UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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ONCOLOGIC DRUGS ADVISORY COMMITTEE

(ODAC)

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71st MEETING

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WEDNESDAY,

FEBRUARY 27, 2002

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The Advisory Committee met at 8:00 a.m., in the Versailles Room of the Holiday Inn, 8120 Wisconsin Avenue, Bethesda, Maryland, Dr. Stacy R. Nerenstone, Chairperson, presiding.

PRESENT:

STACY NERENSTONE, M.D., Chairperson

KATHY S. ALBAIN, M.D., Member

DOUGLAS BLAYNEY, M.D., Member

OTIS BRAWLEY, M.D., Member

PRESENT (Continued):

MASSIMO CARDINALI, M.D., FDA

JOHN CARPENTER, M.D., Member

THOMAS FLEMING, Ph.D., Consultant

STEPHEN GEORGE, Ph.D., Member

JOSEPH IBRAHIM, Ph.D., Guest Speaker

PATRICIA KEEGAN, M.D., FDA

DAVID KELSON, M.D., Member

JOHN M. KIRKWOOD, M.D., Guest Speaker

KENNETH McDONOUGH, Patient Representative

ROBERT M. NELSON,M.D., Ph.D., Consultant

GEORGE OHYE, Industry Representative, Guest Speaker

JODY PELUSI, R.N., Ph.D., Consumer Representative (via telephone)

DONNA PRZEPIORKA, M.D., Ph.D., Member

BRUCE REDMAN, D.O., Member

JAY SIEGEL, M.D., FDA

GEORGE SLEDGE, M.D., Member

SARAH TAYLOR, M.D., Member

HAROLD Y. VANDERPOOL, Ph.D., Constulant

KAREN TEMPLETON-SOMERS, Ph.D., Executive Secretary

ALSO PRESENT:

PAUL B. CHAPMAN, M.D.

KAREN L. GRAHAM

VINCENT LI, M.D., M.B.A.

JOSE LUTZKY, M.D.

STEVEN J. O'DAY, M.D.

STEVEN ROSENBERG, M.D.

LYNN SCHUCHTER, M.D.

WILLIAM SHARFMAN, M.D.

CRAIG L. SLINGLUFF, JR., M.D.

LYNN E. SPITLER, M.D.

MARTIN A. CHEEVER, M.D.

KENNETH VON ESCHEV, Ph.D.

CINDY JACOBS, Ph.D., M.D.

JOHN THOMPSON, M.D.

WALTER URBA, Ph.D., M.D.

STUART KROLL, M.A.

HEATHER TULLY, M.D.

JEFFREY SOSMAN, M.D.

C-O-N-T-E-N-T-S

P-R-O-C-E-E-D-I-N-G-S

(8:12 a.m.)

CHAIRPERSON NERENSTONE: Good morning. I'd like to welcome to the 71st meeting of ODAC. We have an interesting morning and afternoon.

I'd like to start with going around the table and everyone please introducing themselves. Dr. Kirkwood, if you would like to start.

Please turn on your microphone.

DR. KIRKWOOD: John Kirkwood, University of Pittsburgh Medical Center.

MR. OHYE: George Ohye, nominee as industry rep.

MR. REDMAN: Bruce Redman, University of Michigan Medical Center.

DR. BRAWLEY: Otis Brawley, Emory University, Atlanta.

MR. McDONOUGH: Kenneth McDonough, North Huntington Township, patient representative and consultant.

DR. NELSON: Robert Nelson, Children's Hospital, Philadelphia, and the University of

Pennsylvania.

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

DR. GEORGE: Stephen George, Duke University Medical Center.

CHAIRPERSON NERENSTONE: Stacy Nerenstone, medical oncologist, Hartford, Connecticut.

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

And we also have participating by telecon. Jody Pelusi, our consumer rep.

Can you say hello, Jody?

(No response.)

DR. KELSON: David Kelson, Sloan Kettering, New York.

DR. BLAYNEY: Doug Blayney, medical oncologist, Los Angeles.

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

DR. VANDERPOOL: Harold Vanderpool, University of Texas Medical Branch in Galveston.

DR. TAYLOR: Sarah Taylor, University of

Kansas Medical Center, medical oncology and palliative care.

DR. FLEMING: Thomas Fleming, University of Washington, Seattle.

DR. ALBAIN: Kathy Albain, Loyola University, Chicago, medical oncology.

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

DR. TIWARI: Jawahar Tiwari, biostatistics, FDA.

DR. CARDINALI: Massimo Cardinali, CBER, oncology.

DR. KEEGAN: Patricia Keegan, Center for Biologics, FDA.

DR. SIEGEL: Jay Siegel, Office of Therapeutics/Biologics, FDA.

DR. TEMPLETON-SOMERS: I'd like to read the meeting statement of conflict of interest.

The Food and Drug Administration has prepared general matters waivers for the following special government employees who are attending today's Oncologic Drugs Advisory Committee meeting to discuss

trial design considerations and appropriate patient populations for studies of investigational agents for adjuvant therapy of melanoma, given the availability of an approved agent for this indication.

The meeting is being held by the Center for Drug Evaluation and Research.

The people with waivers are Stacy Nerenstone, M.D.; Kathy Albain, M.D.; Douglas Blayney, M.D.; John Carpenter, M.D.; Stephen George, Ph.D.; David Kelson, M.D.; Donna Przepiorka, M.D.; Jody Pelusi, R.N., Ph.D.; Bruce Redman, D.O.; George Sledge, M.D.; Sarah Taylor, M.D.; Thomas Fleming, Ph.D.; Robert Nelson, M.D.

A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A30 of the Parklawn Building.

Because Dr. Otis Brawley, Mr. Kenneth McDonough and Dr. Harold Vanderpool reported they have no current financial interest in any pharmaceutical or biologic firm, they do not need a general matters waiver in order to participate in this morning's

discussions.

Unlike discussions before a Committee in which a particular product is discussed, issues of broader applicability, such as the topic of this morning's meeting, may involve many industrial sponsors and academic institutions.

The Committee members have been screened for the financial interests as they apply to the general topic at hand because general topics impact on so many institutions it is not prudent 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 discussion before the Committee, these potential conflicts are mitigated.

With respect to FDA's invited guests, Dr. John Kirkwood has reported interests that we believe should be made public to allow the participants to objectively evaluate his comments. Dr. Kirkwood has a grant from Schering and receives consulting fees from Schering.

Lastly, we would also like to note for the record that George Ohye is participating in this meeting as an industry representative acting on behalf of regulated industry. As such, he has not been screened for any conflicts of interest.

Thank you.

CHAIRPERSON NERENSTONE: Thank you.

Now we'll turn to the open public hearing. We have a long list. So I ask those who are testifying to please stay within the recommended time frame.

Dr. Spitler.

DR. TEMPLETON-SOMERS: I'd also like to mention for the record that due to the wonders of electronics we have been able to receive a lot of input from the public on this particular issue, mostly in the form of E-mails. These E-mails are available for your viewing in the desk copies at the front desk outside.

All of the Committee members and the FDA have received copies of all of the E-mails that I received as of yesterday. Most of them were shipped

to them last week, and the late ones are in their folders today.

For the most part, the patients in the group are recommending that treatment options be made and discussed between the patient and their doctor with freedom for those options, and there are a few other opinions that you'll find in your book.

Thank you.

DR. SPITLER: I am Lynn Spitler. I am the Director of the Northern California Melanoma Center.

For over 30 years, a major focus of my research activities has been clinical trials of adjuvant therapy of melanoma, and I have published extensively on this subject in refereed medical journals.

I personally paid my travel expenses to attend this meeting and personally paid the cost of preparing this presentation.

I have received research funding from Immunex, Schering and Chiron, am a consultant to Immunex, and am a member of the Immunex Speakers Bureau. None of these companies suggested nor

contributed to this presentation, and I have not discussed it with them.

It is the understanding of the melanoma community that the FDA has instituted a policy that patients with Stage II T4 or Stage III melanoma who are candidates for therapy with high dose interferon and who refuses treatment cannot participate in Phase 2 trials of other agents.

We recommend that this policy be altered. Points to consider regarding this issue are as follows:

High dose interferon may provide clinical benefit as adjuvant therapy in these patients. However, it is an imperfect solution. The clinical benefits are limited, and the incidence of severe toxicity is significant.

Phase 2 trials are needed if the medical community is to develop new agents with more clinical benefit and less toxicity as adjuvant therapy for patients with Stage II T4 and Stage III melanoma.

I have presented a written statement for your consideration, and I hope that has been

distributed. The statement provides additional background regarding the points to consider regarding this issue.

We recommend that patients who choose not to undergo therapy with high dose interferon, after having been fully informed of the risk-benefit ratio should be permitted to choose treatment with investigational agents in approved clinical trials. Such patients should sign consent form, which clearly states that high dose interferon is the treatment approved by the FDA for adjuvant therapy of high risk melanoma.

This statement is supported by 37 physicians specializing in the care of melanoma patients, as evidenced by their signatures accompanying the statement.

It is also supported by 20 patients who wrote letters of support and others who wrote letters indicating their support, including Dr. Richard Shilsky (phonetic), Chair of CALGY; Dr. Robert Dilman, Chair of the Society of Biological Therapy; Jeff Patterson, co-founder of Melanoma Patients Information

Page; Casey Culbertson, Vice Chairman, Melanoma Research Foundation; and Professor Alexander Egermont, EORTC Melanoma Group.

Others have traveled to appear here and make statements personally.

Thank you for your consideration.

CHAIRPERSON NERENSTONE: Thank you.

Dr. Lutzky.

DR. LUTZKY: Morning. My name is Jose Lutzky, and I'm the Director of the Melanoma Multi-disciplinary Program at Mt. Sinai Cancer Center in Miami Beach, Florida.

Our center sees over 200 new melanoma patients a year, and we are involved in several clinical trials encompassing all stages of melanoma. I received research funding from Immunex, Celgene, and Chiron Pharmaceuticals. I'm a member of the Immunex Speakers Bureau, and I have conceived this statement individually and without participation or notification of any pharmaceutical company.

I have paid for this trip from my personal funds.

High dose interferon is considered by the FDA as the standard of care for patients with Stage IIB3 melanoma. I will not dispute this point today.

I would like, however, to point out that survival data is of borderline significance in that 145 months of follow-up, the survival of the interferon treated group in ECOG 1684 is no longer statistically different from the observation group.

While life threatening and irreversible toxicity is uncommon with this treatment, most patients experience prolonged, debilitating side effects, such as fatigue, anorexia, weight loss, and depression.

In my clinical practice, 60 percent of which consists of patients with melanoma, I discuss the data on adjuvant high dose interferon with all patients at high risk for recurrence. About 50 percent of these patients will proceed to receive the standard of care. The other half will elect not to be treated with interferon.

In the patients who are actively in the work force, the main reason is the abundance of side

effects, fear of decreased performance at work, or loss of work.

In the significant proportion of older retired individuals that I see in Florida, they are not interested in toxic therapy that might interfere with their quality of life and/or aggravate their existing medical problems for a borderline survival benefit.

Many older patients cannot self-inject, don't have easy access to transportation, and live alone. These patients could not be monitored appropriately for high dose interferon treatment.

I submit that there is a need for less toxic, novel adjuvant therapies for a significant group of patients who are unwilling to receive high dose interferon adjuvant therapy. These patients end up receiving off protocol therapy with other agents given by their treating oncologist.

I would like to echo the suggestions of many of my colleagues who treat melanoma patients and are present here today. Number one, that patients that choose not to undergo adjuvant treatment with

interferon be offered access to investigational trials exploring novel agents.

Number two, that these patients should sign an informed consent stating that they understand that treatment with high dose interferon is the current standard of care, and that in the informed consent, a brief summary of the results of the pivotal clinical trials with high dose interferon be included.

Thank you.

CHAIRPERSON NERENSTONE: Thank you.

Ms. Graham.

MS. GRAHAM: Good morning. I'm Karen Graham, and I'm the Chair and President of the William S. Graham Foundation for Melanoma Research. We're widely known as the "Billy Foundation."

I would also like to note that I really appreciate the opportunity to address you from the advocacy side of this hearing today. Though we have accepted educational grants from Schering, Chiron, Maxim, and Genta in the past, I've personally paid my own expenses in order to address you here today.

In just three days, on March 2nd, I will

personally be observing the eighth anniversary of the passing of our son Billy to this insidious disease. He died at an all too young age of 22.

When Billy was diagnosed, I made him a promise that we were going to beat this disease. What I didn't realize was that it was not going to be in his timing, but I still have a promise to keep, and there's nothing more tenacious than a mother's promise.

But now, eight years later, it is still not in any melanoma patient's timing, and this is just not acceptable.

In the last eight years, how many new therapies have been approved, and what is this saying to melanoma patients and their families? We want patients to have choices from the onset, not as a second matter of recourse.

In the past eight years, approximately 56,000 lives have died to this disease, and this is not acceptable.

In the past eight years, approximately 360,000 people have been diagnosed with this disease.

They've had to face it with an extremely limited offering of treatments available to them. This is no longer acceptable.

It has been a long time that has passed and that something needs to be done in order to bring hope to these dear people. I'm not here to debate your system of approval, nor am I here to discuss which therapy is the best. What I'm here for is to represent those 360,000 people, many of them who have already died from this disease.

I'm here to represent the dozens of phone calls that we receive on a monthly basis from the patients and their families that literally cry out to us in their battle against this ugly killer.

Choices, that's all. They are simply looking for the ability to retain some semblance of control in a life that has gone totally berserk on them, and right now as it stands, it's not there for them, and this is not acceptable.

With every phone call, what we hear is, "Why isn't something being done to allow us more choice of treatments? I want the opportunity to

choose. I want to fight, but I want to have some quality of life in the process. I just want to be treated like I'm a person with the ability to make an informed decision. It's my body; it's my life. So educate me. Tell me the pros and the cons of it, of what's out there. But then let me choose."

The choices are not acceptable. We're standing on the edge of a research crisis precipice. Researchers are throwing their hands up in frustration.

I've had the opportunity to speak with many leading researchers from around the world with more than one of them suggesting to me that they're at the point of leaving, leaving melanoma research.

Distinguished panel, we cannot afford for that to happen. They have dedicated their entire professional lives trying to create viable options only to see them literally pulled out from under them at a time when we as a foundation are doing everything that we can to bring up the next generation of researchers. We cannot afford to lose the incredible intellects that are currently in this fight. This is

not acceptable.

This, for the most part, is an orphan drug disease, especially for those more advanced patients. Yet I have not seen any urgency from the FDA in working with researchers and companies to make potential treatments available, many of them spending months, if not years, attempting to get clear direction from the agency on how to proceed with their drug developments.

To bring help to these patients we must start working together to make this a common goal. We should be saying what must we be doing together to make this happen. We must move forward and bring more choices to patients and show them that we are not only listening, but we are doing.

As a foundation that was brought up on a personal loss, I have been in those trenches. I have seen the inner workings and had to deal with it myself and have continued to see how melanoma patients and their families for the past eight years have had to deal with the same lack of choices, some of these patients having less than two months to live.

Ergo, there is principle of risk to benefit, a valuation that needs to be addressed and applied here. Again, I do not see the appreciation of this principle and application in working with potential treatments.

We have knowledge that there are treatments that are considered safe and potentially effective by clinicians in recent trials. Yet little effort is being made to accelerate their approval. This can no longer be acceptable.

I will take it as a rally call to make sure that these patients' voices are heard at every opportunity that I can create. I will take it to the streets. I will take it to conferences and different speaking engagements that I have around the world. I will take it to state and national legislators, and I will take it to the press.

I will do whatever I can as the head of this foundation to make sure that their requests, their requests for the right to choose and to have options given to them. They're tired of being treated like they don't exist.

Inform them. Educate them. Give them the pros and cons of what is going on. Have them sign a stack of papers a mile high if you must, but then let them choose. To do otherwise is taking their lives out of their hands, and I'm sorry. This is not acceptable.

Thank you.

CHAIRPERSON NERENSTONE: Thank you very much, Ms. Graham.

Dr. Chapman.

(Pause in proceedings.)

DR. CHAPMAN: Thank you.

I would like to applaud the FDA for convening this meeting to allow an exchange of views on this very important subject.

I'm head of the Melanoma Section at Memorial Sloan Kettering, and my laboratory and clinical research has focused on trying to develop effective immunological treatments for melanoma.

I should state that I have no equity interest in any biotechnology company or drug company. I'm not on the speakers bureau of any drug company.

That being said, I would like to spend my five minutes here explaining why I and many of my colleagues and patients feel strongly that the Phase III data do not support the claim that high dose interferon results in an improved survival and, as such, do not support designating high dose interferon as the sole standard for adjuvant therapy of melanoma.

There have been two randomized trials comparing high dose interferon with observation, E1684 and E1690. These are the only trials capable of telling us whether high dose interferon is superior to observation following surgery.

This is the first of my three slides showing the data from E1684 as originally published in the Journal of Clinical Oncology and as updated by investigators from ECOG and presented at several public meetings.

This was a relatively small trial, only about 140 patients per arm, and at seven year median follow-up on the left, the interferon group showed an estimated five year survival improvement of nine percent.

But the question hanging over these data is: is this difference really statistically significant?

These data were published using a less stringent one sided T test, which gave a P value of .027. The two sided value is .06, according to the FDA document which was distributed for this meeting, meaning that the difference did not reach the standard threshold for statistical significance.

With the data matured three more years, we get the curves on the right, and the differences have become even less significant. This is presumably because more melanoma deaths have occurred in both patient groups.

The small difference between the groups is not significant, even using a one sided test, the P value being .09, and the two sided test being .18.

The data from this first trial then leads us to conclude that the suggestion of overall survival benefit, which was nearly statistically significant after seven years, is clearly not significant any longer, and we cannot conclude with any degree of

confidence that the overall survival improved with high dose interferon.

The second trial comparing high dose interferon with observation was E1690. This was a better powered trial with 202 patients per arm, and the second slide shows the overall survival from this trial as published in the Journal of Clinical Oncology. There was no effect of interferon on overall survival.

And what I don't have time to show is that the effects on relapse free survival were also note quite statistically significant.

My view is that we have two well conducted, randomized trials comparing high dose interferon with observation. Neither trial showed a statistically significant improvement in overall survival, and only the first smaller trial showed an improvement in relapse free survival.

In my mind, no amount of post hoc analysis can turn or should be allowed to turn these negative trials into positive ones. This lack of survival benefit weighs heavily on my view and on my patients'

view of the value of high dose interferon as an adjuvant treatment.

Patients are willing to undergo a year of fatigue, fever, depression, diminished quality of life if there's an increased chance of survival. However, in the absence of convincing evidence of any survival benefit, the interests of patients would be best served by supporting carefully conducted research on other scientifically valid approaches to adjuvant therapy.

Patients should be allowed to participate in experimental adjuvant trials without high dose interferon. Patients should be informed that high dose interferon is an FDA approved adjuvant treatment, and they should be told the likely benefits and toxicities.

However, mandating a year of treatment that has been shown in two carefully conducted and reported randomized trials to yield no significant survival benefit hinders the development of effective therapies and is not in the best interest of patient care.

Thank you.

CHAIRPERSON NERENSTONE: Thank you, Dr. Chapman.

Dr. Sharfman.

DR. SHARFMAN: My name is William Sharfman. This morning I speak as a member of the Johns Hopkins Melanoma Group and as Director of Cutaneous Oncology at the Hopkins Oncology Center.

I'm also privileged to serve on the Melanoma Committee of the Eastern Cooperative Oncology Group, chaired by Dr. Kirkwood, who has taught me a great deal about the treatment of melanoma and whose work I admire very much.

Please be aware that I have received honoraria from the Schering Corporation in 1998, 1999 and 2000 to speak on the subject of melanoma. As the medical oncologist of our group, much of my time is spent counseling and treating patients with high risk melanoma. I discuss high dose interferon with all of them.

I emphasize that as the only treatment shown to be beneficial in Stage IIB and Stage III

melanoma, and it is the only FDA approved therapy.

However, some patients are not fit for high dose interferon because of other health problems. Many patients refuse interferon no matter how much time you take to discuss it with them, and some insurances will not pay for home administration of subcutaneous interferon for 11 months, leaving the untenable option of a patient visiting the doctor's office three times a week for almost one year.

I also discuss vaccine protocols with all of my patients. I emphasize that vaccines are promising, but have not yet been proven and are not FDA approved. We also discuss the option of no therapy.

The patient discussion of treatment options, high dose interferon, vaccine or observation is very time consuming, but this is what is required of our patients based on our current level of knowledge.

The decision making process should be between the patient and the treating physician with the patient and the data in front of them and not

mandated by a third party.

At this point in time, the data on high dose interferon is not so compelling that patients should be required to get interferon before they go onto a vaccine trial. In fact, the updated data on ECOG 1684 of which I am aware shows that there's no longer a statistically significant overall survival advantage for high dose interferon.

The future of adjuvant melanoma therapy is not high dose interferon by itself. It may be interferon plus another agent. It may be a vaccine, or it may be some other agent. A requirement to give all Stage IIB and III patients interferon will seriously slow down our attempts to identify more active and less toxic melanoma therapies.

At this point, I would like to highlight the conclusion of a letter written by Dr. Alex Egermont of the EORTC that I believe has been officially entered into the record of this meeting.

Very briefly, he states that because of inconsistent survival benefit, toxicity and cost, high dose interferon should not be considered as mandatory

therapy for Stage IIB and III melanoma.

On top of that, patients should keep the right to abstain from therapies with a toxicity profile associated with high dose interferon and have options open to them.

Thank you very much.

CHAIRPERSON NERENSTONE: Thank you, Dr. Sharfman.

Dr. O'Day.

DR. O'DAY: Thank you.

I'm Dr. Steven O'Day, and I'm a medical oncologist, Director of Medical Oncology and Medical Oncology Research at the John Wayne Cancer Institute in Los Angeles.

John Wayne Cancer Institute is one of the larger melanoma referral centers in the world, and I actively have committed my time over the last eight years to clinical trials research in a number of different stages of the disease, including Stage II, III, and IV.

I come here at my own expense. I do have research grants from Chiron, from Immunex, and from

Schering, and I am on the speakers bureau for Chiron, but I have not discussed any of my testimony today in front of you with any of these pharmaceutical companies.

I have carefully reviewed the data regarding interferon for Stage IIB and III disease, and I see approximately six new melanoma patients a week. Many of these discussions center around IIB and III disease and the interferon data.

So I am in the trenches. I have these lengthy discussions, and I think it's fair to say that biases aside, the majority of patients that I discuss this with choose to do high dose interferon therapy. However, there is a significant minority of patients who, after hearing the date carefully discussed, choose not to go on therapy.

And we could all agree generally that disesae free survival has been a consistent finding at least in the dosing schedule that the FDA has approved. I think overall survival, as some of the previous speakers have discussed, remains controversial.

But even if we assume best case scenario, and I actually do discuss this with patients, that there is a small survival advantage, this particular unique duration of this treatment and the constitutional and neurocognitive side effects that patients endure leads many of them to choose not to proceed with this treatment and to forego this treatment.

And I think in that setting, we could agree that high dose interferon is a standard, but may not be the standard in the sense that our European and our Australian colleagues, as well as many U.S. physicians and patients, choose not to follow, quote, unquote, the standard of care.

And it is in this setting that I think it is very important that we offer patients novel, innovative therapies. And that is what is critical.

Now, Phase I and II protocols are important to develop new treatments, and before we assume that we could look at Phase 1 and 2 trials in either Stage IV disease or in earlier Stage IIA disease, I would want to remind people that that my

not be the best scenario to look at.

We have a unique opportunity because of the surgical staging of this disease that we've identified a high risk subgroup IIB and III, and toxicity issues may be better addressed in earlier stage disease, but preliminary efficacy issues are optimal in a high risk situation of recurrence with a competent immune system since many of our adjuvant trials are geared toward immunotherapy.

