the potential that you could more easily see that improvement in survival.

So, what I am saying is that I think the paclitaxel/carboplatin is, in fact a good option for patients who have platinum-sensitive recurrent

disease. There is a subset of patients, for sure, who will still have preexisting neuropathy and I think patients need that option, that choice of having another alternative, such as gemcitabine/carboplatin, particularly when neuropathy and alopecia are major issues for that patient. If you ever did a randomized trial of gem/carbo versus Taxol/carbo--I am not saying to do that, I don't think that is a good use of patient resources, I would be extremely surprised--I mean, I just can't believe that there would be a difference in survival between those two regimens in platinum-sensitive recurrent disease.

DR. MARTINO: Thank you. Dr. Perry?

DR. PERRY: Bob, just a quick question, what do you consider first-line therapy for stage 3 ovarian cancer outside of a clinical trial?

DR. OZOLS: I think for sure the overwhelming consensus, again from the consensus conference that we had that we talked about earlier and from every clinical trial, and I think there are about a dozen clinical trials that are ongoing

in the world looking at new combination and new treatments for ovarian cancer, they all use paclitaxel and carboplatin as a standard against which to judge new regimens. So, I think it is pretty universal that the carboplatin and paclitaxel--some people would argue that it could be Doxil/Taxol but I think 90 percent of people are really being treated with carboplatin and paclitaxel and some with a taxane.

DR. PERRY: So, the argument that Taxol/carbo is a good second-line therapy is I think somewhat abrogated by the fact that it is currently used as the first-line therapy. The argument that we have a good second-line therapy with Doxil is I think abrogated by the fact that, so far as I am aware, there have been no cures with doxo. Is that correct? Anybody here have a cure with doxo chemotherapy? So, what we are talking about then is another palliative therapy for women with relapsed ovarian cancer.

DR. MARTINO: Dr. Long, do you have a

comment you want to make or a question?

DR. LONG: No, I think Dr. Perry summarized that nicely.

DR. MARTINO: Mrs. Solanche?

MS. SOLANCHE: As a patient representative, I can't get over the fact that there is no survival benefit. I find it hard to believe that we are going to consider a drug that has no survival benefit. The drug is already available for those physicians and those patients who think that this is a good drug for them, and it may well be on an individual case-by-case basis. But if we are going to give the FDA an imprimatur to this particular combination as the second-line treatment, I think we are giving it to a drug that has not earned it yet, and I think it is time that FDA and the drug industry in general raise the bar on what is a satisfactory, let us say, drug rather than lower it with kind of "me-too" drugs that we tend to see, each drug being judged against another drug that is kind of "oh, well, it's okay" but it has not been shown to have a great survival

benefit.

DR. MARTINO: Dr. Nerenstone?

DR. NERENSTONE: In some ways I would like to echo that but in a little different way. Those of us who treat ovarian cancer know that Gemzar is active. My feeling is they asked the wrong question and they didn't necessarily have the right comparative arm, and that is my dilemma. My question to the FDA--and I agree with your concern that if we give it FDA approval for first-line recurrent disease in combination with carbo., those people who don't treat a lot of ovarian cancer will think that is the standard arm because that is going to be one of the only combinations approved.

So, my first question is if we vote for approval-- recommend because you, guys decide, if we recommend approval can we change the wording a bit to say either single agent or in combination with carboplatin, or does it have to be exactly the way they have asked for it?

DR. WEISS: I think we have a great deal of latitude in terms of how to write indication

statements. We like it based, of course, on the data before us and the application, but it is not uncommon for final indication statements in the label to be other than what was initially proposed to us. What we were showing you is what the sponsors actually proposed.

DR. NERENSTONE: And I have no problem with Dr. Thigpen and my disagreeing how to treat these patients. But I do think that having a secondary indication is important because there are some insurances that it is a hassle for some people to get, and it does reinforce that the drug companies are doing the right thing. They are looking at these drugs that are being used in patient populations for which they are not indicated, and they are doing the research, and I think they are to be commended because I think that is valuable information.

DR. MARTINO: I need to clarify what I think I heard from the FDA. As I understand it, this committee's questions today can only really deal with this issue of this study and this

combination, not whether the agent should be approved in and of its own as a distinct drug.

DR. WEISS: That is right. We have not asked that question. Certainly, we can take your advice and consideration but I think we would have to have some additional discussions with the company about what kind of data they might have in terms of single-agent data. It was not proposed, I don't believe, in the application in that manner. But I think the more general question is that we do not have to have an indications statement exactly as proposed by the company. It is usually the exception to agree exactly on the wording of indications statements.

DR. MARTINO: I will take one last question and then I am going to the questions. Dr. Hussain?

DR. HUSSAIN: I wanted to ask the ovarian experts, in the United States when we are using Taxol and carbo as front-line, what drugs prolong survival in the second-line? I mean, that is what they are asking us here but I don't think I heard

that in the setting in the United States. When you are using Taxol front line and now you are faced with a relapse, are there data that say drug A, or B, or C or combination in fact prolong survival? Because that really goes to the heart of the first question and I don't think we heard any information on that.

DR. LONG: I think we heard the data from ICON4 that Taxol and carboplatin do improve survival over carboplatin alone as second-line therapy. But I think Dr. Ozols has pointed out that 20 percent of patients had substantial neurotoxicity before they were given that option and, as a practicing oncologist, I have to decide whether I want that patient to be wheelchair bound and survive four months longer or to go to second-line therapy with something that is less neurotoxic, and most of the time I will go with sequential single agents in that patient rather than give her more neurotoxicity with taxane.

DR. HUSSAIN: But this is in the setting of second-line after having seen carbo/Taxol in the

first line?

DR. LONG: That is correct.

Questions to the Committee and Committee Discussion

DR. MARTINO: At this point then I am going to turn the committee's attention to the three questions that have been placed before us. Does the FDA actually wants votes on each of these three, or do you want a vote for number three?

DR. WEISS: I think number three would be adequate, question number three.

DR. MARTINO: All right. I am going to read the first two questions. If any of you feel the need to address them, you may do so, and then I will move you on to the actual final question.

Number one, does the committee agree that there are chemotherapy regimens that have been shown in randomized controlled trials to prolong survival in the patient population for the proposed indication, that is, patients with advanced ovarian cancer that have relapsed six months or more after completion of platinum-based chemotherapy?

Do we need further discussion on this

question?

[No response]

Thank you. Number two, if given after progression, subsequent chemotherapy or crossover may confound survival analyses and may obscure the demonstration of a survival improvement. Are there chemotherapy regimens that have been shown in a randomized setting to prolong survival if given after progression in the same patient population as in the Gemzar trial?

I think we are getting to the issue of whether the fact that patients received additional therapy may have simply made it impossible for us to see survival advantage. That is the question. Does someone wish to address that? Seeing no one interested in that question, we will move to the question.

The question is very simply, is the demonstrated increase of progression-free survival, without an effect on survival and with the observed toxicity, a sufficient basis for regular approval of Gemzar in combination with carboplatin for

treatment of patients with advanced ovarian cancer that has relapsed at least six months after completion of platinum-based therapy?

For this we will need discussion and a vote. I will take discussion at this point. Does anyone have anything else they need to say? Yes?

MS. HAYLOCK: I just want to comment that the study itself, the data that were given has participants from all these other countries where treatment is totally different, or at least in how they use growth factors in particular. So, I think the toxicity revelations from this study are kind of irrelevant for practice in the United States.

DR. WEISS: What is the question? Would you have expected it to have been better or worse then? We are trying to extrapolate to the U.S. population.

MS. HAYLOCK: I would think with the growth factors we would have less hospitalizations and less hematologic toxicities.

DR. MARTINO: Then we will start the voting, and as you vote on this question, I need

your name stated and your vote. Again, it is for full approval that we are voting, not any form of conditional approval. I am going to start first with Dr. Levine, who I am hoping is still on the pone. Doctor, do you have anything you need to say or are you ready to vote?

DR. LEVINE: Forgive me, I didn't have the time to just throw in a question. I just have two questions and if that is not appropriate, then forget it. I don't think it is appropriate for me to vote, and I am not, but my questions were two-fold. If you want to forget it, go right ahead.

My first question to the FDA was why was the quality of life data not considered by Dr. Cohen? Why was that not considered important or clinically relevant? My question to the company was why did you not seek external independent review on the progression-free survival? What was your thinking? You got it on the objective response rates and so forth, but your endpoint was progression-free survival. I wondered what your

thinking was.