And I think the Stage IIB and III patients, since they are very high risk for recurrence and death, and they relatively have an intact immune system compared to Stage IV disease, is a group that we don't want to lose that advantage to look at Phase 1 and 2 trials and to see some preliminary efficacy data to take to larger Phase 3 trials.

So I think it's for that reason that we have a significant number of patients that choose not to do interferon, and that this subgroup is an idea subgroup to look at novel, possibly less toxic therapies, to look at preliminary efficacy; that it's very important that we allow these patients the

freedom of choice to participate in well run, well designed clinical trials.

Thank you.

CHAIRPERSON NERENSTONE: Thank you, Dr. O'Day.

Dr. Slingluff.

DR. SLINGLUFF: While he's getting that together, I'm Dr. Craig Slingluff at the University of Virginia. I'm the head of the division of Surgical Oncology, and I run our melanoma program. I'm also Director of our Human Immune Therapy Center.

We live in a small town, and most of our referrals come from other physicians so that most of the patients that we see come to us with an interest in vaccine trials, having already decided not to take interferon after informed discussions with their medical oncologists, although we also insure that we discuss interferon with them as a separate discussion in any and every case of patients who are eligible.

I should also point out that I have been running several clinical trials of tumor vaccines, primarily peptide based trials. I've been NIH funded

for most of those trials.

I have also received industry support from Chiron, Immunex, Schering-Plough Research Institute, and Argonex. I'm listed as an inventor on several patents that the university has filed for some of the peptides that we identified and that we and others use in vaccine trials.

I am Co-chair of the Melanoma Committee of ECOG and recently appointed one of the two Vice Chairs f the Melanoma Committee of the American College of Surgeons' Oncology Group.

The main question I'd like to address is how to design Phase 2 trials, experimental therapies with an FDA approved therapy available, and some of our recent exposure to this issue has arisen with this particular trial, which we call UVA-Mell39, which is a peptide based vaccine trial where eligibility includes patients with Stage IIB and III disease that's resected. We've initially proposed the trial to include patients who refuse interferon or are not candidates for interferon.

The FDA ruling was that patients who are

not candidates for interferon can enter the trial, but for those who simply refuse interferon, they are not considered candidates.

It was pointed out, however, by our product reviewer that those who have refused interferon and have not taken interferon for six months or more after they have definitive surgery are no longer considered candidates for interferon because of the lack of evidence for efficacy at that time point, and that they then become candidates for the trial, which presents an awkward situations where we can discuss with patients who come to us who are interested in the vaccine trial and have decided not to take interferon that they cannot enter the trial now, but if they wait six months, then we can reconsider them.

Obviously we can't make a commitment. Now, we have had a number of patients who have waited six months and have come in. We have had the also awkward situation arise where one patient so far has waited six months, came in at the end of the trial as a candidate in all respects, except that he had a

local recurrence at his site of his primary tumor, which makes apt Stage III disease and a candidate for interferon again. So we tell him he has to wait another six months for entry into the trial.

The argument for legislating against the freedom of patients to decide to enter a clinical trial after refusal of an approved therapy is that patients may be exposed to risk of obtaining inadequate information about the standard therapy, which may be affected by real or intention or unintentional bias of clinical investigators.

However, the process of informed consent is one on which our entire process of clinical research is based. It is what we believe is capable of allowing patients to make informed decisions consenting to clinical studies where there may be unknown benefit and known or unknown risks.

To argue that informed consent cannot provide adequate protection of patients who choose not to take an approved therapy where they can have explanations of the risks and benefits of doing that is tantamount to arguing that informed consent cannot

provide adequate protection of patients in any setting, and this argument then threatens the whole basis of our clinical trial program in the United States.

A tenable policy for the design of Phase 2 clinical trials in patients who may be eligible for an FDA approved therapy should assure a patient protection while also assuring the freedom of self-determination by patients. My suggestion is that for trials where patients may be eligible or ineligible for the standard therapy, they should reach documentation on the consent form of whether they're eligible or not for the standard therapy.

If they are eligible for that, then they should have to review a standard packet of information that would be FDA approved as part of the clinical trial program, which would require them not only to read that information, but also to sign off on individual points that are considered key, if interferon is approved, the survival advantage, et cetera. Several of those could be listed.

The benefits of this is one is that it

would insure that no patient eligible for an FDA approved therapy would refuse that therapy and enter a trial without receiving acceptable information about the standard therapy, but it also would lead to more uniform information dissemination about the standard therapy than currently provided to those who refuse that therapy.

Many patients now see a medical oncologist who may or may not -- who may not feel that interferon is the best thing for them and tell them not to take it. I have patients who come seem me to tell me their medical oncologist said not to take interferon.

Those patients who choose not to take interferon based on that recommendation go home and don't take it. If, instead, they are referred to be considered for entering into a clinical trial where they're forced to review all of the data, then have an opportunity to see all of the data and then make a decision to take interferon or some other standard therapy in a different setting.

This would also permit patients freedom to choose the management they find most consistent with

their priorities and ultimately would actually increase the proportion of patients whose therapy is regulated and monitored by the FDA, thereby improving patient safety generally.

I believe very strongly in the recommendation I've made, which is consistent with many you've heard, and also the recommendation if the FDA does not feel comfortable making that decision at this point would be that since interferon has been tested within 56 days of definitive surgical therapy, and now some patients are being entered into trials up to about three months, but there's really no convincing data about its benefit after three months, its interferon use after three months can be considered experimental.

So it would be appealing if the regulation requiring a six month delay before entry into clinical trials could be shortened to three months.

And that's all. Thank you.

CHAIRPERSON NERENSTONE: Thank you, Dr. Slingluff.

Dr. Schuchter.

DR. SCHUCHTER: Good morning. My name is Dr. Lynn Schuchter, and I'm a medical oncologist at the University of Pennsylvania Cancer Center.

I treat patients with melanoma, with early and advanced disease. I appreciate the opportunity of speaking before you today.

I'll state that I have no conflict of interest. I'm not in any speakers bureaus. Our institution does conduct ECOG trials and we do participate in a number of vaccine clinical trials.

The optimal care for patients in the year 2002 for patients with melanoma, I think, is now clear. While interferon is appropriate for some patients, it is not the standard of care. It has not been adopted as a standard of care by many physicians in the medical community, nor by patients, and the reason for this is really twofold.

One is the issue of efficacy, and the question of whether interferon is associated with improvement in overall survival.

And the second issue is the considerable toxicity associated with the treatment.

I think previous speakers have really outlined the survival issue, but I would just add one more point about 1684, which is really the main trial that we focus on in terms of this question of survival benefit.

In that study most of the patients had node positive disease, and at the time that the study was initiated, it was unclear that the most important predictor of relapse is the number of lymph nodes involves, and that study did not stratify patients for the number of positive nodes.

I can't imagine doing a node positive breast cancer trial without knowing and stratifying appropriately for number of positive nodes.

So while it's stated that the two arms are appropriately balanced, it may not be balanced in an important way which also could affect the overall results.

A second issue is the toxicity issue. In 1684, three quarters of the patients had dose reductions for Grade 3 or 4 toxicity. I know of no other adjuvant therapy that is associated with such a

high incidence of serious toxicity, Grade 3 and 4 toxicity.

I think this debate would be much less heated with this efficacy data if the toxicity associated with the treatment was not so substantial.

Fifty percent of my practice is also patients with breast cancer, and I administer a lot of adjuvant therapy in the breast cancer setting. I think there is on comparison regarding the toxicity of one year of high dose therapy of interferon, even with dose reductions and comparing that to three or six months of adjuvant chemotherapy for patients with breast cancer.

I think there is an analogous situation in patients with Stage II colon cancer where there's a lot of debate about the efficacy of adjuvant therapy. In a number of studies the benefits of adjuvant therapy for survival ranges in about three to eight percent in the adjuvant setting for Stage II colon cancer patients.

Yet right now currently the cooperative groups are offering a side range of options for those

patients. The CELGB has a study of surgery versus antibody, and in patients participating in NSABP studies, the options are 5 FU leucovorin chemotherapy versus 5 FU leucovorin oxaliplatin.

So in a similar situation, patients are offered really a wide range of options after, again, getting full informed consent about the potential benefits of adjuvant therapy.

I urge the FDA to alter its policy regarding the testing of new agents in patients with melanoma. The majority of patients with Stage III melanoma die from melanoma despite high dose interferon. We clearly need better therapies for these patients.

It is not the standard of care to use high dose interferon. It has not been accepted by the medical community, nor patients, and I believe that the current FDA policy is a significant obstacle to our finding better therapies for our patients and therapies that are better tolerated.

Thank you.

CHAIRPERSON NERENSTONE: Thank you, Dr.

Schuchter.

Dr. Li.

DR. LI: Good morning. My name is Dr. Vincent Li, Scientific Director of the NGO Genesis Foundation, a global, nonprofit organization dedicated to advancing the field of molecular targeted therapies for cancer and other diseases.

Interferon alpha IIB was approved in 1997 for the treatment of node positive or deep Stage IIB melanoma. Since then a number of investigational biological agents have been studied as adjuvant therapy, including Melacine, in allogeneic cell vaccine derived from two melanoma cell lines.

A Phase 3 melanoma trial of Melacine as monotherapy using observational controls showed no statistical benefit for overall disease free survival, but benefit was seen for a subset of patients with Class I MHC, HLA A2 or C3 markers.

A major issue is how to design pivotal clinical trials for this patient group, given the availability of an approved beneficial drug such as interferon. This type of question is not unique to

this agent, nor to this tumor type, but in fact, faces a larger number of other novel molecular targeted therapies in development for cancer.

The NGO Genesis Foundation is studying the design of clinical trials for molecular targeting agents that affect tumor blood supply. Melanoma is a highly angiogenic tumor where increased vascularity correlates with invasion, metastases, and poor survival.

Certain melanoma treatments, including interferon alpha, possess anti-angiogenic activity, and their anti-tumor effects are attributable in part to anti-angiogenesis.

Interferon alpha is a complex agent possessing divers and sometimes adverse immunomodulatory effects in patients. Therefore, melanoma trials testing new agents in combination with interferon need to be examined in the context of two issues.

First, the possibility for enhanced efficacy, and second, the possibility for enhanced toxicity.

On the one hand, combinatorial therapies involving interferon with a vaccine may have synergistic effects resulting from combining anti-angiogenic with immunomodulatory actions.

In the field of anti-angiogenic therapy, it is now strongly believed that combinatorial regimens involving a novel agent with the best available standard therapy will generate the most potent anti-tumor response.

In the case of a melanoma vaccine, interferon induces monocytes to differentiate into dendritic cells, and this might enhance immunity against the tumor. Interferon's anti-angiogenic activity might suppress melanoma growth by decreasing the production of stimulatory molecules, such as basic FGF, VEGF, and Interleukin-8 by inhibiting matrix Metaliprotenase-9 and by inducing endothelial cell apotheosis.

Together, a melanoma vaccine plus interferon might generate a more efficacious response.

On the other hand, a combinatorial approach obscures the full evaluation of both safety

and efficacy of the new agent itself. Toxicities in a combination cannot be easily separated, and some toxicities may be additive or cumulative in nature.

Another concern is whether the well known toxicities of interferon might negatively impact a vaccine trial. For example, in a recent trial of a ganglioside based melanoma vaccine, one third of patients receiving a high dose interferon stopped treatment during induction due to interferon toxicity, and 50 percent stopped or had their interferon doses held during maintenance therapy.

High dose interferon has been shown to have significant clinical benefit, while low does use remains unproven.

Attrition of patients due to dose related interferon toxicities may weaken an efficacy study by closing completion of accrual and possibly by selecting out subgroups of patients who share susceptibility to interferon's effects.

Because of such toxicity concerns, it may be prudent to learn how a novel melanoma vaccine performs along when directly compared to interferon,

and such comparisons should, of course, be studied prospectively and not historically inferred.

For vaccine trials of melanoma, we recommend that the FDA consider a three arm trial design, one arm, where the experimental agent is combined with interferon; a second arm giving interferon alone; and a third arm with the agent alone.

Such a design accommodates the study of synergistic drug effects both in terms of efficacy and safety, and this approach may also ultimately identify a drug that is superior to interferon, advancing the frontiers of melanoma management.

Thank you.

CHAIRPERSON NERENSTONE: Thank you very much, Dr. Li.

Dr. Rosenberg.

DR. ROSENBERG: Good morning. I'm Dr. Steve Rosenberg. I'm a surgeon at the National Cancer Institute.

The only conflict that I have in preparing these remarks is to somehow stay on the good side of

the Food and Drug Administration because I almost daily depend on their approval for studies that I do, but at the same time, to talk about how inappropriate I believe the current policy is.

In any democratic society, in any good clinical situation, the doctor and the patient will sit together to discuss the possible benefits and risks of any treatment offered for that particular patient.

And when a treatment does have some possible benefits, but also some toxicities, the doctor and the patient sit together to talk about the impact of the toxicities on that patient's life, and we do that every day; talk about the possible benefits, and then the doctor and patient together make a decision about whether the possible benefits are worth the possible risks.

Now, it's very rare that we mandate a treatment even when it's known to be effective if it has toxicities, and perhaps the best example that I face almost every day is in the administration of high dose Interleukin-2 to patients with metastatic renal

cell cancer and metastatic melanoma. To my knowledge, high dose Interleukin-2 is the only approved treatment by the FDA for patients with metastatic kidney cancer.

And in fact, in our trials of many hundreds of patients and other published trials about eight to ten percent of patients with widely metastatic cancer will have a complete regression of all of their disease. Eighty percent of those will never recur, and we have many patients beyond ten years cured of widespread kidney cancer, and that's true for melanoma as well.

There is one other approved treatment: Dacarbazine. And yet we don't insist that every patient who has metastatic kidney cancer receive high dose Interleukin-2. It has toxicity associated with it, and patients can decide whether or not that eight percent chance of a durable, complete response is worth the toxicity that they may receive due to Interleukin-2, and in fact, those patients are certainly eligible to enter highly experimental Phase 1 trials that have no benefit, and we leave that decision to that patient.

And I believe that that is appropriate, even though I do feel that high dose Interleukin-2 can benefit many patients.

Now, with respect to the situation with alpha interferon and the adjuvant setting that we're discussing today, I think there are two compelling points, and they've been made already. I'll just reiterate them very briefly.

The first is that the data that alpha interferon is beneficial in patients in the adjuvant setting is controversial. There are some data that it is of benefit, but you've heard from Dr. Chapman an elegant analysis showing that it is of no survival benefit.

And in fact, the literature that I try to keep very closely in touch with and analyze tells me as I analyze that data that alpha interferon does not have a survival benefit, and as a physician treating many patients with melanoma, that's a judgment that I make. Other physicians might make other judgments, but it is a controversial issue.

And in fact, the leaders of ASCO, the

Society of Biologic Therapy, the EORTC, and other groups feel similarly and, in fact, they've submitted letters, many of them, saying that, in fact, they do not either believe that alpha interferon is beneficial.

And so there is controversy about its benefit. There's no controversy about its toxicity. It has caused deaths in the adjuvant setting in patients who might have been cured in the absence of its administration.

Many patients who take interferon and then recur and come to us for other treatment will tell me that it was worst year of their life. They were tired the entire year. They find even high dose Interleukin-2 much more palatable than a year of this interferon.

This is certainly a toxic treatment, and personally if I had melanoma in the Stage III setting, I would not take alpha interferon because I do not believe the possibility of benefit is worth the toxicities that one would experience, and I find it therefore hard to understand why the FDA would mandate

that as the only possible treatment.

The second point, in addition to the controversy as to the value of interferon is the fact that in any democratic society, a patient and a doctor should have the right to sit down, look at the data, and together decide whether or not a treatment of marginal benefit or even definite benefit is worth the toxicities and be allowed to decide not to take that treatment and, instead, take a fully informed other experimental treatment that might be beneficial to them.

And, in fact, the current regulation that insists that a patient must be refractory or recur after alpha interferon before they'll accept other experimental treatments has to me the somewhat insulting implication that, one, the doctor is not going to tell the patient all of the data about alpha interferon honestly, plus and minus, and the other rather insulting implication that the patient is not adequate to decide once they're fully informed.

And I believe that the basis of both of these points, the current policy is an unreasonable

one and, in fact, an intrusion into the doctor-patient relationship.

The majority of patients today whether they receive alpha interferon or not, who have multiple positive lymph nodes from melanoma, will die of melanoma. We desperately need better treatments, and I think the current policy of insisting that patients receive alpha interferon, that does not allow us to explore the application of exciting, new developments is actually doing a great disservice to the research community and, in fact, stifling research that could potentially lead to more effective treatments.

Thank you.

CHAIRPERSON NERENSTONE: Thank you, Dr. Rosenberg.

We are a little bit ahead of schedule, but I'd like to continue on. Next is the FDA presentation by the Center of Biologics Evaluation and Research.

(Pause in proceedings.)

DR. CARDINALI: Dr. Nerenstone, members of the Committee, ladies and gentlemen, good morning. My

name is Massimo Cardinali. I'm a medical reviewer with CBER, and I'm going to introduce the CBER presentation this morning and cover the first segment of it.

This morning we want to present you with some background data on the experience that CBER has with product studied for the treatment of melanoma, and also over the basis for approval of INTRON-A for the adjuvant treatment of melanoma.

Then we will have a survey of the literature of randomized controlled trials of alpha interferons in melanoma, and give some information on the comparison of the effect size of other adjuvant treatment for oncologic disease.

We also have two invited speakers Dr. John Kirkwood will give us an update on the ECOG experience of the four trials that they have conducted, and Dr. Joseph Ibrahim will talk about models for adjuvant trial design.

As regulatory consideration, FDA has placed a clinical investigation on hold if a patient can be exposed to a reasonable, significant risk of

injury, and this applies to withdrawal of an effective treatment for that disease.

So the evolution of the regulatory approach in subject with State IIB and III disease has changed over the years because the initial result of 1684 and 1690 did not show a clear effect on survival, but with the result of Study 1694 and other published literature, the evidence of effect on survival was somehow strengthened, and therefore, it was decided to restrict the enrollment of this subject to those patients who were medically unable to tolerate the approved dose and schedule of INTRON-A to a subject who had a lapsed time from surgery of more than six months or to patients who had a recurrence on INTRON-A treatment or had completed INTRON-A treatment.

Let me give now some information as a background of the last 25 year experience in biological treatment for melanoma. We searched our database between the year 1975 and 2000 for cancer treatment INDs submitted to the agency, and of these 26 hundred applications, 196 were for the treatment of melanoma.

We retrieved from our archives the annual report for a large majority of this IND and evaluate the number of subjects that were included in the study and the type of study.

And also we are going to present some data on product category.

As you can see in this five year intervals, the increase in the study for the treatment of melanoma has been quite dramatically particularly in the last five years, and here I have some figures for patients included in different phases of study and divided by number of study and number of subjects.

The investigational products that were studied are presented here. Tumor vaccine gene transfer product, monoclonal antibody, cytokines, and this could include other therapeutic protein, and cellular therapies where we include LAC (phonetic) cell and tumor infiltrating lymphocyte.

The relative frequency of this product is shown here with vaccine having the lion's share with more than 50 percent of the applications received by CBER.

And a few more words about tumor vaccine. Again, in order of frequency, the larger group is tumor cell vaccine is a heterogeneous group of product. It's represented by an autologous cell or allogeneic tumor line either modified or modified by chemical or gene transfer method.

We also have peptide vaccine, antigen presented by the dendritic cell and tumor cell lysates or fragments.

And now briefly some information about the basis for approval of INTRON-A and supplemental data that the FDA reviewed which is reflected in the current label for INTRON-A. The pivotal study is ECO 1684. The data for this study was submitted to the agency in 1995, and the analysis of the agency discussed at the ODAC Committee, and the committee voted for approval of this agent, and the approval was granted the same year.

The structure of the study is shown in this schema here. All patients underwent surgical excision followed by regional dissection for pathological staging of the disease, and then patients

were randomized to high dose and had no treatment.

And here are the results in the analysis of the FDA with the highly significant P value for the relapse free survival and clearly significant P value for the overall survival.

These are the Kaplan-Meiers that were presented in the published report for the disease free survival, and the Kaplan-Meiers for the overall survival.

The label indication reads as follows: interferon is indicated for patients with high risk for systemic recurrence within 56 days of surgery, and this refers to Stage IIB and III subjects.

At the time that 1684 was presented at the Advisory Committee, Study 1690 was already ongoing, and the two major difference between these two studies that the pathological staging was not required for all patients, and a low dose arm was added to the high dose arm, where interferon was administered for a period of two years.

Here I've presented again the Kaplan-Meier estimate presented in the published report, and you

see that for relapse free survival, there is separation of the two interferon arms compared to treatment, where for the overall survival of the curve are much closer.

And in this table, we summarize the data at three years, at the time point of three years for the high dose portion of 1690 compared with 1684. That, again, showed the effect on overall survival was not confirmed, although the data is still leaning on the side of the data presented by 1684.

All of this data was incorporated in the current label for INTRON-A.

The adverse event of treatment with alpha interferon are schematically -- very briefly, the non-serious adverse events are common, but conversely, serious adverse events represent less than two percent, and both non-serious and serious adverse events are reversible with dose modification and medical management.

The serious adverse event observed in the clinical trial are liver failure and depression with suicidal ideation. Two patients died of liver failure

in Study 1684. This is believed to a reactivation of latent hepatitis condition, and with careful screening, this event is not observed in subsequent studies.

Also, retinopathy has been reported from post-marketing surveillance to occur not in patients actually with melanoma, but with other disease.

And finally, I want to present some data on the use of INTRON-A that was provided to the agency by Schering-Plough. These are data derived from the sale survey and should be taken with a limitation of the method to obtain this data.

But it tells us that roughly 60 percent of the subjects with Stage III disease are treated with INTRON-A, and 20 percent of the patients with Stage IIB are treated with INTRON-A.

One thing that should be noted is that there is a possibility that some patients will also be treated with Roferon off label does increase slightly this value.

And now I will turn the podium to Dr. Tiwari if there are no questions.

DR. TIWARI: I'm going to present a survey of the published literature on melanoma and interferon treatment, and this survey is essentially the same that was presented at this Committee meeting in September of 1999.

Since that time we have one major published study by Dr. Kirkwood, ECOC 1694, and the two trials that were published in abstract form were published in full reports, and last year a meta analysis of all published trials were published by Wheatly from England. We'll come to that result a little bit later.

In the survey, we have included only the randomized trials. The randomized trials that have used observational concurrent controls where interferon was used as adjuvant treatment.

And just as usual, we went to various databases and searched all of the published material with the help of the FDA library staff. We had some individual patient data in our IND files, and we used those data to get the estimate of the odds ratio and statistical significance and 95 percent confidence

intervals.

We have used the summary data from published reports. We couldn't get the individual patient data from all investigators.

We did contact some of the investigators to get the additional information so we could get a better handle on the odds ratio and the statistical significance.

The estimates of the odds ratio were obtained using Peto's (phonetic) observed minus expected methods. We used the number of observed events and the number of expected events to get the estimates of the odds ratio, the 95 percent confidence interval, and the associated P values.

We also tried to get some estimate of the survival, the relapse free survival and overall survival at a fixed point at three years.

In the published studies, we had nine trials that were published using interferon as the adjuvant treatment in melanoma, and out of these nine trials, Dr. Kirkwood's Study 1684, 1690, and 1694, they have used high dose of interferon.

Dr. Cardinali has already showed you the primary results from Study 1684 and 1690, and here at the results. These are the published results from the Study 1694 in which interferon was compared with GMK vaccine.

The point here I want to show with respect to the disease free survival and overall survival, the outcome in the interferon arm is better than the vaccine arm.

There were two studies in the literature that have used low dose of interferon. One is study from Italy's Rusciani, et al, and the Scottish Melanoma Group published by Cameron, et al., have used the low dose INTRON-A.

The study by Rusciani, et al., did not give any Kaplan-Meier estimate of the overall survival or relapse free survival. They just gave recurrence rate at three years, and in this history, the control arm at 30 percent recurrence rate as compared with only 13 percent in interferon arm. So here, again, with respect to recurrence rate, interferon shows better outcome.

And the difference of this 17 percent was significant.

And here are the results from the Scottish Melanoma Group where low dose INTRON-A was used. This is relatively small study, but here again, the interferon arm, the outcome in the interferon arm is somewhat better than the control arm.

Then we have four studies in which Roferon was used. The study by Creagan, et al., used high dose of interferon, and the three other studies, Cascinelli does a WHO trial, and Grob did the French trial, and Pehamberger the Austrian trial. The last three studies have used low doses of Roferon-A.

And here are the results from the Creagan trial. Again, just like before, the interferon arm is somewhat better than the control arm with respect to the disease free survival and the overall survival.

This is the result from Cascinelli, et al, the WHO trial, in which low dose interferon was used. The results of the no treatment and interferon arms are very close, but here again, the interferon arm is just slightly better than the control arm.

This is the results from the French study, Grob, et al. Interferon again just like what we saw before. The interferon is just somewhat better than the control arm with respect to the disease free survival and overall survival.

And finally, we have the data from the Pehamberger study, the Austrian melanoma group trial. They give only results for the disease free survival. There is no result with respect to the overall survival in this trial, and here again, the interferon arm is better than the control arm.

So using the data from all these nine studies, we got the estimate of the odds ratio, the 95 percent confidence interval associated with this odds ratio, and we tried to get some estimates of the odds ratio based on all of the data that's available in this literature survey.

In this graph, the small vertical line is the point which indicates the estimate of the axis for that particular study. The horizontal line around that small vertical line is the width of the 95 percent confidence interval.

The blue line at one is the reference point when, if the interferon arm and the observation arms were showing identical results. Then the odds ratio would be equal to one.

And if odds ratio is less than one, then the interferon arm is doing better than the control arm. If the odds ratio is more than one, then the interferon arm is doing worse than the control arm.

So here in the case of the relapse free survival, all odds ratios are less than one. They're very consistent. They're all less than one. However, five of these studies, the 95 percent confidence interval processes the reference line of one showing that there is no significant difference between the treatment and control, and we saw some of these were very, very close.

The overall estimate of the odds ratio based on 3,536 patients all together is here at the bottom in the color bar and that estimate is .8, which is highly significant with a P value of .0001. So with respect to the relapse free survival, we have 20 percent reduction in relapse rate based on all the

data from these nine studies, and that's highly significant.

With respect to the overall survival, the trend is similar. All estimates of the odds ratio for overall survival is less than one, some of them just slightly below one; some of them a little bit better than that.

But here in comparison with the relapse free survival, there is only one study, Dr. Kirkwood's. I think it is the 1694 trial where the difference between the treatment and control is significant. Other studies, individually they do not show significant difference between the treatment arm and the control arm.

The overall estimate of the odds ratio is about .9, and that line, the upper limit of the 95 percent confidence interval crosses the line of one with a P value of .065. So it is of borderline significance, not significant at 5 percent. The P value is .065.

Finally, we saw a published report. It's in an abstract form in last year's ASCO report, a meta

analysis published by Wheatley. This is a British group. They have looked at essentially the same database that we have looked at with the two differences. They have used data from two EORTC trials and one British trial.

They say that they have used only the published reports with the exception that the two EORTC trials and one British trial, they have used the individual patient data.

These three trials have not been published, and we do not have access to these data. Therefore, we have not used in our combined analysis.

However, this group has not used Dr. Kirkwood's 1694 trial in their combined analysis, and they have approximately 3,700 patients. We have a little bit less than that, about 150 or so less than that.

The results published in this abstract is very similar to our results. Those two estimates of the odds ratio for the disease free survival are almost identical. The estimates of the odds ratio for the overall survival are almost identical, and that's

not surprising. We are essentially looking at the same database, and we came up with the same result.

But the point that I want to argue is the two independent groups of people have looked at the same data, and they have pretty much the same conclusion.

Then we also looked at the effect of interferon at a fixed time point, at three years, and if you pull all of the data together from these studies, it shows about eight to nine percent absolute improvement in relapse free survival at three years, and about half of that, four to five percent absolute improvement in overall survival at three years.

So, in summary then, based on all of the published studies, we have clinically important and convincing evidence of reduction in relapse. It's about 20 percent reduction in relapse rate, and the P value is highly significant, that is, less than .0001.

We have some evidence of improvement in survival. Again, the totality of the evidence shows that about ten percent of the reduction in death rate, and this P value is about .065 in our analysis, and

the British group says it's .05, exactly .05, but they have about 150 or so more patients in data. So the difference could be because of the additional patients that they have in their analysis.

And finally, in the last slide, we have listed some effects size in other adjuvant treatment. We have seen in melanoma we have 20 percent reduction of the recurrence rate. In 5 FU/Levamisole in colon cancer the effect size is about 38 percent, but for Taxol and Tamoxifen it's very similar to interferon, about 22 percent.

With respect to the death rate, we saw in the interferon our estimate of about ten percent. It's about 35 percent for 5 FU/Levamisole in colon cancer, 26 percent for Taxol in breast cancer, and 18 percent for Tamoxifen in breast cancer.

So the effect size of interferon is somewhat similar to the effect size of the other adjuvant, especially in breast cancer with respect to the recurrence rate, but is much smaller with respect to the overall survival as compared to the Taxol, Tamoxifen and Levamisole.

Thank you.

CHAIRPERSON NERENSTONE: Next on our agenda, Dr. Kirkwood is going to discuss the efficacy and safety of high dose interferon, the ECOG and intergroup trials.

DR. KIRKWOOD: Members of ODAC and esteemed colleagues, it's a pleasure to return to present these data to you, having been here in 1995 for 1684, in 1999 for 1690, and now with perhaps the chance to review the aggregate of our experience to date.

So I will lead off, and then after my presentation -- and I should say I'm John Kirkwood from the University of Pittsburgh -- Joe Ibrahim, statistician for the ECOG for the last eight years, will present statistical design issues that have been our consideration for the 1690-1694 intergroup trials, and for a host of subsequent trials which we have been designing and undertaking, as he will show you.

The rationale for the inclusion of Stage IIB and Stage III patients into our trials of adjuvant therapy is illustrated here where for Stage III the

relapse free and overall survival is very short. As you know, the survival for these patients, a median of three years or less on the basis of the AJCC data that was as the trial 1684 and 1690 were designed.

According to the more recent AJCC 2002 formulation, the risks are much more precisely defined for subsets of patients, and what I've illustrated here in white are the groups of patients who would have been those entered into the three trials we'll talk about.

I should note for you that we have now T3b, that is to say ulcerated intermediate depth tumors, which have a very similar prognosis to several of the groups that were entered into these trials, and that in overview those patients who have either deep primary tumors or who have microscopic regional lymph node disease have a greater than 30 percent mortality at five years from this disease; that those patients who have macroscopic or palpable node disease, and certainly those with recurrent nodal disease that were included as half of the trials we have talked about, have a 60 percent mortality at five years or greater,

and so the risk for these patients is certainly not low.

Sentinel node mapping has come of age in the interval. We have conducted these trials, and this is data from Jeffrey Gershenwald showing you that for patients who have been identified to have microscopic regional nodal disease, the 36 month relapse -- and here it's plotted in the orange line -- is about 50 percent, and so microscopic nodal disease in Gershenwald's summary studies is certainly also an ominous feature.

So the entry criteria for the studies we'll talk about, for the first two studies, E1684 and 1690, observation controlled trials conducted 1984 through 1995 in terms of the design. We had treatment versus observation.

After the approval of this, the first trial that was initiated after the approval of high dose interferon, we tested a promising vaccine against high dose interferon.

The entry criteria broken out for these trials is summarized here. Stage IIB disesae, where

either the patients were established as an E1684; the were all established to be free of disease by elective node dissection or, in subsequent trials where from five to 20 percent of patients had selective node dissection or elected no dissection.

In 1690 and 1694, as has already been mentioned, clinically node negative patients were allowed to enter, but far and away the largest groups of patients had nodal disease, either presenting lymph node disease, Stage III disease in both the old and the new system, or regional nodal recurrence, as I'll come back to discuss, is one of the most ominous prognostic factors that we have to deal with.

Summarizing the demographics of patients in the three trials we'll talk about, 1684, 1690, and 1694, we see a rise in the number of patients who had node negative disease, from 11 percent in 1684 to a quarter of the patients in 1690 and 1694.

By converse, the proportion with recurrent nodal disease fell from two thirds of the highest fraction in 1684 to half in 1690 and a third in 1694.

The E1684 design, as has already been

discussed, involved observation control induction with four weeks of intravenous daily therapy with 20 million units per meter squared per day, five days a week for four weeks, followed by maintenance therapy at ten million units per meter squared thrice weekly for 48 weeks.

As Dr. Ibrahim will discuss more, this design was an exponential model. We did not know the cure rate data that was the basis for cure rate models in subsequent trials, and stratification used AJCC stratifications that were then currently available, although subsequently we have analyzed this trial for numbers of nodes involved, and there is good balance.

The results of the 1684 study show that median relapse free survival was improved, as has already been mentioned. P1 value, the one sided P test as designed in the trial, .002. The overall survival improved, again, one sided test, .023. And the estimate of five year relapse free survival rose from 26 percent to 37 percent. The estimated five year overall survival from 37 to 46 percent.

This is the graphic that you've seen now

to many times. High dose interferon with after four years an apparent plateau in the relapse rate of patients who were treated. Observation in blue. The prolongation of median interval to relapse from one year in 1684 observation arm to 1.72 years, for a nine months' gain, from this treatment.

The overall survival as published at seven years of follow-up, again, an apparent plateau beginning after five to six years and a rise from 2.78 years' median survival in the observed population to 3.8 years in the treated population.

The conclusions we drew from this study, that both relapse free and overall survival are significantly prolonged with high dose interferon; that after surgery alone, half of patients in the observation arm relapsed. So, again, not a favorable group, even though that has been said otherwise.

High dose interferon was proved on the basis of testimony in July of 1995, and basically to stack this up against the available other therapies, the 11 percent relapse free survival, nine percent overall survival gain compare well with the NSABP-93

publication for FU leucovorin, nine and seven percent, for rectal carcinoma as you see here, and for breast cancer, nine percent for both relapse and survival.

So 1690 was designed already at the time that these data became available. It was already accruing. This trial was an attempt to define where the low doses of interferon might have similar benefit to the high dose interferon that was seen already in 1684.

The goal now by cure rate model, as Dr. Ibrahim will discuss in detail, to analyze this impact and to stratify both by numbers of nodes involved and by the old AJCC stage groupings.

The benefit now expressed in terms of hazard ratios with observation compared to treatment show that for high dose interferon the hazard of relapse is 1.28 times greater for the observed patients than those who receive the interferon; low dose interferon, 1.19.

This approached marginal significance. This, of course, is not, and there was no survival benefit, as you see with hazard ratios, one for both

survival impacts.

The graphic that you've seen already for high dose interferon, a benefit compared to observation that was significant, .05; for survival, obviously no difference in this trial.

So we looked at this trial, and we asked what could have been the difference, and this is a graphic display in histogram fashion with observation groups in blue, treatment groups of high dose interferon in yellow. The period of time up until relapse in the darker portion of the bars.

And what one sees is that in observation of 1684 versus treatment in 1684, we gained nine months in relapse free survival. In comparison, in 1690 we gained ten months in relapse free survival, but the anomalous feature in this histogram presentation is the post relapse survival of the patients entered into the observation arm in 1690.

So the question became what could this be due to, and the answer, apparent because we had already testified and we already had the approval of this, is the patients had access to interferon in the

1690 observation arm, and when we looked at these patients who had failed observation with regional resectable nodal disease, we discovered that in every single case but one resection had been done and treatment after the fact, crossover to interferon had been given.

And so unplanned, because at the time that this study was designed we didn't know 1684 would be proved, we have asymmetrical crossover that may have provided the explanation for some of these differences.

The overall survival plots have taught us some other things. For 1684 in the dark blue, 1690 in the light blue, the evidence that we need prospective, randomized Phase III studies to draw any conclusions is illustrated here.

This is the survival of patients in 1684 who were observed. This is the survival of patients in 1690 who were observed, and this difference, the improvement in survival of observation patients between these trials, is as significant as any difference in the trial itself as it was planned to be

analyzed.

But we wondered further could it be due to things before relapse since much of what I said could have been all post relapse differences, and so we looked at the largest single subset which is one node positive patients, and this is from Tom Smith's analysis of the single node positive patients, but basically here for the one node positive patients in 1684, the one node positive patients in 1690, the survival outcome for observation patients has also improved.

And so it is both relapse free differences and post relapse differences that may have confounded these differences between the trials, and we do not have the explanation for why 16980 did not confirm 1684 completely.

There is certainly a consistent relapse free survival benefit for high dose interferon as observed between these two trials. There is no significant benefit with low dose interferon.

There was a lack of a survival benefit with either high doses or low doses in the 1690 trial,

and I said already the post trial crossover may have explained some of this.

We then had the opportunity to develop a trial based upon the work out of Paul Chapman's and Phil Livingston's studies at Memorial Sloan Kettering with what we thought was the most promising vaccine in 1994. This trial, based upon the GM2 vaccine work that Phil Livingston had published, incorporated the Progenics (phonetic) produced GM2 KLH 2S21 vaccine known as GMK, and patients received 96 weeks of this vaccine compared to the high dose interferon, now the first trial in which we have compared a new agent against the high dose interferon modality.

These patients, 880, were randomized within 70 days of surgery to determine if GMK was superior to high dose interferon, and we employed early stopping rules because we had benefit for interferon already defined, and we did not want this trial to proceed if the patients assigned to the vaccine would be at increased risk of death or relapse in the study.

We employed a cure rate model, as Dr.

Ibrahim will more eloquently than I can describe go through this, and we stratified by numbers of nodes in entry to this trial.

These are the data that led to the early unblinding and closure of this study in 2000 when the data suggested that there was both highly significant survival advantage for interferon over the vaccine and relapse free interval benefit for the interferon compared to the vaccine.

For the intention to treat and eligible populations, we have a hazard ration of 1.49 for relapse. It means that the patients who were assigned to the vaccine had a 50 percent higher, a 49 percent higher relapse rate, significant as you see here to a log rank P value of .001 to .004 -- 00045, both by log rank and by cost analysis.

In terms of survival, we have a hazard ratio of 1.52 to 1.38, again, a significance of .20 to .009 for survival benefit of the interferon recipients over the vaccine recipients at the time of early closure of this study and unblinding in 2000.

These are the published results from last

year's JC article, interferon in yellow, vaccine now in red, showing the relapse free survival benefit of interferon compared to the vaccine.

As you see, the numbers in the interval below show about a 50 percent higher number of relapses in each of the intervals for the vaccine as compared to the high dose interferon.

In terms of survival, again, the published results, interferon, and the vaccine for each of the intervals. Again, a death rate that has increased for the recipients of vaccines, about 40 to 50 percent higher than for the interferon alone.

We were interested to look back at subsets because much ado has been made about the differences in the 1684 trial where the patients with no nodes involved did not fare well with interferon. This is by all odds the largest subset analysis that we have had to work with in terms of node negative patients, and here we have one node positive, two to three nodes positive, and four or more nodes positive.

And the first conclusion is that there is a homogeneous impact across all four of these subsets

favoring interferon. To our surprise, the node negative population, a quarter of the patients who entered this trial, have a significant impact in this subset alone.

This has been a source of confusion, and in fact, a letter to the JCO next week will be published suggesting -- and I would like to reiterate here that this does not mean there was no impact in these groups. It just means as a subset the node negative population, the T4 node negative Stage IIB patients derived benefit, which by itself was significant as analyzed in this trial.

So the largest trial to date, highly significant RFS and OS benefits for high dose interferon; confirms the 1684 benefits for relapse free and overall survival.

And I should note here, although I haven't put it into this talk, the evidence that there is no suggestion of an adverse impact of the GMK vaccine upon either relapse rate or survival in this trial. In fact, to the contrary, when we look at antibody responders to the vaccine, they actually almost had a

P of .06, a benefit in terms of survival in this trial.

The benefit was consistent across all of the stratification subsets, and this then is a summary of the 1684, 1690, and 1694 populations for subset impact with no nodes involved, one node, two to three, and four or more nodes, where in 1684 the one node positive population did the best. In 1690, as I've not had a chance to mention, the two to three node positive group had the best outcome. And now we see the best impact and the overview take on this is that there's only one subset, the smallest and one that we knew was unbalanced that has not shown a benefit. That was in 1684.

So I think the highest level of evidence that we have for evidence based medicine now, based on the analysis of trials is they were designed and the primary endpoints of these in a randomized head-to-head setting is that high dose interferon is an active regimen, is the only one that has demonstrated consistent relapse free and overall survival benefits compared to either observation or vaccine.

The benefit of the high dose interferon is consistent across the nodal subsets in all of these trials.

The obstacle, as you've heard already, is toxicity, and illustrated here for the patients in the 1684 trial is the numbers of patients who had the various toxicities listed here in any grade, and what I've listed here is the percentage of patients for 1684, 1690 and 1694 who have experienced Grade 3 or 4 toxicity according to fatigue, or about a quarter of patients may have Grade 3 to 4 fatigue, and where myelosuppression rose in the fraction of patients who experienced severe myelosuppression from a quarter to, say, two thirds of patients.

And similarly, the fraction of patients who had Grade 3 to 4 hepatotoxicity rose from 14 to 29 -- 27 percent in the more recent trials. We have had no toxic deaths in any of the intergroup studies, either 1690 or 1694, and the two deaths that were already mentioned occurred in 1684 before rigorous monitoring of liver functions were adhered to.

A summary of toxicity then is that all

patients have some toxicities with the interferon. Some patients experience more severe side effects, including fatigue and flu-like symptoms, neutropenia, abnormal liver functions, and neuropsychiatric depressive toxicities.

But I think the bottom line is the numbers of patients who complete a year of this treatment, if they do not relapse, the fraction of patients who can complete one year of treatment is 24 percent in -- I'm sorry -- is 76 percent. We only had to stop in 24 percent in 1684; 87 percent in 1690 completed a year of treatment. That is to say only 13 percent had to stop and remove themselves from treatment; and we now have 90 percent of patients in the largest study completed to date in the 1694 study who have had to come off treatment due to toxicities.

And so this is a deliverable regimen.

I'd like to now turn to a pooled analysis that we presented in part to ASCO, and it's been conducted with the intergroup participants from SWOG, from CALGB, and from the M.D. Henderson in these studies. For these I'll pool the results of the 1684-

1690 trials, which were observation controlled, and we'll also include for prognostic analyses the 1694 and the 2696 studies, which did not have observation control, as you've already heard.

We'll also update the results of these three trials to the April 2001 time point and try to identify factors of prognostic importance, and that may be related to treatment outcome in these studies.

The methods were that we updated each of the trials because all of these had their data stored in the ECOG database. Relapse free and overall survival data were analyzed using two sided univariate log ranked statistics. The covariates were treated as dichotomous variables or continuous variables as we had them in the bank, and that log rank statistics were used for the dichotomous variables. Then a Cox model was developed.

These are the patients who entered these trials and the intervals of follow-up that we have. So 1684 is now 12.6 years in median follow-up, and 1690 is 6.6 years in median follow-up; 1694 is 2.1 years in follow-up, and the smaller Phase 2 study,

nearly three years in follow-up.

There were 352 patients who were observed for these analyses, 799 who received high dose interferon, and 474 who received the vaccine GMK.

I should note that we have both the failures and debts separately. We have the debts for each of these studies plotted and analyzed.

The demographics are the demographics that we expect from Intergroup Melanoma Studies, two thirds of patients male. A third of the patients who entered these studies had ulceration of their tumor and half had recurrent disease, an adverse factor that we will come to in a minute.

So this is the 12.6 year data for the E1684 study in terms of relapse free survival, and the curve has the flattening that we talked about before. This is stable out as far as we can go, and it should be noted again that every patient that entered these trials had elected node dissection. So failures in this trial are distant failures. This is distant relapse free survival, which the EORTC has taken as a surrogate for overall survival.

The 12.6 year data for survival, as you've already heard, has a one sided P value of .09, but this is all causes of death. So this is patients who are in their middle 60s because they entered the study at 50 years of age, and all causes of death, whether melanoma or otherwise, are included in this attrition which exhibits a plateau out as far as the median that we have here of 12 years, but certainly is not what we had seen at seven years completely.

The 1694 study relapse free survival has interferon in dark yellow on top still. The significance is still the one sided P of .05 that we published, and so this is stable, and there is no survival impact as there was none as this study was originally reported.

The 1694 study, now more than two years in median follow-up, preserves a significant P value for relapse free survival. The differences that we have here in terms of relapses, 159 dead or relapsed on high dose interferon, 202 on the vaccine pulled up exactly as they were published a year ago.

The differences in overall survival also

remain significant for the 1694 interferon arm, the 1694 vaccine arm, the one sided as it was designed to be analyzed, .02, but if you'd like to double it for the two sides test, .04, retains significance.

For the pooled observation controlled studies we have a significant relapse free interval impact, and this is interferon at 1684 and 1690 together. Observation in 1684 and 1690 together. The hazard ratio, 1.3, a 30 percent increment in the relapse risk of patients who were assigned to observation in the aggregate of these two studies.

The overall survival pooled between these studies where the 1690 study was larger was a negative study, does not have significance. The hazard ratio, 1.07.

So looking at prognostic factors that may be identified in this pooled analysis, the importance of recurrence of disease, highly significant in terms of relapse free survival. Ulceration of the primary, as is well known.

Curiously, entry into the 1684 study, an independent adverse prognostic factor of significance,

and the previously reported LDH, depth of tumor, age over 49, and site entering in.

In terms of overall survival, ulceration remained significant. Occurrence of disease remained significant, and still the entry to the 1684 study is a significant independent adverse prognostic factor.

Looking for treatment effects, if we ask then from these pooled data what is the adverse impact of assignment to observation in the pooled analysis, the hazard ratio, 1.28; the significance, .01. Accounting for all other prognostically significant factors, ulceration, 1684 trial entry, and recurrence of disease remained significant as well.

In terms of overall survival, 1.07 for the treatment effect, not significant, and we retained the 1684 recurrence of disease and ulceration as already mentioned.

So in summary then, 1684 we have a significant relapse free survival benefit of high dose interferon versus observation, still evident at a median follow-up of 12.6 years. Overall survival benefit, significance is diminished, but there are

many competing causes of death that has eroded this in all likelihood.

Sixteen, ninety, neither relapse nor survival benefit in aggregate, and overview now: 1694, high dose interferon significantly, superior to the vaccine GMK for both relapse free survival and overall survival at 2.1 years.

Based on the two sided unit variate log rank analyses, high dose interferon significantly improved relapse survival compared to observation. The factors predictive of reduced relapse free survival and overall survival, ulceration, recurrence of disease, the old study entry of 1684 and age over 49.

Adjusting for these prognostic factors, we preserve relapse free survival benefit for high dose interferon. We do not confirm overall survival benefit.

The highest level of evidence, as I mentioned already, from the three trials taken together, high dose interferon has demonstrated consistent relapse free and overall survival benefit

compared to either vaccine or the observation arm.

Pooled analyses show significant improvements for relapse free survival, but not for overall survival, and the meta analyses that you've heard about from Dr. Tiwari also support this with a trend to dose effect as well.