DR. MARTINO: We will take your questions, doctor, and FDA may answer the first question which is the issue of quality of life. Why is that information considered unimportant in this analysis, or invalid, or however you wish to think about it?

DR. LEVINE: Dr. Cohen said I think not clinically relevant.

DR. COHEN: Well, there were several issues. First, generally when we look at quality of life we prefer blinded studies because that would eliminate investigator bias in quality of life. A second issue in this study is that quality of life went both ways. In most comparisons the Gemzar/carbo was better. In other areas, fewer carbo alone was better. Third, a lot of these statistical analyses of quality of life were post hoc and they weren't in the statistical analysis plan of the document that we originally received.

DR. LEVINE: I see. That answers it really.

DR. MARTINO: The next question will be answered by Eli Lilly.

DR. MELEMED: When we initially designed the study we used the cooperative group, the AGO, as our source and it was not standard of practice to do independent assessment at all. Eli Lilly requested additional assessment to be done, which was really to investigate investigator bias. Again, the primary endpoint was progression-free survival which was accepted by the AGO, which has resulted in global rules around 50 countries but, again, the main point was the added additional assessments to actually get a better idea of investigator bias, and that is why we did that.

DR. LEVINE: Thank you.

DR. MARTINO: Dr. Levine, we accept your decision to not vote and we will take that as an abstention. Dr. Nerenstone, we will start with you, please.

DR. NERENSTONE: I sort of feel like I am on the horns of a dilemma. As I said, I really feel very strongly that this drug is active in

ovarian cancer. I think this is a very relatively poorly designed study, I think of two-month progression-free survival, with soft endpoints of progression-free survival, because there can be investigator bias. In ovarian cancer it is not as clear-cut as lung cancer; it is not as clear-cut as other cancers, and where progression-free survival may not be the correct surrogate for survival, I have a very hard time approving this with full approval. It is giving the FDA an imprimatur on the study for saying that this should be the first-line treatment used in recurrent disease. And, I just don't think the data is there to give that kind of resounding approval. So, my urging to the drug company would be to come back, let us approval it as a single agent and let the doctors figure how to use it in whatever setting and whatever way they want to, and let the cooperative groups figure that out. But this study itself is very disappointing so I would say no.

DR. D'AGOSTINO: D'Agostino, I vote no. I am very concerned that there isn't a real

indication of progression-free survival as a surrogate for survival and I think that would be needed in order to get a yes vote. So, my vote is no.

DR. HARRINGTON: Harrington, I vote no.

DR. PERRY: Perry, I vote yes.

DR. MARTINO: Martino is having a very hard time on this one. Oh, I am sorry.

DR. RODRIGUEZ: With regards to the progression-free survival I concur that it would be no. In reference to the issue of neuropathy as an alternative single agent for people who cannot tolerate other neuropathic drugs, I think that it should be strongly considered.

MS. CLIFFORD: Is that a yes or a no?

DR. RODRIGUEZ: For the totality of approval, no, but I think there is ample evidence that it is an available and usable drug in patient subsets.

DR. MARTINO: I am taking that to be a no vote to the question, doctor. Correct?

DR. RODRIGUEZ: If the only question is

about the evidence presented here convincingly that this should be the premiere second-line treatment, the answer is no.

DR. PERRY: No one is saying, unless I heard things incorrectly, that this is going to be approved as the only second-line drug or the first second-line drug. It is approved as a second-line drug. Have I missed something? A combination, but has anybody said it is the combination or it is mandated?

DR. CHESON: The approved combination.

DR. PERRY: Well, an approved combination.

DR. CHESON: The approved combination.

DR. PERRY: Topotecan is approved too--

DR. CHESON: Not in combination.

DR. PERRY: So, pick your poison, literally.

DR. MARTINO: Having struggled and heard all of you struggles, my answer is going to be no.

MS. SOLANCHE: Solanche, no.

DR. HUSSAIN: Hussain, no.

MS. HAYLOCK: Haylock, yes.

DR. REAMAN: Reaman, no.

DR. CHESON: Cheson, again concerned about the way the study was done, no.

DR. MARTINO: The vote is 9-2, no being the winner, and one abstinence, Dr. Levine. With that, I thank you all and you may now leave and get to the airports. We wish you all the best.

[Whereupon, at 4:25 p.m., the proceedings were adjourned.]

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