Where we are going, since Karen very clearly pointed to the fact that we need new studies, is to evaluate more aggressive combinations. Chemo-biotherapy, for instance, may have an impact which is superior to that of a high dose interferon. This trial, this SWOG 0008 intergroup trial testing three cycles of chemo-biotherapy versus high dose interferon as a head to head comparative Stage IIIB and Stage IIIC trial.

We would like to improve the therapeutic index of the high dose interferon modality. We'd like to ask the question whether one month is necessary and perhaps sufficient.

So the intergroup 1697 studies testing whether one month alone given to patients with Stage IIA disease who do not have an effective available

therapy may be superior to observation, and DR. Ibrahim will run through the statistics of this in a much greater detail. So I'll skip over those now.

If we fail to answer that question about whether one month is the kernel of the 1684 regimen, we'll have to test this in equivalence design. The 1601 has been a trial that has been our first effort at designing equivalence trials, and Dr. Ibrahim will also discuss this in some detail.

We'd obviously like to introduce new cytokines and peptide vaccines for interferon failures. The trial which is now going on in the intergroup testing, GMCSF and multi-epitope peptide vaccination is a test of the potential utility of GMCSF in patients who have failed interferon or have disease beyond the spectrum of what interferon was designed to treat originally.

Strategies to develop new adjuvant therapies built from Stage IV experience are the 1696 trial where we're testing multi-FFO peptide vaccination with or without interferon and with or without GMCSF, and this trial is more than half

completed now to try to pave the way for new adjuvant interventions of interferons combined with the peptide vaccination.

Dr. Slingluff's trial, E1602, is a multi-epitope peptide vaccine trial which also may be a source of adjuvant efforts in our committee. We would like to define the molecular intermediate endpoints of interferon action and the current trial testing this in terms of the marker EFGF. Basic fibroblast growth factor is E3601.

So I think with that I'll close and turn it over to Dr. Ibrahim to talk about the statistical design.

DR. IBRAHIM: Thanks, John.

I'm going to focus much more on trial design for adjuvant studies in ECOC and really not discuss data analyses, but how we've designed the trials 1684, 90, 94, and other studies, 1697 and future trials and current trials that are open now in ECOG.

So just a brief outline of what I'll discuss. The cure rate model has played a very

prominent role in trial design for all of these ECOG studies. So I'll talk a little bit about the rationale for using that model, and we'll talk about what it is because it's very important in the studies that we've been designing in all of these ECOG trials, and then I'll talk a little bit about how we design these trials using cure rate models, and in particular I'll focus on designs for 1684, 1690, 1697 and 1694.

Some of these, 1697, for example, are still open. The others are now terminated and published, and then we'll turn it over to non-inferiority designs using cure rate models, in particular, proposed Study E1601 is designed as a noninferiority study.

And then we'll talk about future trial designs involving high dose interferon.

Okay. What's a cure rate model? The cure rate model is used for designing studies with any time to event endpoints as the primary endpoint, such as RFS and OS, and it's most useful -- these models are most useful when a plateau is reached in the survival curve after a sufficient period of follow-up.

And we have observed in these ECOG studies in adjuvant melanoma studies this plateau occurs usually after five years of follow-up, and as an example, we see here in 1684 this is based on the updated data. We see that about after five years of follow-up a plateau starts to occur in the survival curve for both of the arms, and it's important then in designing trials to try and capture this plateau because the behavior of the right tail of the survival curve really is important to characterize in trial design, and this is exactly what the cure rate model tries to do.

And we see the same behavior even with respect to overall survival. So regardless of endpoint, we see this plateauing effect occurring in all of these adjuvant melanoma trials.

The same thing for 1690. Relapse free survival, we see this plateauing effect in both of the interferon and observation arms.

So the cure rate model basically works like this. It assumes that the study or the population can be subdivided into two subpopulations,

those that are cured and not cured, and the word "cured" here is being used loosely to just mean that a plateau occurs in that particular time to event.

So it's relevant to use the word for relapse free survival. All it means is that a plateau occurs after sufficient follow-up.

So the subdivided populations then consist of a proportion of patients who were cured. We'll call that proportion pi, and a proportion of patients not cured. We'll call that one minus pi.

And the proportion that are not cured experience events according to an exponential model with a hazard rate lambda, and then one can write down the probability of surviving beyond a certain time point as a mixture between those that are cured and not cured, and this second bullet here then gives the survival function for the cure rate model.

And so one can view SFT as representing the vertical axis in the Kaplan-Meier plot, for example.

So just to see how things work here, pi equals .26 means that 26 percent of the population is

cured and 74 percent are not cured. Pi equals zero means that zero percent are cured, and then this just reduces to the exponential survival model, and these are the models that have been traditionally used to design both adjuvant and metastatic disease trials.

And so we're trying to go beyond that now, and the exponential model then is a special case actually of the cure rate model.

And we've found the cure rate model to actually fit the data better than an exponential model when this plateau actually occurs in the data, as did for 1684. So it turned out that once the 1684 trial was unblinded, the cure rate model actually fit the data better than an exponential model, and that's what led us to design 1690 using a cure rate model.

One of the nice properties of the cure rate model is that if one uses the log rank test to design the study, the cure rate model actually has nice properties and yields high statistical power when this test is used to design the trial.

Okay. So now what I want to do is review ECOG Study 1684, 1690 and 1694, and talk about how

these trials were designed and then move on to future designs of trials.

Sixteen, eighty-four, as John mentioned, was a two arm study of high dose interferon versus observation, and here in the design of this study, since we had no previous data to guide our design, an exponential model was used to design the study since there was no prior experience to guide the design. Four years of accrual were assumed, three years of follow-up, and a sample size of 285 gave 83 percent power to detect a 50 percent improvement in median RFS from 1.5 to 2.25 years.

Sixteen, ninety was a three arm study involving high dose, low dose, and observation, and this was the first adjuvant melanoma study in ECOG that used a cure rate model in its design, and the cure rate model was based on the E1684 experience, which I'll discuss in a moment.

In this study then we had four comparisons of interest, high dose versus observation, and with respect to both of these endpoints, and low dose versus observation also with respect to both of these

endpoints and a one side significance level of .025 was used.

And the way we designed 1690 is that we fit a cure rate model to the 1684 data and obtained estimates of the cure rate and the hazard rate for those not cured, and so for the RFS endpoint, the estimate of the cure rate for the observation arm was 26.4 percent for the 1684 data and 32.5 percent for overall survival, and the estimate of the median relapse free survival for those not cured was about a half year for RFS and 1.32 years for OS.

And so these numbers then were used to design 1690 and we fit the data both to the observation arm and to the high dose interferon arm, and the cure rate for the high dose interferon arm for 1684 was estimated to be 27.9.

And so this led to the following design. We assumed four and a half years of accrual, two and a half years of follow-up, a sample size of 625 yields 81 percent power for RFS to detect a ten percent absolute increment in the cure rate, and a 50 percent relative increase in median time to event among the

non-cure group.

And these were the estimates observed in 1684. So they weren't coming out of a vacuum, and the same increments for the overall survival endpoint giving 82 percent power.

So precisely here at the known alternative hypotheses for both of these endpoints. The cure rate under the null hypothesis, 26.4 percent. This was, again, the estimated cure rate from the observation arm. Median time to event for not cured is 6.9 months, and under the alternative, this is the high dose arm of 1684, 36.4 percent and 10.4 months, median time to event for the high dose interferon arm, and similar increments for the overall survival endpoint.

So these were the design specifications then that were based on fitting the 1864 data to cure rate model, and then we used a sequential monitoring plan, and we actually -- any Phase 3 study in ECOG involves a sequential monitoring plan. So we use that for 1690, which four interim analyses were planned at corresponding equal increments of statistical information.

So these two tables give the sequential monitoring plans for the four comparisons for both endpoints, and we see here that four interim analyses were done, and this column is the information time, which is just a fraction of the number of events at each interim analysis. So 65 over 252 is .258, and so forth.

The third column is the nominal significance level and the same information for the other comparison, and here since E1690 and 1694 both had RFS and OS as primary endpoints, we line up the analyses to correspond to the same chronological time. Since the events were occurring faster on the endpoint of RFS for these two studies to be analyzed at the same chronological before the DMC, the information times would be slightly different.

Okay. So let's then move on to 1694. Sixteen ninety-four was a two arm study comparing GMK to high dose interferon, and this was the first melanoma trial in ECOG using HDI as the control arm.

This was also designed as a superiority trial and a cure rate model was also used in the

design, and one sided significance level of .025 and the cure rate at median time to event for the high dose interferon arm were estimated from the 1690 data.

So the design specifications for 1694 actually came from fitting a cure rate model to 1690. So the assumptions for the design were 3.3 years of accrual, two years of follow-up, a total sample size of 851 patients led to 86 percent power for RFS, 80 percent power for OS, and this, again, was based on a ten percent increase in cure rate and 15 percent relative increase in median time to event for the non-cure group.

And so specifically here with the design specifications, these cure rate percentages were being estimated from the 1690 data, as well as the median time to events for the high dose interferon for both relapse free and overall survival. And the increments that we specified were similar to those for 1690.

Again, here is the sequential monitoring plan for 1694. Four interim analyses; again, information time. The expected number of relapses under the alternative, and both 1684 and 1690 and 1694

were designed with O'Brian-Fleming upper boundaries for rejecting the null hypothesis, and that's what these boundaries were at each of these interim analyses, and this was the nominal significance level corresponding to that boundary.

So, again, RFS and OS were primary endpoints in this trial. So to line up these interim analyses at the same chronological times, the information times will be slightly different. So the sequential monitoring plan was driven by overall survival here, and the goal was to try to do the interim analyses at equal increments of statistical information, 25, 50, 75 and 100 percent.

Okay. Now we move on to 1697. Sixteen, ninety-seven is a trial that's still open. It hasn't terminated and is still accruing patients, and it involves a different patient population than 1684, 1690, or 1694.

In particular, 1697 involves the T3, as John mentioned, for the U.S. and for NCIC and Australia, T3NO, T4NO, and NET and N1a, node one positive patients.

And so this is the first ECOG trial for this patient population actually, and it was a two arm trial of one month high dose interferon versus observation, and it was also designed as a superiority trial.

Again, the primary endpoints are both RFS and OS, and again, a cure rate model was used in the design with a significance level of .025. The sample size of 1420 patients is based on three years of accrual, three years of follow-up. Eighty-eight percent power for both RFS and OS to detect a seven and a half percent increase in the cure rate.

So this trial design involved an increment of less than ten percent, and a 15 percent relative increase in median time to even for the non-cured group.

And so here's a summary of the design specifications for the cure rate model. We notice here since this is a slightly healthier patient population than 1684, 90 or 94 the estimates of the cure rate were higher than these studies, and in particular, actually these estimates were coming from

the node negative and node one positive patients in 1684 and 90. So we fit a cure rate model to that subset and obtained these figures from that subset.

And the same thing with the median time to event. These figures were coming from the subset of patients on 1684 and 90 that were node negative and node one positive.

Here's the sequential monitoring plan for 1697. The same kinds of numbers as before, except the one distinction here is that with healthier patient populations and especially when you expect this plateau to occur in the survival curve, the events are going to start occurring much less frequently once you get beyond a certain period of follow-up, and so we inserted an extra interim analysis here so that there wouldn't be a long time between the third interim analysis and the final analysis.

And so here we inserted another interim analysis at 90 percent information so that there wouldn't be such a long wait in between interim analyses.

Again, the same story for OS. The

boundaries here are O'Brian-Fleming upper boundaries and the nominal significance levels correspond to those.

One of the critical issues now in ECOG trial design is conditional power, and conditional power considerations are essentially playing a prominent role in any ECOG trial, especially ones in which you might not expect the experimental arm to be doing much better than the control arm.

So the idea of conditional power, it's a conditional probability calculation, and it's the probability of observing a significant result, given the current data and the specified alternative under the statistical design.

So what this conditional power calculation allows us to do is essentially compute the probability of getting a significant result at full information at the final interim analysis, given the current data and the specified design parameters under the alternative.

And again, the idea behind conditional power is it allows us to stop the study early if the experimental therapy is not much better than control,

and one issue that I'll discuss later is the timing of the conditional power calculation is critical, I think, because we want to do this calculation when we have sufficient follow-up in the trial.

So as I noted in most ECOG studies now, we implement traditional power calculation as part of the interim monitoring plan, and in particular traditional power is very important in trials that have observation arms and trials that are of the form A versus A plus B, that is, a regimen called A versus A plus something else.

And clearly here the A plus something else is generally more toxic and more expensive than A. So we want to stop the trial earlier if A plus B is not much better than A.

So these are two scenarios under which conditional power is very important, and 1697 conditional power was part of the monitoring plan, and we see that conditional power plays now a very prominent role in these types of studies, as well as noninferiority designs which I'll discuss now.

So noninferiority designs, I think, will

play a prominent role in future designs of ECOG, and especially future designs that involve high dose interferon as the control, and in particular, we envision future trial involving HDI and a vaccine or HDI and a combination of HDI and a vaccine, and my conjecture is that these trials will be designated as noninferiority designs rather than superiority designs.

We learned a great less from 1694 that perhaps it wasn't the best idea to design it as a superiority trial. So within the context of the cure rate model, these designs can be constructed by essentially taking small differences in the cure rates, and I think that's where the cure rate model really has a great benefit here, is that you can dictate equivalence trials essentially by specifying the cure rate difference.

Again, the cure rate difference is the tail area in the survival curve, and I think most people would agree that that's where the important action is. We want to know what the tail behavior is in the two arms after a sufficient period of follow-

up, and that's what would dictate then in an equivalence trial.

So you don't get it for free though because the sample size is increased dramatically when the cure rate differences become small, and so there's a price that one pays in the sample size. So there's the issue of feasibility versus how small of a cure rate difference you want between the two arms in an equivalence trial, and so typically in noninferiority or equivalence trials -- I'm using these two words interchangeably here -- the higher significance level than a nominal level of .05 is acceptable to use in these types of trials.

Sixteen, oh, one is a currently proposed study in ECOG, and it involves a slightly different patient population than 1697. It involves T4NO, NET, and N1 and N2 patients. So it involves one node positive and two nodes positive, and this is a study that's currently being proposed in ECOG.

It's designed as a two arm, noninferiority trial of one month high dose interferon versus one year in which the primary endpoint is relapse free

survival. And so when designing a noninferiority trial, you need a definition of noninferiority, and that depends on the disease site. That's disease site specific, as well as patient population specific and study specific.

And the way we've defined it here is that we'll declare one month noninferior to one year if there's less than a 25 percent absolute difference in median RFS for those non-cured and less than a three percent absolute difference in the cure rate between the two arms.

So these are the two design parameters that one needs to specify in a cure rate model, and we claim that the much more important parameter is the cure rate rather than the median time to event in those not cured.

We really are willing to allow a bigger difference in the median time to event for those not cured, but are not willing to specify a large difference in the cure rates. In other words, we want the tails of the survival curves to be virtually closed, and that's what we'll declare equivalence.

And so that's the way we've defined it for 1601, and equivalence trials are ones in which you allow the significance level to be higher than the .05 level, but ones in which you desire a higher power than the usual 80 percent. So 1601 was designed with 95 percent power and using a one sided significance level of .075.

And we assume four years of accrual, six years in follow-up. A sample size of 2,780 patients yields 95 percent power for RFS. To detect this three percent increase in cure rate between one month and one year of high dose interferon and the 25 percent increase in the median time to event for the non-cure group, and again, here is a summary of the cure rate and median time to event.

We assume 63 percent cure rate on the one year high dose interferon arm, 60 percent on one month, and .9 years on one year, and .65 on one month.

Again, we use a sequential monitoring plan in which we use an O'Brian-Fleming upper boundary for early stopping in favor of superiority of the one year interferon, and so we'll stop early in favor of one

year using an O'Brian-Fleming upper boundary.

Again, we insert five interim analyses, one year at 90 percent information. However, conditional power then will be used as the lower boundary to declare equivalence or noninferiority.

So the conditional power will be computed to determine the noninferiority of one month relative to one year, and again, this is based on RFS endpoint, and the timing of the conditional power calculation is critical here because conditional power will essentially dictate whether the one month high dose interferon is noninferior to one year. That's what is going to dictate noninferiority here in the trial design.

And so the timing is important, and the first time the conditional power will be calculated for this study is at 75 percent information and then again at 90 percent information, and the rationale behind that is that we want to allow for sufficient follow-up, and the 75 percent information is one where you would expect the accrual goal to be attained for the study.

So it makes sense to do the first conditional power calculation at that information time.

This table here gives various sample size scenarios when you vary the cure rate percentages, as well as the difference in the median time to event. So this first column represents a cure rate difference between two hypothetical treatment arms. The second column represents the difference between the median time to event between the two treatment arms, and third column gives the induced sample size that would be required.

And so the main thing to glean from this table is that as one decreases the cure rate, so if we just focus on the last row here for a moment, ten percent difference in cure rate, 15 percent absolute increase in median time to event, again, requiring 95 percent power, say, leads to a sample size of 760, and as we fix this increment at 15 percent and decrease the cure rate, we see that the sample size more than doubles as we decrease the cure rate by a moderate amount.

So once we start getting in the five percent area, we here that it's essentially tripled, and then here at three percent it's quadrupled. And so there's a big price to pay in terms of sample size if one wants to do noninferiority studies.

The price is not nearly as much if we fix the cure rate and decrease the difference in median time to event. So here the differences are only in hundreds of patients.

So in other words, if I just look at the difference in cure rate of three percent and look at these increments here, there's not much of a price to pay at all, and so the cure rate parameter is the one that really drives the sample size and is one that's critical in designing noninferiority studies.

Okay. Future trial designs then we envision would be ones that would be similar to those of 1601. So noninferiority designs of the type used for 1601 will be used, we envision being used for future Phase 3 trials comparing investigational therapies to high dosage interferon, and again, the definition of noninferiority is critical.

There is not a benchmark or a conventional definition of noninferiority. It depends on the trial, and it's something that differs from trial to trial.

But the bottom line is that in any non-inferiority study with these cure rate models needs small cure rate differences. And conditional power also plays a key role in these designs, noninferiority studies, and as I mentioned for 1601, as well as 1697.

And we envision the next ECOG adjuvant Phase 3 trial will be something like high dose interferon versus the best vaccine from 1696 or the best vaccine -- actually this John called the 1602. This is the 12 peptide vaccine trial, Phase 2 trial, that's currently being proposed for other regimens, combinations of high dose interferon and vaccine.

This is where we're headed in ECOG, and we envision trials of this sort, of high dose interferon versus these as the control, and these being the experimental arms to be noninferiority studies or equivalence trials.

And one can use the methodology similar to

1601 to design these trials.

One last comment that I'd like to make about future trial designs is that we'd like to also investigate Baysian and monitoring schemes for future trials. I don't want to get into the philosophical issues of Baysian design and non-Baysian design here, but I do just want to mention that Baysian designs offer special advantages other designs may not have.

So one can do a Baysian design within the context of this cure rate model, and one of the advantages that Baysian designs have over these traditional designs that we've been discussing thus far is that they allow us to formally incorporate historical data into sample size calculations.

And the reason this is important in the context of melanoma is that we've got quite an abundance now of historical data for 1684, 1690, and 1694 for the high dose interferon arm. So this is one advantage of these types of designs, is that they allow us to directly incorporate this information into the sample size calculation.

Another advantage is that they allow us to

do continuous monitoring without paying a penalty in the Type 1 error or the significance level. So one of the practical advantages of this is that one can do an interim analysis at every DMC meeting, for example, rather than way until a certain information time has been reached.

And so this is what we mean by continuous monitoring, and this is one of the advantages that Baysian design has to offer.

And, again, as I mentioned, we have now an abundance of historical data on high dose interferon from these three studies, and so one can use the data from these studies to construct appropriate prior distributions for the effect of the high dose interferon using these data, and then these distributions can be incorporated into the sample size calculations and will often result in greater precision and smaller sample size than the traditional designs.

And as mentioned a moment ago, Baysian interim monitoring rules can be easily developed, and what we would do then at each DMC meeting is just

compute the probability that the treatment works, compute the posterior probability that a given treatment is better than the control treatment, given the current data, and this can be reported at every DNC meeting without an issue of inflating the significance level, and this is one of the practical advantages that I see in doing Baysian design.

And that's all I have.

CHAIRPERSON NERENSTONE: Thank you very much.

I would like to ask you to hold your questions until we take a break. We should be back at 10:45. Thank you.

(Whereupon, the foregoing matter went off the record at 10:34 a.m. and went back on the record at 11:05 a.m.)

CHAIRPERSON NERENSTONE: I'd like to start by asking the Committee if they have any questions for the presenters this morning.

Dr. Przepiorka.

DR. PRZEPIORKA: Questions for Dr. Kirkwood or Dr. Ibrahim.

Dr. Kirkwood, could you please give us your opinion? Did patients with locally current disesae have the same prognosis as those with newly diagnosed disease going into trials when compared node for node?

DR. KIRKWOOD: The prognosis of local recurrence, I think, is significantly more ominous than for primam presentation. The date from Urist (phonetic) in Alabama is probably the best for recurrence, now ten, 15 years old, but I think the prognosis for those are at least as bad as nodal involvement.

DR. PRZEPIORKA: But for patients with locally recurrent disease and no nodal involvement?

DR. KIRKWOOD: That includes in the absence of nodal involvement. Realize that most of the data that I'm referring to came from an era before sentinel node mapping, and I think it's only now that sentinel node mapping is being done off of recurrences, but there may be -- and Dr. Slingluff and surgeons here may be able to speak to this more directly.

DR. PRZEPIORKA: Dr. Fleming.

DR. FLEMING: Dr. Kirkwood, I'm trying to sort through, in particular, the evidence on survival effects, and in the studies you've presented, the 1694 seemed to be particularly intriguing on survival effect.

You had mentioned in your presentation that you had evidence that the GMK vaccine wasn't harmful, hence, in fact, inducing the different to a harmful effect by the vaccine. Could you again clarify what that evidence is?

DR. KIRKWOOD: Three bits of evidence. The first is as we plot the outcome for the GMK arm of 1694 against the 1684 and the 1690 observation arms, it certainly is intermediate and no worse than those, and I can present that to you on a slide if you'd like.

DR. FLEMING: Well if I could just take it one at a time, you had also clearly made the point at how hazardous those kinds of --

DR. KIRKWOOD: I agree.

DR. FLEMING: -- comparisons could be

because there are so many factors that could be confounding that. So that seems to be a fairly controversial piece of evidence at best.

DR. KIRKWOOD: Right, and the second is when we looked at the hypothesis that drove the design of the 1694 study, it was that the induction of an antibody response to the GM2 molecule is potentially favorable to patients, and so when we actually measured the antibody response at the end of the first month for patients who entered the vaccine arm, plotted those who had an immune response and antibody titer above a threshold of one to 80 versus those who did not, those who had an antibody response actually did better to a P value of .06 in terms of survival that I alluded to briefly in my talk.

So those who made the immune response, which was the goal of the immunization, did better than those who did not.

DR. FLEMING: So what does that tell us in any way about what the vaccine globally is providing effect or non-effect? Those that are immunologically different, in fact, would have that immune response,

could have been intrinsically better and would have had a better outcome so that it's not clear when I see those that have the intended immune response that they do better than those that don't, that that provides me any sense of whether globally the vaccine is helping or harming survival?

DR. KIRKWOOD: No, that's true, and in fact, we have to admit that we didn't have an observation arm. Following 1684, 1690, we decided we had to compare it to interferon, and we'll never really be able to address this head to head.

So I'm not arguing that it's clear to me that the GMK vaccine is harmful. It's just not clear to me that there's any evidence to know whether the difference that we see that's so favorable in that trial could in some way have been partially explained at least by a potential adverse effect of the vaccine.

CHAIRPERSON NERENSTONE: Dr. Kirkwood, I don't know if you or perhaps the folks from Dr. Chapman's group could speak, but there was also preliminary data from a randomized controlled trial that made you choose that particular vaccine to go

forward with, and I don't recall the details of that, but perhaps you do better.

DR. KIRKWOOD: Yeah, this is the publication of Phil Livingston for the GM2 plus BCG trial and Paul Chapman is here. So perhaps he would like to speak to that, but certainly in that trial there was a trend to relapse interval benefit. They did not have survival benefit, but there certainly was no hint of an adverse effect.

CHAIRPERSON NERENSTONE: Dr. Blayney.

DR. BLAYNEY: Yes, two questions for Dr. Kirkwood.

First of all, in your Slide 28, which goes to the number of patients who discontinued the interferon regimen for toxicity, is that different for patients who discontinued interferon for a year or did not complete a year for any reason?

Because I think those numbers are low for the number of patients who could discontinue the year interferon.

DR. KIRKWOOD: That was discontinuations for any cause other than relapse.

DR. BLAYNEY: Okay. Thank you.

Secondly, if one hypothesizes that as you showed in the 16, then your earlier trial or in your second trial that the salvage for alpha interferon once relapsed may have contributed to the survival benefit and thus the dilution or the equivalence of the various arms in your later trial, how many in the early trial, the 1684 patients, received alpha interferon who were in the control arm and received alpha interferon when they relapsed?

DR. KIRKWOOD: Yeah. We've gone back through the charts of the 1984 patients, and no one who failed observation then crossed over to receive interferon. It was, of course, not approved at that point in time, and it's subject to the retrospective review of the charts for this.

And since your next question may be if that's the case, what happened in 1694, we've just completed a sweep of the 880 charts from the 1694 trial for exactly that information. I don't have that right now, but I suspect it was much less for 1694 given the prevailing negativism about interferon after

1690.

DR. BLAYNEY: So it might be a reasonable -- a statement is reasonably made that interferon at time of relapse is a reasonable salvage treatment, which might extend survival in patients who are, as you've told us, destined to die because they have relapsed.

DR. KIRKWOOD: I think that's a hypothesis that can be taken from the 1690 study.

DR. BLAYNEY: Thank you.

CHAIRPERSON NERENSTONE: Dr. George.

DR. GEORGE: You showed us information about toxicity tables, and I don't think we had in our materials nor did you present today anything about quality of life kinds of studies. Have you done these as part of these trials or are you planning to?

DR. KIRKWOOD: Yeah, we've done and published in 1996 in JCO a study of quality of life, a Qtwist retrospective analysis of 1684 patients which showed benefit in terms of quality of life and quality adjusted life years gained which favored interferon. We actually presented those to the committee in July

of 1995 as the basis of the first approval.

We have completed studies of both Qtwist and Qtility, the time utility analyses that Kerry Kilbridge, Chip Cole had been doing. The latter will be presented or submitted for ASCO this year. The former were published in the fall of last year by Kerry Kilbridge.

DR. GEORGE: These were retrospective kind of? I'm not sure.

DR. KIRKWOOD: Yeah, the Qtwist analyses were all retrospective analyses of the chart data for toxicity. The utility analysis was a study of a separate population of patients who were asked given the likely toxicities of interferon, how would they weight time with the toxicity as opposed to time with relapse of disease, and from those I think we learned that the value of time with relapse of disease is so poor that the patients favored the toxicity on that basis.

CHAIRPERSON NERENSTONE: Dr. Sledge.

DR. SLEDGE: John, actually I really appreciated your presentation which I thought was

quite clear. Listening to your colleagues in the melanoma community and the advocacy folks, however, what I hear from them is that while they're willing to at least possibly buy the relapse free survival advantage, they have a fairly high degree of skepticism about the idea that we have a proven overall survival advantage, something that I'd say actually your pooled analysis may provide some further skepticism about, and that even if there is a small advantage from an overall survival standpoint, I've heard folks in your community doubt whether or not it might be worth it for the average patient just from a toxicity standpoint, rather that if, say, for instance, we were looking at polio in 1955, we were being required to randomize patients to the Salk vaccine versus an iron lung.

Do you think that's a reasonable position? And do you in your heart of hearts think that we should be requiring all future trials to involve high dose interferon as a standard arm? Because I think that's really what we're being asked here.

So the first question, I guess is how much

do I take the negative comments of some of my colleagues who are venerable members of the community that preceded us today, and I think that you could pick from the cooperative groups that have actually done the studies an equal number who would be ardent supporters of the survival impact.

I think in my heart of heart if you ask me do I think there's a cure fraction for high dose interferon, my answer is yes, and I think that's the basis of the statistical design for all the studies after 1684.

So I think that cure fraction is enough for me to believe that this is a reasonable standard against which all future treatments that are potentially going to be superior ought to be compared.

Do I think that patients who are either medically unable or unwilling to participate in this should not have access to other therapies? No, and I think that some compromise of the sorts that you've heard about, you know, some of those that Dr. Slingluff has presented, for instance, might well be reasonable intermediate grounds.

I think that the treatment of patients is, in fact, as we heard from Dr. Tiwari 60 percent of patients across the country are actually getting treated. I'm actually surprised, but I think that's a reasonable penetration. It's certainly not a dismal and very sparse use of high dose IL2 that Dr. Rosenberg talked about, which you know, clearly is another paradigm here.

I think that trial design in Phase 3 randomized controlled trials will establish if anything else is better or anything else is active. Right now, this is al we've got.

CHAIRPERSON NERENSTONE: Dr. Vanderpool.

DR. VANDERPOOL: Dr. Kirkwood, I'm seeking to make some sense about your rhetoric over against some of your statistics. I'm just puzzled a bit by it.

In the printout of your slides, on C13 you say that both relapse free survival time and overall survival were significantly prolonged with high dose interferon, but then at C33, I note that over 12.6 year period 95 persons died without treatment and 93

died with interferon.

And then you can look through the rest of those statistics and see similar actually very small differences. E1690 had 103 die without treatment, 108 die on interferon, and then the totals are similar.

So I see a small, very small numbers here, and I don't know how to match that up with your significantly prolonged rhetoric.

DR. KIRKWOOD: Well, I think the significantly prolonged was in the analysis of the randomized head to head, Phase 3 trials as we calculated events per unit time and analyzed these by log rank analysis as they're designed to be analyzed. Those event rates were different both in 1684 and in 1694, and the numbers at the bottom of the survival curve and the numbers at the bottom of the relapse curve for 1694 are perhaps the most graphic for this.

The overall analysis for trials when 13 years' median have elapsed since patients were 50 when they entered these trials is tallied, I think, best, is likely to come together. Certainly if we get out to 20 years with median follow-up, I suspect the

curves will all be together because, you know, as some of my colleagues from England have said, live is a banana. I mean, it all comes together if we follow things far out enough.

In this particular initial analysis, we were seven years in median follow-up. That was when the P of .023 was found for the significance of the survival impact analyzed as the study was designed to be analyzed, and I think that the fact that they come together somewhat at 12.3 years of follow-up and will doubtless come together as we follow things out farther later doesn't surprise me. I mean, those are all events. The survivals, again, for ECOG and for all cooperative group studies tally all events, deaths due to cardiovascular disease, strokes. I mean, many, many other things are competing for melanoma at the time point that we're seeing these curves come together.

DR. VANDERPOOL: And to also repeat one of the comments by Dr. Sledge just now, I suppose what this committee will be asked to decide is at what cost do those increased survival times afford.

You can procure increased survival and disease free status, but at what cost must that be procured?

CHAIRPERSON NERENSTONE: Just a point of information. I wanted to remind everyone that we are actually not going to be voting. This is a non-voting discussion, and this is completely advisory to CBER. So just a point of information.

Dr. Nelson

DR. NELSON: I'd partly like to follow up on the comment about the high dose interferon as a control group and ask really two questions. The first is the reason why then 1697 was designed in a way that, in fact, there was no group that included the high dose interferon as tested within the earlier trials, that that's a one month course raising similar issues, but not to get into a different political quagmire of the low dose AZT within the international community.

Also, the follow-up question from a design is why one would be content with a non-inferiority design when, in fact, if you look at the overall

statistics, even if you accept the nine month extension and benefit, I certainly would be interested in finding something better than that.

So both of those questions I'd be interested in from a study design perspective.

DR. KIRKWOOD: For 1697, the design targeted T3 node negative patients in the main. This was targeted upon intermediate risk patients for which no therapy has ever been shown to have survival benefit.

So that was the specific reason we included patients below the risk category for which we had shown benefit in 1684 before that.

The design for 1697 is not equivalence. It is superiority. It is seeking a superiority of 7.5 percent in cure rate, and so we agree with you. It should not be equivalence with observation. We're looking for superiority to observation.

DR. NELSON: I guess I was struck though by at least the ending of Dr. Ibrahim's presentation where he advocated that perhaps noninferiority studies would be what ECOG would select going forward, whether

that should be the standard.

DR. KIRKWOOD: Yeah, I think that really meant for the groups for which we think there is benefit, and 1601, for instance targets node positive patients and T4D primaries that are exactly the group that we see the benefit in 1694.

CHAIRPERSON NERENSTONE: Dr. Albain.

DR. ALBAIN: Yeah, Dr. Kirkwood, I'd like to come back to your life is a banana comment, if I may. I've been troubled a little bit by some of the discussions comparing these results with Tamoxifen adjuvant data, and if you, in fact, look at the worldwide overview for Tamoxifen, five years receptor positive, no treatment controls. It's not a banana. It does not come together. In fact, it's robustly separated with years of follow up, and these are elderly women, competing causes of death, also treated on relapse with numerous other active agents.

So I don't think it's quite the same scenario. I'm not disagreeing that you're not seeing a survival effect here, but I don't think it's similar.

CHAIRPERSON NERENSTONE: Dr. Fleming.

DR. FLEMING: Just following that up, the FDA also drew our attention to the 5 FU/Levamisole, and life certainly isn't a banana there. The JCO report update, I think, in '96 or '97 that presented the seven year follow-up showed a very large, substantial, I think, 57 versus 43 percent difference in survival.

Speaking of, however, the banana configuration, one of the things I'm really trying to get better sense about is the nature of the effect on survival. The argument that's been made, I believe, if I'm understanding it, is we're dealing with a setting here where there's a cure rate model or what we might be dealing with is effects on survival that could be mediated through, in part, an achievement of cure which would mean that if we take -- and I found very helpful and informative the FDA meta analysis that said individual studies in this setting really are inadequately powered to address survival. Let's look at the aggregation of data.

That aggregation says there's about a ten

percent reduction in risk. Well, is this reduction of risk essentially representative of transient benefit or is this really representative of being able to achieve a cure and sustained long-term benefit in a sub-cohort of the population?

If we go to -- and I don't think Dr. Tiwari numbered his slides -- but if you go to his slide on the odds ratio for survival, one finds that all of them go in the right direction, although several of them are relative risk estimates just barely below one, and then the more impressive ones are the original 1684 trial from ECOG and the 1694 trial, along with the Cameron studies and the French study.

And what's interesting is when we look at your updated data in 1684, it does show more a banana type configuration, although granted it doesn't come back together until about ten to 12 years, but if you look at the data that Dr. Tiwari presented on survival for the Cameron study, those curves definitely come back together at about five to six years.

And if you look at the data from the

French study, those curves also come back together, and then the remaining positive study is the one that I'm already struggling a bit about that we talked about earlier, which was the 1694 trial against the vaccine, and it's unclear to me to the extent to which that difference could at least have partially been due to an adverse vaccine effect.

So the bottom line is if we take a look at these odds ratios for survival in Dr. Tiwari's summary, the four studies that tended to show the signal here, studies that seem to show a loss of the benefit, and so is there, in fact, a basis for us saying here we're dealing with something more than a ten percent risk reduction that's a transient effect? Is there, in fact, evidence that we can use to say there is, in fact, an increase in cure that should translate into a true long-term sustained benefit?

CHAIRPERSON NERENSTONE: Other questions? Dr. Brawley.

DR. BRAWLEY: The two last questions brought this up. When I treat breast cancer adjuvantly with Tamoxifen or even with other

chemotherapies, if I treat 100 women, I actually have an estimate of how many women I'm actually benefitting in that 100. It's usually going to be a small number because there's a large number who will not relapse no matter what you do. So they're getting adjuvant therapy unnecessarily, and there's a group that will relapse even though they get the adjuvant therapy.

So I treat 100 women with the premise that I'm going to help some number, usually 15 or 20. Is it possible that figure out approximately how many people benefit from adjuvant therapy with interferon?

And then, of course, the last question actually brought up the issue of what benefit is it. Is it that the disease does not come back or is it that life is actually prolonged?

But is it possible to quantify the number of people who get this adjuvant therapy now who don't really benefit from getting it and the number who do?

I don't know. Dr. Kirkwood, Dr, Tiwari, can you help me with that?

DR. TIWARI: Well, the reduction in the overall survival from all of the data is at ten

percent. So you would think that ten percent of the patients will benefit with respect to the survival.

DR. SIEGEL: I think that's a relative difference. I think the difference in the number of patients who never get their tumor again or at least over ten, 15 is 20 percent relative, but it's ten percent absolute. So there are differences of the meta analysis that suggest that ten percent more patients have long term survival without evidence of melanoma.

But closer to four or five percent would be the point estimate on survival, a relative difference of survival of ten percent, but an absolute difference of four or five. So may be one -- again, wide confidence intervals around that, and we can argue as to whether that is statistically significant or not, but even if it isn't, it may be much smaller than that amount, but that's where the point estimate came out.

DR. BRAWLEY: So are you suggesting that if we treat 100 people right now for melanoma -- let's be really conservative -- 80 don't benefit from it?

DR. SIEGEL: Yeah, I think that's about right, but it's worth noting like one of our best treatments out there, one that people think is one of the greatest drugs out there, for example, is thrombolytic therapy in which we believe that if you treat 100 people with heart attacks with like TPA, you know, 98 of them won't benefit, but you reduce mortality from seven percent to five percent.

So it's probably true of many of our best drugs that, you know, that ten percent may not be as small a number as you make it out to be or 20 percent or whatever it is.

CHAIRPERSON NERENSTONE: Dr. Kelson.

DR. KELSON: Following up on Dr. Fleming's question, I was also looking at the graphs on page 15 of the presentation. I was equally struck or maybe more struck by the graph on the bottom of the page. Again, they're not numbered, but it's the meta analysis, and I guess this is an open question to Dr. Kirkwood or others.

The meta analysis looked at two different meta analyses, but if we looked at survival, in both

cases the 95 percent confidence lines either touched or crossed unity, and that means to me -- and this is a question -- there's not a super amount of confidence I have that you're really seeing a true effect.

The effect is modest, as absolutely looked at. The confidence limits are not that broad around those observations because it is a meta analysis, which I found very helpful.

But it touches one or crosses one, and that to me suggests a null effect or at least a possibility of a null effect, and I wonder how that strikes Dr. Kirkwood and the others.

DR. TIWARI: That's true. In our analysis we have a P value of .065, and the analysis by Wheatley, et al., gives a P value of .05, exactly .05. So it is borderline statistical significance.

DR. KELSON: Just following up as a GI oncologist, the colo-rectal comment and the breast comment, I mean, you don't see that when you look at meta analyses. You know, we're not touching one.

CHAIRPERSON NERENSTONE: Dr. Nelson.

DR. NELSON: This discussion reminds me of

a point I was just thinking about during Dr. Ibrahim's presentation, which is how you would present this kind of data to make sense to someone trying to make this sort of decision, and since as a non-oncologist, I only approach this area as a potential consumer, let me take a stab at that.

I found presenting, for example, a nine month extension of event free survival more useful than giving me percentages, but in listening it occurred to me that what you really want to know is what are my chances of being in the group that's going to be cured versus my chances of being in the group that's not going to be cured and will, in fact, have then nine additional months of life if I'm in that group.

So as you think about the complexity of weighing those decisions against the potential toxicity of treatment, you're really balancing a number of different variables, which I don't think are fully captured by just giving me a percentage of ten percent, for example.

And having said that, I guess I'd be

interested to hear if that's at least in the right direction. If we're going to put weight on the informed consent, as some have argued, how would we go about transmitting this information in a way that makes sense to non-statisticians and non-oncologists?

CHAIRPERSON NERENSTONE: Dr. Brawley.

DR. BRAWLEY: Well, what I think, and please correct me if I'm getting this wrong because, you know, I design clinical trials, but I try always to go for the statistics to real numbers whenever possible.

I think what we just talked about is if you treat 100 people, 80-plus of that 100 people derive only the side effects and no real benefits from the current therapy. Some where ten-plus may derive some benefit. It is -- did I -- am I being correct? Okay.

CHAIRPERSON NERENSTONE: Dr. Carpenter.

DR. CARPENTER: One distinction to be made is whether this is an absolute benefit or a relative benefit. Now, understand that the ten percent which is discussable since the confidence limits overlap

with one is a relative benefit.

DR. SIEGEL: The percent that turns out that approximately the relative benefit and overall survival in the absolute benefit on relapse free survival. So they're 20 and ten or ten and five roughly, depending on --

DR. CARPENTER: So it would be five percent would be the number you're speaking of?

DR. BRAWLEY: Oh, I'm doubling just to give the drug benefit of the doubt.

(Laughter.)

DR. CARPENTER: That would suggest that 95 percent of the people.

DR. FLEMING: Just to be explicit, if you had and we often hear the figure about 65 percent five year survival for this cohort, if in that cohort that had 65 percent five year survival, if you provide ten to 11 percent reduction in the hazard ratio, the relative risk, that translates to improving that survival from 65 percent to 68 percent.

Does that help>

DR. BRAWLEY: I was still doubling the

number to try to give the drug as much benefit of the doubt as possible, but, yeah, it unfortunately is very helpful.

CHAIRPERSON NERENSTONE: Dr. Carpenter --

DR. SIEGEL: Well, we're talking 40 percent survival. So most of these cases -- so the ten percent relative changes is somewhat larger.

CHAIRPERSON NERENSTONE: Dr. Carpenter, did you have another comment?

DR. CARPENTER: I just think that some idea of the absolute benefits are helpful, and the position that most of us end up in, which is talking to a person, and particularly with the new staging system, one's ability to estimate prognosis is fairly precise, if I understand it, given these new numbers.

And you're going to know. It's helpful in trial design because you're going to have a pretty good idea of the prognosis of the people that you enter. So you know how to affect it, but to me the number that means the most is the absolute benefit in what Dr. Brawley is calling real numbers, I think, but it's probably on the three to five percent range to

balance against a year of toxicity.

And it's apparent from the discussion that how the toxicity is viewed is very different to different observers.

CHAIRPERSON NERENSTONE: Dr. Nelson.

DR. NELSON: I continue to follow on this notion of how it would be understandable in terms of an informed consent process. What I'm hearing is if I fell into this particular risk category without interferon I would have a roughly 65 percent chance and with it I would have a 68 percent chance of being in the cure group.

So you're basically telling me that I want to trade off a three percent chance? I mean --

DR. SIEGEL: These numbers aren't that hard. I don't want to address the questions, but let me just provide some clear numbers. If we look at relapse survival, this 1684 is pretty representative of what we find from the overall study, from an overall analysis.

What you can say as you go out to the five to ten year range to put into real numbers is that

maybe it was the three or five year follow-up, but the differences hold up pretty closely, and that is that you had 41 percent of patients alive without any recurrence or any evidence of disease if they got interferon and 32 percent alive without any evidence of disease or any recurrence if they didn't get interferon.

Now, that is in absolute terms a nine percent difference, and we said in our overall meta analysis maybe that's a ten percent difference, and in relative terms, that's about a 20 percent difference because nine is 20 percent of 41 or 30 percent of 32, whatever.

So that's the size difference we're talking about in relapse free survival. If you look at survival curves, what you find is that in the observational group there's a few more people who are alive who have had tumors. Because when you look at overall survival, you're not just looking at alive without tumor or what in design features was termed cure, but you're adding also those who are alive who had tumor, and it turns out there's more people alive

with tumor in the observational group. So that makes those differences smaller, approximately half of the size.

DR. CARPENTER: That's certainly true. I think one of the -- my sense is that one of the things that's pulling at us is this difference between relapse free survival and overall survival. Most other therapies for approved adjuvant therapies for malignant diseases, such as, let's say, breast cancer and colo-rectal cancer because those are perhaps the least controversial, are based on substantial differences in overall survival, not just on relapse free survival.

And I think what we're hearing here is that there is a probably substantial and fairly agreed upon difference in relapse free survival that's supported by virtually every analysis that we've heard, and a smaller discussable, much less confident benefit in overall survival.

So in terms of how one would phrase that to a patient, I'm sure that it's observer dependent, but usually when I discuss adjuvant therapies, I talk

about the chances of being alive at a certain point because we can discuss relative merits and benefits of toxicity and extension of relapse free survival, but death is pretty quantitative event.

This treatment is going to make you live longer by a substantial amount of time. Then it gets to be very focused discussion about how much toxicity it's worth for you to take.

If, on the other hand, there's a lot less confidence in the true extension of survival, then the toxicity to me at least would play a much larger role.

So I think it's helpful to get at the absolute numbers wherever we can, and to make sure we're talking about the same thing when we talk about benefit.

I think most physicians, I think, would be talking about overall survival benefits.

CHAIRPERSON NERENSTONE: Dr. George.

DR. GEORGE: A couple of points about some of the issues that have come up. With respect to the curve models, I think it's worth pointing out that just to be explicit, these models are not correct in

the long run with respect to cures, when you're talking about an endpoint being survival and disease free survival.

As far as we know, nobody lives forever. So in the long run these curves will come together. This has been pointed out.

So the models aren't correct and that's it. They're correct in a shorter term. They're correct or useful, as George Bach said, that no model is correct, but some are useful. This can be useful in the short run, five to ten years it looks like, but it is an issue about what happens later.

And I was a little surprised that we didn't know about those long term people, the ones that -- the long term deaths, if they're due to melanoma or to just some of the competing risks of aging.

The second point is Dr. Brawley's point. This is a well known concept of the number needed to treat, and what you do is you look at the inverse of the absolute benefit, in this case ten percent, say, in terms of the disease free survival, and that gives

you a point estimate of the number you would need to treat.

So it would be a ten for ten patients to treat for one patient benefitting. However, you'd have to worry about what's the confidence interval in that, and that, the way I would do it is look at the meta analysis to give you a best feel for how precise that estimate is, and doing it that way, you get your numbers like somewhere between, you know, maybe five and 100.

I don't know. I didn't do the math, but it's a straightforward thing you can do. But the hard part is getting what that absolute benefit is. And I think that is relevant though to the discussion of what patients or individuals would like to know about how it might benefit them, and we said absolute benefit.

We talked a lot, and I like it, relative risk and things, but it's the absolute benefit that really, I think, people can understand.

CHAIRPERSON NERENSTONE: Dr. Vanderpool and then Dr. Nelson, and then we're going to turn to

the questions.

DR. VANDERPOOL: When you say turn to the question, is that when we're going to deal with the issue of what our final commission is?

My only comment, I was just going to ask you that question. When are we going to get away from interpreting the data, which obviously our presentations primarily direct us to do the kind of clarification that we've been doing, but when are we going to get to the issues of the commission, the last two sentences on our FDA report?

And so if we're going to turn to that soon, then I'll wait to comment at that point, and please put me on the list.

CHAIRPERSON NERENSTONE: Dr. Nelson.

DR. NELSON: Since my comment was looking forward to the discussion of what significance means, you can certainly read the question before I comment.

CHAIRPERSON NERENSTONE: Dr. Blayney.

DR. BRAWLEY: I'd just like to come back to this issue of cure, and perhaps what we're struggling with in an analogy to breast cancer and

colon cancer, nodal relapse in both o those diseases is unusual. Whereas it's much more common, as has been pointed out in melanoma.

In the 1684 study, most of the survival benefit was seen in patients who were treated at the time of nodal relapse, and it may be that there's a small beneficial effect of melanoma -- I'm sorry -- of alpha interferon that is useful when applied at nodal relapse or nodal involvement, whether that be at time of presentation or at time of nodal relapse.

So there may be a small treatment effect when applied in those situations, which may explain the survival coming together in the later study, because those patients when they did relapse, many of them, I think relapsed nodally and then may have survived longer. So that may explain some of the discrepancies we're seeing.

CHAIRPERSON NERENSTONE: To turn to the questions then -- Mr. McDonough.

MR. McDONOUGH: I'd like to just ask and make one or two comments here. I've been sitting, and I'm getting overwhelmed with some of the statistics.

One, I am a Stage III melanoma patient. I did take interferon. I was in 1690.

Two, between my going into 1690, from 1989 to 1992, I was in the infamous observation group. That's a hell of a place to put somebody. Observation means we're going to watch you and see if you get sick. That's what it means to me, and I'm sure it means the same to every patient.

Number three, these discussions that take place between doctor and patient, how long do you think they're listening to what you're saying?

I'm a public school teacher, and if we could get them three, three and a half, four minutes of attention span, we were doing a job. Now, you introduce fear. You introduce stress. You introduce feeling lousy. You introduce lack of education on many of the people's parts that you're talking to, and do you really think they're going to grasp in the five minutes you have between this room and the guy that's sitting in the next room?

And I don't castigate you at all. I'm not saying that. What I'm saying to you is really how

much time do you really have to deal with this? It's a hard task.

As far as toxic, I took the high dose. Now, I just went '89 to '92 in observation. Now I'm presented with I may be in the observation again or I might get low dose and I might get high dose. I prayed for high dose. I was lucky. I got it.

How hard was it to tolerate? First week, very rugged because I didn't realize what was going on, because I took it later in the day, and I started to believe what they were telling me. Take your Tylenol, this and that. I started to adjust to it.

Six months into the treatment, I was back playing senior softball. I was traveling around the country with a little cooler with the drugs in it. Nobody wanted to room with me. They thought I was a junkie.

Speaking of rooming with you, this room is cold. I'm waiting for Rocky Balboa to come in.

But getting back to the whole thing, the handling of the fever was fairly easy to do. The handling of the malaise, I mean, I got my energy

levels back. I'm certain some people are having a terrible time with this drug. I'm certain of it. But by the same token, I talked to a lot of people around the country as a patient, consultant, counselor, whatever you want to call me, through several different cancer groups, and most of them come back with this particular point that bothers me, and it bothers me a lot.

When you talk to your patient about your particular clinical trial as opposed to interferon, do you talk to them about the other 101 that are available, too, or do you just compare yours to interferon?

There's 103 clinical trials out there. What guy in this audience is conversant with all 103? If you are, you are the man. And that's what these people are faced with. That's what they come up with on the phone. Should I take interferon or should I take this trial at University X or University Y or University Z?

And me as just a survivor, an interested person trying to help, how do I advise these people?

I can't advise them. I do refer them to you people many times, but it is a very confusing situation for a patient, very confusing.

And I strongly urge you to take into account when any clinical trial is designed this observation group. That's a terrible place to be.

Thank you.

DR. BRAWLEY: Can I ask Mr. McDonough a question? Is that allowed?

CHAIRPERSON NERENSTONE: Go ahead.

DR. BRAWLEY: Mr. McDonough, realize that we didn't know this information when you went into the trial, and one of the reasons that we now know this information is because you and heros like you went into the trial.

But would you take interferon today if diagnosed today if it was explained to you that for every 20 people we give interferon to 19 do not benefit? They get all of the side effects, but none of the benefit and one out of every 20 would benefit?

MR. McDONOUGH: Short answer, yes.

Long answer, from what I can gather here,

I'm hearing ten percent, 15 percent, five percent. I frequent Atlantic City not a lot, but now and then.

(Laughter.)

MR. McDONOUGH: If I walk in and they tell me I've got a 40 percent chance on that table and I've got a 50 percent over there, I'm over there.

If one of you gentlemen stand up here and say, "I've got the cure and it's right over there," I'll be the first guy in line with my arm out.

I know it's an insidious disease. I know it has a terrible toll. Why do you think I'm on this Committee? Financial gain? I'm 70 years old. I'm on this Committee because if the real bullet comes down the line, and it may be this bullet down at the end of the table here. It may very well be. I don't know that. I don't know the Xes and Os like you folks.

I'm a coach. You want to talk about baseball, I can talk to you about that, but honestly, yes, sir, I would take it again because I did the observation. I did the not treatment deal, and I would never not treat something again.

CHAIRPERSON NERENSTONE: Dr. Siegel.

DR. SIEGEL: Thank you.

I just want to make a comment or two to put in context the questions we're asking and what we're asking and why, particularly in light of some of the public comments from earlier this morning.

And I appreciated hearing the perspectives of all the public commenters, and I think they're all important and I'm sure sincere and valid and useful perspectives.

But I want to provide some background to the notion presented by a number of people that it was -- well, different words were used -- undemocratic, perhaps paternalistic, restricting people's choice, undermining the informed consent process to state that a trial couldn't be done provided that there was informed consent, and to say that the framework in which medical research is conducted in the United States and worldwide tells both at the ethics as well as law and regulations, tells us otherwise.

There is, as I think everybody here knows, a raging debate about when placebo controlled trials are -- with full informed consent -- are acceptable

where there is a proven effective therapy. Some have argued in very prestigious medical journals never. Others, including many at the FDA, have argued that that's the wrong place to draw the line, that there are many therapies for symptomatic disease, transient benefits or whatever that it's quite appropriate to as long as there's adequate informed consent to do placebo controlled trials.

But there is a broad consensus and a broad, I believe, societal consensus that somewhere there's a line, and I think that's really what this is about as to where that line, where this treatment is relative to that line; that at some point there are therapies whose benefits, whether on irreversible morbidity, serious morbidity, mortality, taken perhaps and probably appropriately in conjunction with their harms and adverse effects, are such that it's inappropriate to do a placebo controlled trial, even with full informed consent of the patient.

Now, you can look into what is the reason or what is the logic behind that. I'm sure a part of it reflects as was noted, you know, imperfections in

the consent process. Part of it reflects, as some of our commenters noted, maybe a lack of trust of the community fully in medical researchers not to take advantage in certain settings.

I don't want to do a lot of speculation. We have ethical experts here who I'm sure can answer that question better than I can, but suffice to say that there is rather broad agreement that there is a level beyond which when there's a proven therapy it's inappropriate to do a placebo controlled trial, and I can tell you that in the international community and nationally, as the FDA has advocated for broader placebo controlled trials, we've often been severely criticized saying, you know, even though they have full consent, people will say, well, this is, you know, capitalistic exploitation of third world populations, you know, and how can you offer people placebo when you know there's a proven therapy out there, and how do we really know that they're being informed and this trial is just unethical to do?

So it's important to know that at least from our perspective we're not proposing something

that undermines informed consent or that is on the face of it just inappropriate to say you can't do this trial even with informed consent, but rather to determine where against that spectrum, an analogy that this trial and what we know about this drug falls are its known benefits, and that's what the discussion has been about, and I think that's very useful. Are the known benefits together with the risks such that it is appropriate to ask people to consent not to get this therapy, knowing the risk of consent, knowing people who consent to be in trials often have undue expectations about the experimental therapy?

Just to carry that one step further, that notion of what can or cannot be consented to, although it's a slightly weaker analogy, there's also a broad, supported by law, public expectation and regulation, consensus that the FDA can and should stop clinical trials that we deem to be unsafe.

There's not an expectation that, well, if we think it's unsafe as long as you tell the patient all of the safety information and the patient thinks it's safe enough, they can take that trial.

So the informed consent is underpinning our ethical basis. It's an important part of clinical research, but there's a limitation to when a trial with informed consent, even with informed consent, is appropriate, and also there are issues that we may get to address about how to insure that there is a good quality of informed consent.

CHAIRPERSON NERENSTONE: I think we should probably turn to the questions and direct our discussion back to them specifically.

Just the paper that the committee was given, in the review of the clinical development program for an investigational agent, FDA considers the risk to human subjects. FDA may place on clinical hold a proposed or ongoing investigation if it finds that "human subjects are or would be exposed to an unreasonable and significant risk of illness or injury." Withholding an effective treatment may constitute an "unreasonable and significant risk" for trial participants, depending on the known benefits of the treatment and the consequences of withholding it.

Given that INTRON-A is an effective

adjuvant treatment for high risk melanoma, please discuss the following.

Well, I think the first question is -- that's the whole crux of the debate: is it an effective adjuvant treatment?

But the first question is: data regarding the efficacy of interferon ad adjuvant therapy for melanoma has been summarized in detail. The toxicity is well described. Of note, Schering estimates that approximately 60 percent of patients with Stage III disease and 21 percent of those with Stage IIB disease in the U.S. currently receive adjuvant therapy with INTRON-A.

Based on this information are patients who forego INTRON-A therapy to enter a placebo controlled clinical trial exposed to unreasonable and significant risk?

And then would the answer differ for patients with Stage IIB disease versus those with Stage III disease?

I'm going to take the chair's prerogative and comment a little bit about what I think part of

the problem is. With the weight of the evidence, interferon is clearly not a home run, but I think it's a beginning place. So I would be uncomfortable with a placebo controlled trial in a large Phase 3 study, looking to advance the adjuvant treatment of melanoma, of high risk melanoma, however you want to define that patient population, especially if you're going to keep it in the FDA wordage that interferon is already approved for.

The problem I see is really for those people who do not want to go on an interferon or interferon controlled trial. I think you could get around that by your informed consent, and I certainly appreciate Dr. Brawley's concern that you are treating nine patients or ten patients and one patient will have benefit maybe.

But I think it's very important for us to point out in the informed consent for somebody who's going on a Phase 2 trial or a Phase 1 trial that you may have to treat 100 patients with no benefit because these are very, very experimental treatments, and I think investigator bias and I think physician bias

play a very important role here.

And I think when you extrapolate results that work in a mouse and say this is our most promising vaccine and it has no toxicity, that's an investigator bias that the patient wants to hear, and we have this drug that really is very toxic and only, you know, one person out of ten is going to benefit, but we have no data that any patient is going to benefit from this new treatment, and I think that has got to be put into the informed consent.

And patients have a right to know that no matter whether in University A or University B or University C.

Other comments? Yeah, Dr. Vanderpool.

DR. VANDERPOOL: This is a complex issue in light of the FDA's responsibilities to see that approved drugs are efficacious and also to protect the public from unproven treatments. So in a sense, I can empathize quite deeply into why the FDA has made this determination that patients should not be allowed to enter Phase 2, not to speak of Phase 1, trials without first going through the standard approved therapy.

On the other hand, for the FDA or any other agency to keep patients from entering clinical trials that have to have rationality, that have to have the three requirements of the Belmont report, harm benefit analysis, informed consent, and justice, but to keep patients from entering any of those trials seems to me to go against the grain of self-determination both in ethics and the U.S. law.

Persons have a right to refuse treatment. They have a right to decide such matters on the basis of their own values.

The predominant value I've heard all morning is that of extending life. We've talked some about the other value of pain and suffering. Some patients would choose no pain and suffering over a lower continuity of life.

And then there's the question of just hassle, having to go back and forth and spend one's year in oncology clinics.

It seems to me the right of determination, self-determination, is a very strong reason why this decision should be taken away. I mean the decision

would be reversed.

Also, the right to privacy. The right to privacy has to do with the constitutional protections of physician-patient conversations and decision making with the interference of others.

So it seems to me that both on ethical and constitutional grounds that there are some strong reasons why this decision to keep patients from being able to enter clinical trials even if they haven't taken interferon as the approved therapy -- their right to enter those trials should be preserved.

Now, the question of informed consent, of course, comes into all of those decisions, both informed consent within the physician's office, informed consent within any clinical trial setting. So informed consent, both the process and the document, would have to be full and thorough, but I'm talking about the more basic principles of what values patients have for their decisions.

Obviously, Coach McDonough would go with extension of life over pain and suffering. I suppose in his sports career he probably endured a good bit of

pain and suffering even, you know, just for the purposes of winning the game. I did also.

But those of us who value extension of life over pain and suffering should recognize that other people have different values and they ought to be able to operate off the base of self-determination with those values in mind.

CHAIRPERSON NERENSTONE: Dr. Kelson.

DR. KELSON: First of all, we're discussing melanoma. This obviously has implications for many other diseases. It's a very good paradigm though.

As I read Question 1, I think that you're -- correct me if I'm wrong -- you're really focusing on a Phase 3 trial when you talk about a placebo controlled arm or at least that's the point I would like to address in this, and it seems that much of the discussion here is what would be the comparator arm in a future adjuvant trial, and are patients compelled to accept a randomization to receive interferon high dose or an experimental arm, or is it, as we heard a lot this morning -- could one imagine a study in which

there would be an observation or placebo controlled observation?

DR. SIEGEL: Just for clarification, regardless of which question one addresses, we're being faced with a spectrum of questions, and we're interested in input on all of them, both for a drug which already has been shown to be promising, is it appropriate to compare it to placebo, but also for folks with less data where you know very little . Is it appropriate just to withhold interferon and do an open label?

DR. KELSON: Right, and I think Stacy alluded to this. The issue that struck me at least in this particular disease is is it so compellingly efficacious that a patient would be put to an unreasonable risk by not receiving that therapy and, therefore, we should say, "Listen. I don't care how you feel about this. It's just not in your best interest to not receive this drug"?

I'm struck again by the meta analysis in which, since this is curative therapy if it's adjuvant, the upper limits of the 95 percent

confidence tightly draw across one. I'm not compelled that there's overwhelming evidence that this is a clearly efficacious therapy.

And that strikes me a great deal when you talk about unreasonable and significant risks of withholding treatment. That would make me much more sympathetic to the problem of forcing a patient to receive interferon.

And lastly, I am struck by the fact that although it is an approved agent, if we turn the number slightly, 40 percent of Stage III patients are not being treated, and 80 percent of Stage II patients are not being treated with the approved therapy, and therefore, clearly not everyone has been convinced that this is putting these patients to an unreasonable risk.

CHAIRPERSON NERENSTONE: Just a point of information about that, Dr. Kelson. I think that those of us who are in the world of treating patients, if you look at the ECOG studies, there were very clearly and carefully screened patients who were performance status zero and one, and we have lots and

lots of patients who are not performance status zero and one and who, therefore, many of us feel wouldn't even be candidates for interferon.

So I think interpreting those numbers are fraught with difficulty as to what they really mean about the acceptance or not acceptance of the treatment.

DR. KELSON: Right. Also being in the world of treating patients, as a card carrying member, since this is adjuvant therapy, I suspect, and these are melanoma patients who have had the primary resected, I mean, we also face older patients who have had resections for colo-rectal cancer, but I would suspect that a pretty substantial hunk of that 80 percent who are turning it down are relatively fit people who ordinarily would be treated. They don't have advanced disease.

DR. SIEGEL: It's worth noting that there are probably a lot of weaknesses to those data. Another one, for example, is that we also believe that there are, but we don't know numbers, but we understand that there are some patients being treated

off label with other interferons that are similar in activity but not approved for this indication.

That said, we felt, and I think your responses reflect that, that this information was relevant to how people are weighing the data and this indication and what choices people are making.

CHAIRPERSON NERENSTONE: Dr. Nelson.

DR. NELSON: I'd like to comment on the unreasonable and significant issue and try to place it actually in the context of the international debate that you referred to. What strikes me about that language, which is the first time I've really looked at it closely, though I've probably read it often, is it needs to be both unreasonable and significant, and I think we would all agree that the risks we're discussing are significant. So the question really comes down to whether it's unreasonable to decide not to have high dose interferon therapy and, by extension to have a control group that does not include that as part of that treatment.

I mean the Declaration of Helsinki in Paragraph 29 talks about proven. That's the language

that's used there. What strikes me as problematic with often people's understanding of what proven means is that they don't appreciate that safe and effective means safe enough and better than what we tested it against.

As a culture we tend to think safe and unsafe and effective and ineffective, which turns into a categorical variable that really is a continuous variable.

So what strikes me in this entire discussion is that equipoise -- I mean, the uncertainty about the decision to do this rests at two levels. One is the professional level of the statistical determination, which is in debate, but even if you say, yes, we agree that you have a ten percent difference or we agree that you have a ten month extension in expectancy of life if you're not going to be cured, we can still then debate the reasonableness of that tradeoff. There's still uncertainty about that decision. So equipoise is existing at both levels.

The other document that's part of the

debate is ICHE-10 choice of control group, and in that document basically you can allow for -- and I'd like to have other language suggested about observation and placebo. It would be great to have another term, but basically even if proven treatment exists, you can have that if one of two conditions exist, and there's some uneasy tension between them: so-called assay sensitivity, which I notice is the third question coming up. Can you really tell in the trial whether it's effective? The question raised about the vaccine trial earlier against high dose interferon.

The other is informed consent if there's no serious morbidity or mortality. So the difficulty there is that informed consent is tied to the lack f the seriousness of the outcome of withholding, in which case, you know, it may or may not apply here, but in E-10, I think it's assumed that equipoise exists. That's the difference. It assumes that we accept that it's safe and effective, and we're willing to withhold it if, in fact, the disease is not serious, doesn't have serious morbidity or mortality as a result of that.

So in this case the approach I would take, which really does go towards informed consent to some extent, but I wouldn't rely on it entirely, is that it doesn't strike me either within the expert community, in listening to the experts here, or within the community of patients who would be the ones going into these trials, that, I mean, there's sufficient uncertainty in my mind at least listening to it to where I wouldn't necessarily apply the choice of control group, E-10, to that, but would really analyze whether uncertainty still exists, maybe not in some minds, but at least within enough of the expert community to where not having high dose interferon, even though it's, quote, proven safe and effective, is an appropriate position to take.

CHAIRPERSON NERENSTONE: Dr. Pelusi, can you hear us? Dr. Pelusi, can you hear us?

(No response.)

CHAIRPERSON NERENSTONE: Dr. Redman.

DR. REDMAN: Dr. Siegel said he was open for all comments. So I'm going to avoid the Phase 3 and come back to it in a minute, but you know, I mean,

there's a great discussion among the experts in melanoma of what control groups should be, and I'm not surprised patients are confused.

I get the sense that one of the restrictions being looked at is to imply or impose on patients that decline receiving interferon not being able to participate on a Phase 2, single arm study that is trying to ask a basic either clinical or laboratory question regarding the disease and treatment.

Most consent forms do have unknown benefit clauses in them. At least most are required to have that for a drug. You know, until we have a national informed consent policy, which probably won't happen, but, I mean, until we do, everybody's consent is going to be different.

And Dr. Slingluff had a suggestion that may overcome that, and I'll just leave it at that, but I am definitely, as a physician who treats predominantly melanoma, greatly against restricting somebody from being able to participate in a Phase 2 single arm study because they've declined interferon.

Regarding a control arm for Phase 3, I think that's between, you know, industry or the holder of the IND and the FDA, hopefully will come to the FDA at the end of Phase 2 and say, "We want to do this trial," and at that point in time determine is interferon an adequate control arm.

I think if they're going to product license application in that regard, I think it is the FDA -- and I know you're asking for our opinion. I'm not sure I know the answer to that question of whether that should be construed as the standard, but as far as Phase 1 or Phase 2 single arm studies at single institutions or even sometimes multi-institutions, I think those trials should be available to patients who decline interferon because I imagine a lot of physicians would decline interferon.

So I don't think imposing that will on the patients is appropriate.

CHAIRPERSON NERENSTONE: Dr. Przepiorka.

DR. PRZEPIORKA: Thank you.

I had the pleasure of participating in a discussion over the weekend regarding the imposition

of benevolence over autonomy, and living unrelated donors of stem cells and whether or not it would be ethically appropriate to go back and ask them to donate once again since the procedure has substantial toxicities, a risk of mortality, and absolutely no benefit whatsoever to the donor.

And after a minimum of just 15 minutes of heated discussion, it was concluded that we as physicians do care for our donors, but if they really want to do this, we should not deny them the opportunity as long as they pass the psycho-social review and we're sure they're not crazy.

(Laughter.)

DR. PRZEPIORKA: And I think if any patient would look at the data that we saw today, they would say there was a substantial risk of toxicities with interferon, and as far as I can tell, there is no proven benefit with regard to survival that I think would entice a patient to take this if there was something else available.

And I think that's the key. So if one uses the acid test of did we really improve survival

with this drug and to say that then this should be the standard of care and the comparator arm in every future trial, I would have to say no.

But I'm a firm believer in looking at relapse free survival, as well, since we now have all sorts of ways to keep our patients alive, and certainly they would prefer to be alive without disease rather than with disease, even if they end up dying at the same time point.

And clearly relapse free survival is significantly improved, statistically significantly improved with interferon, but I'm not certain I would conclude that it's clinically significantly improved if there is something else available either.

So I would not have any hesitancy in saying yes to a placebo controlled trial for this group of patients with melanoma, with the caveats that they are appropriately consented, and there is a safety monitoring board watching this closely.

And I'm a Baysian kind of person rather an intention to treat kind of person. So I like to see a trial that's as small as possible as well as monitored

closely.

That's not to say that I would actually do this for every drug under any situation. I think this is a specific situation where we really don't have statistical significance and improvement in survival, and the relapse free survival is there, but not a whole huge amount, and that would be the only other caveat I would add to this.

CHAIRPERSON NERENSTONE: Dr. George.

DR. GEORGE: I have a couple of comments. One is I'd like to make something explicit that may have been implicit. We're talking about melanoma, but I think maybe the FDA is worried about the slippery slope issue, that is, having this be, decisions that are made in this case be used as precedent for this in this situation.

There is, as we heard, a huge and growing number of INDs that are a lot more in line, I think, with the biologics and the biologically targeted agents, but to me this doesn't bother me because there is a -- FDA made a judgment call in this case with respect to unreasonable and significant risk. This

was on this particular case.

Some of us might disagree with that. A lot of us do, apparently, but it's an individual case, and I don't think it sets the precedent.

The corollary to the above and something I'd like to also mention that I don't think has been brought up is that we all want better therapies, and we want them seen. And one barrier to that is the number of patients that enter on clinical trials. This is notoriously low in cancer, and so anything that stands in the way of that that is not absolutely essential, I think, should be removed.

I think we need to encourage people to enter trials.

CHAIRPERSON NERENSTONE: Dr. Siegel.

DR. SIEGEL: Yeah, thank you.

Just a quick comment about both that issue, the issue of developing new drugs and treatments, as well as on a couple of comments.

There have been some comments, and I don't think anybody misunderstands this issue, but there have been a number of comments to be suggesting that

our policy had mandated interferon therapy or denied patients the right to refuse interferon therapy, and I'm sure -- I hope everybody on the panel and everyone in the audience appreciates that what we're talking about is not -- of course patients have the right to decide whether or not they want to get interferon. The issue is who's enrolled in clinical trials.

And I assume that the comments from Dr. Vanderpool on self-determination were not addressed specifically to self-determination in terms of a choice to take interferon, but the implications of that on one's access to clinical trials.

But saying that, so I would just turn it around and say the question we're asking is if you're doing -- well, let's put it now in terms of Phase 1 or 2 of a clinical trial in a vaccine in which you're looking to see if you get antibody responses. You have an option of studying that in people who have a low stage lymphoma, a low stage melanoma, grade melanoma for whom interferon hasn't been proven to be a benefit, and you have an option of studying that in patients who are also getting interferon and looking

at its toxicities and its antibody response in patients who are getting interferon.

Those are not perfect options, and some people don't like that option, and so the question in that setting boils down to: is it an appropriate alternative?

So those I don't think would not get developed. The question is: is it an appropriate alternative option for a sponsor and investigator to go to a patient and say, "I have an experimental therapy. Here's a consent form," and the consent form, of course, describes that I don't know whether it works or not, "and you're eligible to get this experimental therapy provided you refuse interferon therapy, and here's the risks and benefits of interferon therapy"?

Suffice to say that that raises important questions. Those are the questions we're asking the Committee to help us think through.

CHAIRPERSON NERENSTONE: Dr. Sledge.

DR. SLEDGE: I don't know if I'm a Baysian sort of guy or not, but I do think statistical issues

actually are fairly central to this discussion.

When I look at this data set and compare it to other adjuvant data sets, what I'm struck by is the tiny number of patients who have gone onto these trials.

For instance, by comparison six, eight weeks ago in San Antonio there was a 9,000 patient adjuvant breast trial that was presented whereas we have what, seven trials here that have a total of 3,700 patients?

A large part of the argument that I've heard today surrounds what represents clinical benefit for adjuvant therapy of melanoma. The data that I see are pretty compelling for relapse free survival. I don't think there's any serious question about that from a statistical issue.

The overall survival data I think are more questionable. I mean, I think we're talking about fairly modest differences with confidence intervals that either approach or cross unity, and I think given that relatively modest survival differences, given the real toxicities, I think there's a legitimate question

to ask whether or not high dose interferon should represent standard of care in this setting.

And based on that, I don't think it's currently appropriate to mandate it because I don't think we have compelling evidence for a survival advantage.

Now, I also say that these things change. You know, if you look at overview analyses in breast cancer and adjuvant trials over time, there have been real shifts in our interpretation of the data both in terms of relapse free and overall survival data both for adjuvant chemotherapy and for adjuvant hormonal therapy over time as more data has come in and as more trials have come along.

So what may not be striking and impressive and representing, you know, whatever the current equipoise is today may well change two years from now, five years from now as more data comes along.

So I'd say, you know, specifically on this issue talking about today's data set, I mean, my bias is that we don't yet have sufficiently compelling data that we should require this, though it certainly could

change a few years from now.

CHAIRPERSON NERENSTONE: Dr. Fleming.

DR. FLEMING: Let me begin by acknowledging that the informed consent process is really critical to the ethics and integrity of clinical research. Having acknowledged that, Mr. McDonough's comments, I think, bring to mind again the reality though that it's not perfect, and it's my sense then that there certainly can be interventions that have such substantial benefit to risk evidence that I think withholding effective treatment could constitute an unreasonable and significant risk.

So I think there are settings in which the FDA could appropriately judge that there should be a restriction in the design of clinical trials and what the control regimen would need to be. Simply having acknowledged that we have an approved intervention though I don't think is necessarily stating that we have that level of evidence. It's stating that we have done adequately controlled trials to establish efficacy and safety such that we have a favorable benefit to risk profile that warrants making these

products available and allowing people the opportunity to choose to use them.

So where are we? Jay Siegel talks about the line. Where are we in this specific setting? What is the strength of evidence?

As we look at the 1684 trial and we look at recurrence free survival and the cure rate analysis and we're saying in that analysis there's a 12 percent increase in the estimated cure rate, if, in fact, that translated into a long term survival benefit of ten to 12 percent, we're talking about something on the order of a 30 percent reduction in the failure rate.

And if we're talking about that kind of survival effect, particularly with a very tolerable regimen, if my own opinion were being solicited, I would say that could readily be interpreted to be across the line such that one would need to protect patients against being asked to go on clinical trials that wouldn't offer them that level of benefit.

My concern is trying to understand what these data really tell us reliably about effects on what I would particularly care about, which is the

survival effects. The survival effects that we apparently are seeing here are much more modest in magnitude than what might have been suggested by the cure rate analysis of 1684, effects that are relative risks, ten percent reductions, absolute reductions, three to five percent, with some uncertainties as to whether that truly is the long term benefit and whether that's, in fact, established benefit.

That's the point estimate, and as Dr. Sledge has just pointed out, this is, even though a substantial aggregation of data, it's still not sufficiently substantial when we're trying to nail down differences on the order of ten percent.

There has been a lot of discussion as well that there are substantial toxicities associated with achieving this level of benefit. So this is, to my way of thinking, Jay, this is why this is such a difficult issue. I think there are definitely settings in which the benefit to risk evidence is so strong that it would be appropriate to restrict access to clinical trials that would require those trials would provide access to those interventions.

The nature of the evidence we have about survival here is sufficiently uncertain and what we do have is suggesting a relatively modest benefit in the context of what is a substantial amount of toxicity that's required to achieve that benefit.

Hence, this is why it seems to me that it's very appropriate to suggest that whereas the ideal would be to inform participants of the benefit and risks of interferon, encouraging designs of trials that can build on interferon to at least acknowledge that there could readily be substantial participants who would choose not to enter into a trial that would require them to receive interferon.

CHAIRPERSON NERENSTONE: Dr. Blayney.

DR. BLAYNEY: Yes, I agree that looking at the totality of the data that we saw this morning that requiring patients with either Stage II and probably with Stage III interferon, Stage III melanoma to enter a trial that randomized to interferon is not something that you should do. I think that society, to take Coach McDonough's analogy a little further, society does put a fence around who can enter an Atlantic City

casino. We don't allow minors, and there's pressure not to have people spend the rent money at those casinos.

But once you have those fences, I think the line of entering patients with melanoma with either Stage II or Stage III, to enter them in a placebo controlled trial, for my view, should be okay.

Basically if we're worried about setting a precedent on data that was evaluated seven years ago, this is a moving field, and I don't think that we should be compelled to look at that as a gold standard or something we can't back away from because times do change. We are seven years down the road, and I think it is reasonable to allow a trial design that does not include an interferon arm.

CHAIRPERSON NERENSTONE: Dr. Vanderpool.

DR. VANDERPOOL: Dr. Siegel, you can be sure that when I referred to self-determination I didn't imply at all that self-determination only applied to patients making decisions in the clinic, but to other areas.

I agree with the last three speakers,

Sledge, Fleming and Blayney, on how there doesn't seem to be a compelling case for forbidding patients from entering other clinical trials before they take interferon given the data about interferon.

At the same time, I would argue from an ethics and legal perspective that even if the data were much stronger, that patients in consultation with their physicians do have a right to say, "No, I don't want that standard treatment," and they should have the right to enter a Phase 2 trial under a variety of circumstances.

Now, does that, Jay, take power away from the FDA? No, I don't think it does. The FDA has a right to decide which drugs to approve. It has a right and responsibility to decide which clinical trials for new drugs can go forward. You don't want an untried drug in a Phase 3 trial, et cetera.

So you can determine what the trials are. You can determine what the drugs to approve are, and you can protect the public vis-a-vis clinicians not using unproved remedies in clinical practice. All those are under the purview of the FDA.

I think the only problem I have here is the FDA stepping into the realm of determining what patients should decide with those things that are already approved, clinical trials, on the one hand, and therapeutic measures on the other.

So I think the FDA has overstepped its bounds on this, but it doesn't mean that it doesn't have and shouldn't continue to have the vested authorities that it has with respect to approval of drugs, approval of different kinds of clinical trials and protecting the public's health.

DR. SIEGEL: Let me just get a clarification, but first, I want to assure everybody here that (a) this is not about our concern about what power we have; just our concern about how best to delegate and carry out the responsibilities that we do have, although, if I understand your question -- well, let me get some clarification on that.

But also I want to reassure Dr. George that our question here really isn't, although I appreciate your thinking about that, one of a slippery slope. It really is an issue of what's the right

thing to do in melanoma. This is something where we're particularly troubled about, and we're getting some very useful advice in that regard.

I think as you all know or as you heard today, we did not make this decision based on the rather compelling evidence on disease free survival. It was only as more evidence of survival accumulated we made that decision.

We're here because we want the feedback we're getting on that decision.

Dr. Vanderpool, let me ask you this, and this does go to our authorities. It sounds like from what you're saying that you're carrying this to an extreme, which would be very different from what we're hearing in other circles, that there would be no case in which the FDA should say patients can't with consent forego a therapy even if proven life saving and very well tolerated.

Are you suggesting that that is not an appropriate use of our authority, that we're not supposed to review trials to determine that?

DR. VANDERPOOL: That's a tough one. I

think the devils are in the detail of the particular circumstances you would have, but I think I can think of a variety of circumstances where patients would not want to take a certain drug regimen based on worries over quality of life and so on, but should have the right to enter clinical trials with drugs that were wanting to treat that condition that have not yet been approved.

This is a new problem in biomedical ethics that I discovered as I was reviewing these materials. So I certainly would need to think about the issues further, but generally, I think the patient's rights do trump, although the FDA has the authority, as you say, not just for power reasons, but for the protection of the public, to decide which trials are available.

But my worry is other FDA's reaching further and deciding what patients have to have decided to have done before they can enter those trials.

DR. SIEGEL: Well, let me just say from a philosophical point of view -- and Dr. Rosenberg

raised this issue -- that I was involved in both of these decisions, and the FDA determined within actually the space of a year or so and on the same database, both that Interleukin-2 should be approved for renal cell carcinoma because it was quite reasonable for many patients to elect that the demonstrated benefits outweighed the substantial risks and side effects.

And at the same time we did allow, I think, within a year of that the onset of a placebo controlled trial of interferon gamma in the same population base provided those patients were told of the risks and benefits and chose not to get interferon, based on the fact that we also felt it was very reasonable for patients and the physicians to decide otherwise.

And I couldn't agree more with the notion that patients and physicians should have those choices.

On the other hand, I have to tell you the agency has been roundly criticized in many areas for allowing placebo controlled trials with new drugs

where there are proven therapies out there, and I think our rather broad understanding with the agency is that there's a gray zone that this is in probably, but that somewhere there is this line.

And it would be interesting at some future point to have other discussions about whether there should be such a line, but I can assure you that in practice there is such a line, and that there is a broad expectation in many circles that we do draw such a line; that there comes a point that there are therapies out there that are cured of live, prolonging life saving, well tolerated therapies out there that we will not allow a sponsor who has got an experimental therapy to say, "Look. Here is this proven therapy, but if you'll agree, you can get this experimental one or placebo," or something like that.

So it's not -- you know, it's not been that black and white. It's not been that that's outside our purview. At least that's not the way it's been viewed in much of the patient advocacy community, much of the international community, and within the agency, as well.

CHAIRPERSON NERENSTONE: Dr. Albain.

DR. ALBAIN: I'm struggling a big going back and forth as we've been doing in our discussion between Phase 2 and Phase 3 here. And I was struck with all of the advocacy letters and E-mails that we got that really they were addressing the issue of Phase 2 trials in probably over 95 percent of those.

And that being said, if we could be fully convinced that the consent would be informed about a Phase 2 trial, I'm left with what exactly are the endpoints of a Phase 2 adjuvant trial, and in fact, at least in breast cancer, you know, you really can't do a Phase 2 adjuvant trial. You can try if you were certain you had a good, intermediate biologic endpoint, a surrogate, such as, perhaps in the neoadjuvant settings for pathologic CR.

But I would have to defer to the melanoma experts here today. Are you fully convinced that in a small Phase 2 trial with a vaccine or other biologic therapy that you can come up with a surrogate that would then allow you to be excited enough to take that particular approach into a Phase 3 trial?

And if you are, then in that Phase 3 trial, ideally you don't want to be confounded by the presence of another biologic, I suspect. You don't want to be confounded by interferon being on board in high doses when you're testing another novel biologic.

So then you argue back around to the placebo, and then will you, in fact, get a patient to accrue to such a Phase 3 trial when they have to go onto an observation arm?

So then you're back again at square one, and I think a lot depends on the experts here in melanoma biology and what can you do with smaller sample sizes in a Phase 2 setting.

CHAIRPERSON NERENSTONE: Dr. Taylor. Oh, okay. Go ahead.

DR. SPITLER: Is this microphone one? Oh, it's on.

That was a great question, and I'd like --

CHAIRPERSON NERENSTONE: Please identify yourself for the record.

DR. SPITLER: I beg your pardon?

CHAIRPERSON NERENSTONE: Identify yourself

for the record.

DR. SPITLER: I'm Dr. Lynn Spitler.

I can give you a specific example where that has occurred, and it's a study that I did of GMCSF as adjuvant therapy for a Stage 3 and 4 melanoma. At the time I went to Immunex in 1993 there was only preclinical data that GMCSF would activate macrophages, and activated macrophages would kill tumor cells.

Now, you wouldn't go to a prospective randomized Phase 3 trial with that without getting some idea would there be clinical benefit, and I proposed to them a Phase 2 trial, and they accepted it.

We treated 48 patients and compared survival with matched historic controls from the University of Alabama database. Not great, you know, but the best -- it wasn't a prospective randomized trial. We were just getting an idea would there be some clinical benefit that would warrant doing a prospective randomized Phase 3 trial.

Well, that data were sufficient, which we

published a year and a half ago in the JCO, were sufficiently compelling that ECOG accepted that data and did launch a Phase 3 prospective randomized trial comparing GMCSF with placebo, and there's some vaccine arms in there as well.

So in that circumstance, the Phase 2 was sufficient to get to the Phase 3.

DR. ALBAIN: Given now that your new staging system shows such an exquisite differential with very minor variations in these prognostic factors, I think if you would have to, if you were to design such a small Phase 2 trial, be very rigorous in who went into it.

And thus, you would then be exclusionary in that way. Because if you're using historical controls, you can't use it the way we used to five or ten years ago now that you have your new system that's much more refined.

DR. SPITLER: If you apply the new system, the new system is wonderful because it very specifically identifies prognostic indicators, and if you match patients in the historic data base according

to those very important prognostic indicators, including the ulceration, including the number of nodes positive, including whether it's microscopic or macroscopic disease, you can match the patient populations, and I think that that gives you a reasonable approach to suggestions of efficacy.

In our current study we used the AJCC database, which was the same one that was validated with the new staging system, 17,000 patients, and matched 1,000 patients from that database with 50 patients in our study.

DR. ALBAIN: Could I just follow up?

If this is kosher, Madame Chair, could I hear from one of the other experts here, Dr. Rosenberg, Chapman, Schuchter, any of you over there, what you think about this issue of confounding on Phase 3 trial if you have another biologic on board, and are you concerned about missing benefit to one of your new approaches?

I know ECOG has obviously struggled with this, and they've chosen to build onto the control arms, interferon alone.

DR. CHAPMAN: In fact, I'd like to also mention that there's another paradigm for a Phase 2 trial.

CHAIRPERSON NERENSTONE: Please identify yourself for the record.

DR. CHAPMAN: I'm Dr. Paul Chapman from Sloan Kettering Cancer Center.

There's another paradigm that we use actually even more commonly for Phase 2 trials that are one sided, that is, where we use a surrogate endpoint of an immunological response, and we use that sort of as an endpoint to determine whether to carry that vaccine forward.

That's I think even the more common scenario between our trials and Steve's trials and a lot of other people's trials.

And that's an example where a Phase 2 can really direct you as to where you're going to go.

In terms of having an interferon board, I think we have very little data, except for the ECOG 2696 trial that we did with ECOG, which showed that the high dose interferon, when given with the GMK did

not appear to affect or inhibit or deter the immune response to the GM-2 gangliocyte.

But you're right. I think many of us would be a little hesitant to go forward with the Phase 3 without a least a little pilot data for the individual live vaccine that we were looking at.

CHAIRPERSON NERENSTONE: Dr. Taylor.

DR. TAYLOR: I think that one of the things that hasn't been mentioned, and it's truly why I think we have bioethicists is that to complicate things is that although you go into the casino with your clothes on and your ego intact and you're not sick, as a group of patients who have melanoma, you're a vulnerable population.

As you alluded to earlier, you may not feel well. You're also very frightened, and it's in that setting plus the setting that I see physician researchers who are very biased and very excited about their new study, that I feel that the FDA has to maintain that role as the policeman for us.

Now, in this setting, I don't think the data is adequate to say that interferon is the home

run, and I'm not willing to say that everybody has to have it.

But I do think we have to keep the FDA looking at those type of issues because we are dealing with vulnerable populations, and we are dealing with excited doctors.

CHAIRPERSON NERENSTONE: Dr. Brawley.

DR. BRAWLEY: Dr. Taylor's comments are well taken. I don't treat patients with melanoma. So I'm not, I guess, your definition of an expert on this issue.

I will tell you that the FDA in terms of proven versus experimental therapy, I was thinking about in testes cancer where the FDA approved therapies can cure 70, 80 percent of folks. It would be shame if those individuals were allowed to forego what is a really high likelihood of cure in order to go onto an experimental therapy because I really don't think that the patient very frequently -- and I'm not one to baby patients or government taking care of patients, but I fear the investigator selling his investigational drug in that example.

I think one of the things that we have to bring forth here is that one of the reasons why we have so many questions in melanoma is only about three percent of melanoma patients have gone onto clinical trials over the last ten years.

If we're going to move forth melanoma therapy, we have to increase the number of people going onto those clinical trials.

Now, in terms of INTRON-A for melanoma, and again, I speak as not an expert, and indeed, I'm probably one of the least likely people in this room to get this disease, but I honestly think that I would forego interferon.

Coach McDonough, I don't gamble when I got to Atlanta, but I really do think I would forego interferon A as being just not likely to give me much benefit at all, and in that sense I think it would be fine that individuals who felt like me could be randomized to trials that included a placebo, especially since we're talking about so many people get interferon who wouldn't benefit to begin with.

Now, is a placebo control trial ethical in

any of these stages? I think the answer is yes.

Is it unreasonable in any of these stages? I don't think it's unreasonable at all. Indeed, as I just said, I think interferon therapy may be unreasonable for some people, but again, I would defend folks' right to get interferon therapy if they wanted it.

Is a placebo control trial wise? In some instances the answer is it may be very reasonable and very ethical, but not necessarily very wise in terms of recruiting people in clinical trials.

I'll conclude by saying I, like Dr. Sledge, have difficulty with saying that interferon currently is the standard of care. I think it is a care option, but not necessarily the standard of care.

CHAIRPERSON NERENSTONE: Dr. Carpenter.

DR. CARPENTER: I just want to second what Dr. Brawley said and my comments are very similar. We have -- you can envision breast cancer with a hormonal therapy where it would probably be not reasonable to suggest that somebody forego some kind of first line hormonal therapy as an adjuvant to taking unproven

treatment as just not being in that person's best interest, much like the testes cancer.

This just seems at the other edge of the slope. While there is a therapy, there's at least a log of discussion among fairly knowledgeable people about just how compelling the evidence is for it, and given that uncertainty or the softness of that endpoint, then I think more choice is appropriate.

CHAIRPERSON NERENSTONE: Dr. Nelson.

DR. NELSON: A couple of quick comments. I would modulate the emphasis on self-determination a little bit, and I think it's an important distinction to make between Phase 2 and Phase 3. Certainly many of the arguments do appear to be presented as sort of the choice against interferon in favor of some other therapy, which would be the case in a Phase 2 uncontrolled fashion.

But when you move into Phase 3 efficacy trials, in effect, the choice then is to enter the trial, and you're taking your, quote, risks about which arm you may end up being randomized to.

So the complexity of the relationship

between choice and the clinical trials, I think, would have to be a much more nuanced discussion about the justifications of choice.

I think a challenge to statisticians that would be interesting to see how well it could be tackled is the extent to which you could incorporate choices within trials that wouldn't undercut randomization in a way that you could still make inferences.

But that goes way beyond my expertise in analyzing dropouts and crossovers and all of that kind of effort, but that would be a worthy kind of direction to move toward in the future.

CHAIRPERSON NERENSTONE: Does FDA sort of have a feeling of -- okay.

DR. SIEGEL: You've not only answered Question 1, but Question 2 as well, except perhaps for the last sentence in it. So maybe that would help move along. If you look at the last paragraph, should this further be expanded?

The question asks if those patients who are allowed to go into protocols using placebo or

unproven adjuvant therapy should be expanded to include those who refuse to receive interferon therapy. We have certainly received a great deal of comment on that, although the last part of that question would be one if there are additional comments, that would be helpful.

If so, should any particular steps beyond IRB and FDA review of informed consent documents be taken to insure that the patient has made an informed decision?

CHAIRPERSON NERENSTONE: Dr. Redman.

DR. REDMAN: Regarding that last point again, going back to Dr. Slingluff's, I am one who spends 20 to 30 minutes in a room talking to a patient about adjuvant interferon, and we make our own material that we give them even in a non-study situation.

I think it would be extremely helpful if there was some -- I'm not for government regulation, but if there was some standardized summary of information that uniformly we can give patients that they could do as we do in breast cancer regarding

different surgical options, that they actually sign saying that they've read this material, and it would be supplementary to IRB approval of Phase 2 trials. did the patient sign the interferon consent form or such?

We're still going to talk to our patients, and that's never going to end. And then we're going to have different biases as physicians, and we always will have those biases, but at least it levels the field somewhat so that you're sure at least the patient did get some information on interferon before being considered for an investigational therapy.

CHAIRPERSON NERENSTONE: Dr. Nelson.

DR. NELSON: I would suggest if you're concerned about the quality of the informed consent that you're going to have to move beyond simply reviewing the documents. I don't have an answer about what that beyond might be, but the whole issue of trying to measure and actually insure adequate voluntary and informed consent is one that I think should be tackled.

There are creative ways in more high risk,

visible activities, such as the artificial heart trial where consent, sort of patient advocate people have been involved as well.

I'm not sure that this would reach that sort of threshold, but I think you should do something more than just look at documents.

CHAIRPERSON NERENSTONE: Dr. Blayney.

DR. BLAYNEY: Yes, as someone who working through ASCO and others has helped to get payment for clinical trials, I think that is also a mechanism. To use Dr. Taylor's term, we have a lot of excited investigators in this field, and perhaps if informing the patients of whether Medicare, to take an example, will cover their clinical trial and their specific features in the law as to whether Medicare will cover that trial, that may be a useful check on some of the entry criteria.

CHAIRPERSON NERENSTONE: Dr. Siegel, do you want us to go to the end of Question 3 or have we discussed this to your satisfaction?

DR. SIEGEL: Well, are there other comments on that or those are all of the comments on

this questions? If so, that's fine. If not, we'd certainly welcome others.

As far as current Medicare policy, I believe if it's under IND at FDA, it's automatically covered. So that's one of the -- I was involved in that policy, and I believe that's one of the conditions.

CHAIRPERSON NERENSTONE: Dr. Przepiorka.

DR. PRZEPIORKA: Just one additional comment for Question 2. Another way that's frequently done for other types of procedures is to initiate a waiting period between the initial discussion and the decision by the patient, but I have to tell you that that's not very practical because many times patients who are really on clinical trials come from else where, and sometimes even a 24 hour delay in initiation of treatment is enough to impose a significant financial burden.

CHAIRPERSON NERENSTONE: Dr. Vanderpool.

DR. VANDERPOOL: Just a brief comment to what Dr. Nelson said about informed consent. I do think it makes sense to move beyond the document to

questions of process and comprehension of informed consent, and there's been a lot on process, but one thing the FDA or any institution can do is simply ask the researchers, "And how od you plan to seek recruitment for your subjects?" and determine some of the process that way.

The other thing is certainly in high risk trials to seek to insure comprehension of consent by asking, "Can you repeat what I told you?" and you can offer a very simple test to assure comprehension.

But I think those no question the way the committee is going in its recommendation would mean informed consent does bear a heavy load, which is the load it does bear in the Belmar (phonetic) report.

CHAIRPERSON NERENSTONE: And the third question: does the Committee believe that a noninferiority or trials designed to demonstrate an effect of a new agent on relapse free survival, but unable to assess the effect on overall survival could constitute acceptable evidence of efficacy?

Comments? Dr. Fleming.

DR. FLEMING: Let me address the

noninferiority question, but just slightly broaden it first to respond to a question that Dr. Nelson asked a little bit earlier.

As we look at designs that we could undertake for a vaccine, one of the approaches is an add-on design, and Dr. Nelson was referring to this where Interferon would be offered as the control, and the intervention group would be interferon plus the vaccine, although an option could be provided to those participants at baseline who after informed consent had judged that the benefit to risk profile of interferon is not such that they would want to receive it, and they could then elect to go into a randomization of observation versus interferon and essentially have two strata.

Such an approach could be an appropriate design, particularly if one didn't have strong prior evidence that interferon in this case would be, in effect, modifier. If there isn't substantial concern that the efficacy of adding the vaccine to interferon would be substantially different than the efficacy of adding the vaccine to observation, one could, in fact,

allow that choice at baseline, essentially forming two strata for the overall analysis.

Another approach is the one raised in Question 3, which is can we do a noninferiority comparison. So can we do a head-to-head comparison of interferon against an intervention such as a vaccine?

My sense about this depends on what the end point is. If the endpoint is survival, the strength of evidence is not adequate to justify a non-zero margin. so if we were using survival as the endpoint, I believe we would have to be looking at superiority.

If we were looking at recurrence free survival, there is sufficient signal here and precision in the estimate of that signal that one potentially could justify a margin. If you look at the estimates and the meta analysis that was done by the FDA, the overall reduction in the rate of recurrence is, I think, 21 percent with a confidence interval indicating that it's at least 11 percent.

And so if one said, "All right. I'll use that 11 percent estimate and preserve at least half

the benefit, there is still, in fact, a margin there that could be provided.

Let's say that margin, just to go back to the exact data that was discussed by Dr. Ibrahim, if we said that, for example, the same as a cure rate of three percent, then essentially if you were assuming that or you were trying to detect the efficacy of a vaccine that was seven percent better than -- seven percent superior, you could rule out that it was three percent inferior with half the sample size that it would take to prove superiority.

So there is something here in terms of what the benefits could be in terms of allowing you to establish efficacy on recurrence free survival with a more modest sample size.

The difficulty that I have is the last part of this question, and that is: is such evidence of noninferiority on recurrence free survival without corresponding evidence about what this means in terms of survival going to be judged in the end as adequate evidence of efficacy?

And my won view is recurrence free

survival is certainly a relevant endpoint, but not nearly as relevant as being able to establish a survival impact, and so whereas I think it's not possible based on current strength of evidence to justify a noninferiority design for survival, it is for recurrence free survival with a very modest margin here, but I have difficulty in knowing how we would interpret the results if we simply establish noninferiority on that measure alone.

DR. SIEGEL: Just for clarity for the Committee, that is right at the heart of what we're asking. Our analysis of the current data as summarized briefly in that paragraph is exactly the same as yours, that we could, we believe, probably. It depends on the stage a patient is enrolled and other factors, come with an appropriate margin as ECOG apparently believes as well.

We've heard for noninferiority on recurrence free survival, but not on survival, and I think the assessment of this group on the data would support that conclusion.

That means if we accept a new drug trials,

we get applications based on trials compared to interferon, we will come back to this Committee with a data set and we'll say based on this drug's effects on recurrence free survival, it is similar enough to interferon that we can say with some level, a high level of certainty that it is effective on recurrence free survival.

But at the same time we'll probably be saying that based on its similarity to interferon on survival, this trial can't tell us anything about whether it is affecting survival or not affecting survival because we don't have that level of data about interferon.

So we need to know from this Committee is that sort of trial going to -- you know, are you going to say, "Well, why did you even let them do that trial in the first place since it's not going to lead to a drug approval?" because if you're not going to approve on the basis of a trial that shows a clear effect on long term, let's say, recurrence free survival form which we can't determine even in the long run overall survival, then it's probably not worth doing the

trials.

CHAIRPERSON NERENSTONE: Dr. George.

DR. GEORGE: A lot of what I was going to say has just been said in the interchange between Dr. Fleming and Siegel, but the answer to the question as I first read it was, yes, but. I mean, yes; yes, you could do this study, and I strongly agree that you couldn't do it with respect to survival, that is, the noninferiority survival can't do -- it's essentially, you know, zero. You don't have the same wiggle room there to define a margin.

But you could with respect to disease free, but would you?

And secondly, what margin would you choose?

I'm a little concerned about that. I'm thinking that it would -- I haven't thought it through completely, but I would think it would have to be because of the modest evidence, that it would have to be so small that you would have a pretty big study, and the pretty big study would end up saying just what you said. If it were successful, it would say it's

not inferior with respect to disease free survival; might be with respect to survival, and that's bad.

So I think it is a quandary, and I don't know. It might require some more creative thinking about designs with respect to what you would require with respect to survival even though you wouldn't be able to do this noninferiority in the usual way.

CHAIRPERSON NERENSTONE: Dr. Blayney.

DR. BLAYNEY: Yes. I agree with what the statisticians have said about the noninferiority, but from a clinician's point of view, it's going to be quite apparent to the investigators who's getting high dose interferon and who's not, and there will be substantial potential for bias in determining that progress endpoint, and it won't take, given the magnitude of the benefit, it won't take many errors in not investigating that mole that popped up or not investigating that lymph node that could or could not be there during that time.

And so there's substantial -- you know, hearing Dr. Temple talk about sloppiness in noninferiority trials, there's substantial potential

for sloppiness in the progression endpoint in such a noninferiority trial.

CHAIRPERSON NERENSTONE: Dr. Nelson.

DR. NELSON: Just a brief comment. As to whether or not or a question whether you would factor in the toxicity profile, I mean, I would think if I was a patient and you told me interferon for a potential for nine months, putting cure aside, something else for a potential of 14 months with a much lower toxicity profile, I might be inclined to take that.

DR. SIEGEL: Well, absolutely, and that's why this is perplexing. If you could show a drug had the same effect on recurrence free survival, say, a vaccine that's extremely well tolerate, the same effect, and you knew it was a real effect and didn't have the toxicity of interferon, you would think that would be desirable, but again, if that's the trial that's done, we would be coming before this Committee not only with a trial where we don't know the outcome on overall survival, but with a trial that can't determine it no matter how many years you follow those

patients because you don't have a right group to compare it to. You have a group that may or may not have an effect on overall survival.

Because that then leaves you with the other options. Adding onto interferon is certainly one of the options or studying different stages of disease or, in fact, studying the drug only in those people who opt to be randomized to placebo and forego interferon therapy.

And so we're past that issue, but this is another important study design issue, and it would be helpful if we can -- we're not coming to a vote, but I gather, and I think we weren't aware how far along ECOG had progressed in this area, but I wouldn't be surprised if these trials are coming down the way, and it sounds like, you know, the Committee is going to be potentially faced with them.

And if you're thinking that they're not the right way to prove a therapy effective for the purpose of licensure, we need to hear that now.

CHAIRPERSON NERENSTONE: Dr. Przepiorka.

DR. PRZEPIORKA: I just want to agree with

Dr. Nelson regarding the issue of toxicity, and I think there is a precedent for such a trial right now. I mean, I said before if I were going to die in five years, I would prefer to spend four and a half without disease than with disease. So relapse free survival makes a difference on my quality of life.

So if you go back to your design for quality of life studies, relapse free survival plus toxicity can, I think, be viewed as a clinical benefit on which you can improve a drug.

For example, if you had a drug which gives you the same sort of CR rate in a malignancy and was given as a pill as opposed to interferon, and you can guess what the drug is, even though you don't know the long-term survival differences, you know, clearly that's a drug worth getting approved.

CHAIRPERSON NERENSTONE: Dr. Kelson.

DR. KELSON: Looking on the other side, if relapse free survival in this disease was a good stalking horse for survival, and I heard some comment about that, that the Europeans may feel that way. Then I think it would be a slam dunk. You wouldn't

have a problem.

The trouble is looking at the data set that you showed us from the meta analysis, relapse free survival was not a surrogate for survival.

CHAIRPERSON NERENSTONE: Not seeing any more comments, I'm going to let us break for lunch. I'd like everybody back at two, please, to being the afternoon session.

Thank you.

(Whereupon, at 1:12 p.m., the Advisory Committee meeting was recessed for lunch, to reconvene at 2:00 p.m., the same day.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(2:12 p.m.)

CHAIRPERSON NERENSTONE: If the Committee would please take their seat, we'll get started in the afternoon session.

Good afternoon. We'd like to start this part of the session by again going around the table and everybody introducing themselves.

Mr. Ohye, if you would like to start.

MR. OHYE: George Ohye, industry rep.

DR. BRAWLEY: Otis Brawley, medical oncologist, Emory University.

MR. McDONOUGH: Ken McDonough, patient representative, North Huntington VA.

DR. NELSON: Robert Nelson, Children's Hospital, Philadelphia, and the University of Pennsylvania.

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

DR. FLEMING: Stephen George, Duke University Medical center.

CHAIRPERSON NERENSTONE: Stacy Nerenstone,

medical oncology, Hartford Hospital.

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

And, Jody Pelusi, are you on the line? Can you please speak up if you are?

(No response.)

DR. KELSON: David Kelson, Sloan Kettering, New York.

DR. BLAYNEY: Douglas Blayney, medical oncologist, Pasadena, California.

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

DR. VANDERPOOL: Harold Vanderpool, Institute for the Medical Humanities, the University of Texas Medical Branch in Galveston.

DR. TAYLOR: Sarah Taylor, medical oncology and palliative care at the University of Kansas.

DR. FLEMING: Tom Fleming, University of Washington, Seattle.

DR. ALBAIN: Kathy Albain, medical oncology, Loyola University, Chicago.

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

DR. TIWARI: Jawahar Tiwari, biostatistics, FDA.

DR. CARDINALI: Massimo Cardinali, FDA.

DR. KEEGAN: Patricia Keegan, Center for Biologics, FDA.

DR. SIEGEL: Jay Siegel, FDA.

DR. TEMPLETON-SOMERS: The following announcement addresses the issue of conflict of interest with respect to this meeting, and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the following exception.

Dr. Bruce Redman is recused from participating in the Committee's discussions concerning Corixa's Melacine

We would like to note for the record that George Ohye is participating in this meeting as an industry representative acting on behalf of regulated industry. As such, he has not been screened for any conflicts of interest.

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 participants are aware of the need to exclude themselves from such involvement, and exclusion will be noted for the record.

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

Thank you.

CHAIRPERSON NERENSTONE: We will turn now to the sponsor presentation, the appropriate study design and control for the proposed Phase 3 trial of the investigational new drug Melacine or melanoma vaccine by Corixa.

DR. CHEEVER: It's with a great pleasure

that this afternoon I have the opportunity to present the clinical development of Melacine vaccine; that the purpose of today's study is to discuss the proposed second pivotal trial of Melacine vaccine as adjuvant therapy for intermediate thickness Stage II melanoma in patients that are HLA-A2 and/or HLA-C3.

The first point I want to make is that the category of patients that were studied is not the category of melanoma patients that were discussed this morning. This morning we discussed patients primarily that were Stage III that had no positive disease. These patients have no negative disease.

This morning we talked primarily about those patients with Stage 2 that had thick tumors, meaning tumors greater than four millimeter, the primary tumor. In this circumstance we're dealing with intermediate thickness Stage II. Those are patients with primary tumors of less than four millimeter.

In large part this morning's discussion was silent on this group. Despite that, this group comprises approximately 25 percent of melanoma

patients. The five year survival is between 63 and 79 percent. Even though they're less than four millimeters, their survival depends upon a thickness within that parameter.

There is no approved adjuvant therapy to prevent relapse in this disease category, and there's no adjuvant therapy routinely being recommended, and the one comment that Dr. Kirkwood made this morning in reference to this group, if I quote him correctly or paraphrase him, that there is no therapy that has been tested or is approved for this category of patient.

This clearly is an unmet medical need. The Southwest Oncology Group, in an attempt to meet this unmet need, conducted a trial called SWOG 9035, and this slide will very quickly go over the conclusions from that SWOG 9035 trial, but please be aware that I'll only present the capsule summary at this point in time and will go over each one of these points in detail later on in the presentation.

SWOG 9035 compared Melacine versus observation in patients with intermediate thickness Stage II melanoma. SWOG's analysis demonstrated a

nonsignificant trend in relapse free survival for Melacine in the intent to treat population.

There was a highly significant relapse free survival benefit for Melacine in patients that expressed two of five predefined HLA antigens. The domino effect was in patients who expressed HLA-A2 or HLA-C3 or a combination of both of them. And for the rest of the presentation I'm terming patients who have A2 or C3 or both as A2/C3 positive.

In this A2/C3 positive population, Melacine was associated with a highly significant increase in both relapse free survival and overall survival.

Accelerated approval for A2/C3 positive patients was discussed with the FDA and was considered not to be an option because these patients were subpopulation of the intent to treat population.

A second pivotal trial that confirms the efficacy of Melacine in A2/C3 patients will be required for approval. Therefore, the goal of Corixa is to replicate SWOG 9035 as closely as possible, but with only A2/C3 positive patients in order to confirm

the benefit of the vaccine in this particular patient population.

However, there area number of issues that affect the design of the second pivotal trial. Importantly, the first pivotal trial took ten years, and the second pivotal trial may take up to another decade.

Given this time frame, the key issues of trial design need to be addressed now in order to design this second pivotal trial sufficiently to confirm the first pivotal trial for regulatory approval.

Since initiation of this trial a decade ago, there have been some substantial changes in the standard practice of melanoma that affect attempts to replicate the first trial. At the suggestion of the FDA, guidance from ODAC is being sought today on trial design.

The primary question is whether the patient populations chosen are appropriate for an observation only control arm.

The presentation today will have as topics

an overview of Stage II melanoma, an overview of the clinical development of Melacine vaccine, detailed results of SWOG 9035, issues affecting further development of the vaccine, the proposed second randomized pivotal trial, and finally, the issues for ODAC and the FDA.

The first topic will be an overview of Stage II melanoma, and I should read into this an overview of intermediate thickness Stage II melanoma. I can gloss past this slide. Melanoma is a substantial disease. I think everyone is aware of that.

The outcome of the disease is really dependent upon the stage at the time of diagnosis. Stage I and II are differentiated primarily by size of the primary tumor. Stage III are those patients that have regional lymph nodes involved, and Stage IV are those that have disseminated disease.

This morning the discussions on interferon focused primarily on patients with Stage III and that portion of Stage II that had tumors of greater than four millimeters. For the talk today or this

afternoon, we will be focused on Stage II patients, but those that have the smaller tumors, the intermediate thickness tumors.

The intermediate thickness Stage II melanoma is defined as tumors that are between one and four millimeter by the old AJCC staging system that was discussed this morning and was in place when the SWOG trial was initiated. That thickness was 1.5 to four millimeter.

Now, the new AJC staging system quantifies the tumor thickness as one to four millimeter. All patients are node negative. All patients are metastasis negative, and, again, the five year survival is between 63 and 79 percent depending upon the thickness as well as the new prognostic criteria, which is ulceration.

Twenty-four percent of the patients were in this category in the AJCC database, which was included as Balch's manuscript in your briefing document.

This slide, also taken from Balch's article in your briefing document, shows that 15 years

disease specific survival for Stage II melanoma, and this is the new AJCC staging systems. For this morning when we spoke of Stage IIB, we were not dealing with the same Stage IIB. Rather, we were dealing primarily with Stage IIC in the new system, which is not on the slide. A Stage IIC would have had a worse 15 year overall survival than what is up here.

What I really wanted to point out with this slide is that patients with Stage IIA have approximately 80 percent five year survival. It's patients with IIA that were in the SWOG trial and will be on the proposed trial.

Also, some patients with Stage IIB, in particular those patients that had tumors less than four millimeter, and those patients had a slightly less optimistic outcome.

The other point to make from this slide really is that even though the five year survival is 80 percent, these patients continue to relapse and die over 15 years here, and even though a plateau was spoken of this morning, that the AJCC database really does not discern a plateau to 15 years. The reason we

saw a plateau this morning could have been because if there were a lack of patients far out.

But these patients with Stage II melanoma continue to relapse up to 15 years, and patients that relapse, in general, in general, die.

Despite this substantial nature of the disease, there is no adjuvant therapy to prevent relapse. There are no approved drugs. There are none routinely recommended. There's only one ongoing U.S. pivotal trial in this category of patients, and that's ECOG 1697, which was mentioned briefly this morning, and it should be noted that this is a trial of observation versus four weeks of INTRON-A; that the cooperative groups have not take upon themselves yet to test the approved proven effective regimen of interferon in this category of disease.

There are no other ongoing U.S. Phase 3 trials in this disease. So given these points, it's highly likely that we're going to be back here a decade from now still giving you the same message that there are no approved drugs and no routinely recommended drugs for this category of disease.

The next topic is the overview if the clinical development of Melacine vaccine. These are primarily time lines, but first start with the vaccine itself. The vaccine has two components, a melanoma lysate and an adjuvant, detox. adjuvant; that the lysate is the lysate from two melanoma lines. One is a rapidly growing, very aggressive melanoma. One is a slow growing, less aggressive melanoma.

They were originally chosen to represent a spectrum of the disease of melanoma. We know now -- we didn't know at the outset, but we know now that it contains virtually all of the antigens that we now consider to be melanoma vaccine candidates, including gp100, the gangliosides, Melan-A, the mage (phonetic) antigens, tyrosinase, tyrosinase related proteins, as well as high molecular weight melanoma associated antigen or chondroitin sulfate.

If you just inject antigens into patients, even the foreign, you do not get much of immune response. In order to get a substantial immune response, you really have to inject the antigens with an adjuvant. In this circumstance we're using a

detox. adjuvant, which is a combination of cell wall skeleton derived from mycobacterium phlei, as well as MPL, or monophosphoralipid A, derived from Salmonella Minnesota, and we have substantial experience with this particular adjuvant.

The clinical development of Melacine in advanced stage patients began 17 years ago now in 1985 with trials initiated by Malcolm Mitchell, then at USC. In 1988, the trials were taken over by RIBI Immunochem, which was later bought by Corixa. RIBI Immunochem treated over 300 patients with Stage IV disease.

An independent review of 198 of these patients validated six percent or 11 objective responses. Of these objective responses, most importantly there were five complete responses and four of those complete responses were maintained at seven plus the ten plus years at the time of the independent review.

Moreover, the vaccine was well tolerated, had a reasonable safety profile.

Based on the data in advanced patients,

Melacine was approved for use in Canada in the year 2000 for disseminated malignant melanoma.

In 19990, the decision was made to test Melacine in Stage II patients as adjuvant therapy. This was based on the modest efficacy, as well as low toxicity in advanced patients, and the commonly accepted theory that anything that works in advanced disesae is likely to work must better as adjuvant therapy because of the smaller tumor burden, because of less tumor induced immunosuppression, and because of the longer time over which the immune response has to operate.

In 1990 then, the Southwest Oncology Group initiated design planning for the trial 1935. In April of 1992, SWOG enrollment began.

At about the same time, Dr. Mitchell published in JCO analysis of his advanced stage patients showing an association of HLA phenotype with response to Melacine.

Okay. His results, again, were in advanced patients. He analyzed the outcome of 70 patients with disseminated melanoma, and what he

demonstrated was that there were five HLA types associated with Melacine benefit, and I'll read these the first time, but they're the same on multiple subsequent slides. They were HLA-A2, A28, B44, B45 and C3.

His association really made tow points, and the first point was that there was benefit from Melacine in patients that expressed two or more of these five HLA, and second, the benefit from Melacine was strongest in patients who expressed HLA-A2 and/or HLA-C3, again, A2/C3 positive patients.

Based on Mitchell's publication and analysis of the data in advanced patients, SWOG in 1994 began to HLA type all of their patients.

In 1996, their enrollment was completed. At that time they enrolled 689 patients. They had been able to HLA type 80 percent of their patients. Out of those, approximately 70 percent that were typed were typed prospectively and 30 percent were typed retrospectively.

In 2000, SWOG performed their primary data analysis, and at that time, there was a relapse free

survival benefit for the vaccine in all patients' intent to treat analysis with a P value of .04.

In September 2000, SWOG analyzed HLA data and demonstrated a relapse free survival benefit for vaccine in patients that expressed two or more five of the predefined HLA. Again, this was Mitchell's first finding, which was confirmed by SWOG.

Mitchell's second finding was that there was benefit in A2/C3 positive patients. This was also confirmed by the SWOG analysis. There was a relapse free survival benefit from the vaccine in A2/C3 patients with a P value of .004.

This part of the talk is to just present you with an overview of the time line, and I'll get back and present the data later on in the talk.

In September of 2000, we had an end of Phase 3 meeting with the FDA and discussed at that time an additional data sweep. The additional data sweep was to try to confirm the outcome of the study at a time, after a greater time had occurred and after more events had occurred.

Between November 2000 and April 2001, SWOG

conducted the data sweep. In May 2002, Corixa analyzed the follow-up data. The relapse free survival in all patients' intent to treat analysis which previously had been statistically significant lost its statistical significance with a P value of .141.

However, the relapse free survival in A2/C3 positive patients continued to be positive, with a P value of .005. Moreover, in a new analysis of overall survival, SWOG demonstrated a benefit for the vaccine in A2/C3 positive patients with a P value of .003.

These analyses that were performed by Corixa were later confirmed by SWOG.

In June of 2001, the results were submitted to the FDA. In October 2001, accelerated approval as adjuvant therapy in Stage 2 A2/C3 positive patients was discussed with the FDA, and it was decided by the FDA that a second Phase 3 trial would be required.

Therefore, today we're consulting you all for advice concerning appropriate patient population

in order to confirm the first pivotal trial results in this disease population.

The third topic is details of the result of SWOG 9035. SWOG 9035 was titled randomized trial of adjuvant immunotherapy with an allogeneic melanoma vaccine for patients with intermediate thickness, node negative malignant melanoma categorized as T3N0M0. This is a multi-centered, open labeled trial conducted by SWOG with IND held by Corixa.

The study coordinators are Vern Sondak and Jeff Sosman, Ray Kempf, Ralph Tuthill and P.Y. Liu.

The objectives of the trial were to compare Melacine versus observation for relapse free survival and overall survival.

Number two, to evaluate the toxicity of Melacine as adjuvant therapy.

And, number three, to explore the interaction between patient HLA types and vaccine effectiveness for relapse free survival and overall survival.

This third objective was added by protocol

amendment in response to Mitchell's analysis. It was added in September of 1994.

For trial design, after the primary tumor was removed, patients were stratified and randomized in a one-to-one ratio between observation and vaccine. The vaccine was given intramuscularly, 40 doses over the first two years.

The observation group and the vaccine group were followed equivalently for disease relapse. They were evaluated every three months for the first two years and then every four months for the next three years and then annually thereafter.

The major inclusion criteria were primary cutaneous melanoma that had to have been completely resected. Patients could have been clinically or pathologically nodally staged. They were categorized either clinically or pathologically as T3N0M0.

If clinically staged, that meant that the regional nodes were not palpable. A number of the patients, 25 percent had the regional node dissection, but a regional node dissection and sentinel node evaluation or biopsy was not a requirement for the

trial. There could be no evidence of metastatic disease.

The patients were categorized as T3 and 0M0, and the circumstance T3 was defined by AJCC staging criteria as being 1.5 to four millimeters in thickness or in circumstances where for technical reasons thickness could not be determined, T3 mean Clark's Level IV invasion.

The technical reasons for which thickness couldn't be determined were things such as shave biopsies, and again, this corresponded to Stage IIA in AJCC staging system, and just to reiterate once more, this morning we were discussing primarily Stage IIB disease as well as Stage III disease.

Patients were stratified according to gender. In general, females do better than males with this disease. They're stratified for lymph node dissection. Obviously patients that have a lymph node dissection do better than those in which it's unknown whether the lymph nodes are positive or negative. All patients with positive lymph nodes were excluded from the trial.

They're stratified according to primary tumor thickness. In general patients with smaller tumors or less thick tumors do better than patients with thicker tumors. Pardon me. Thin tumors do better than thick tumors.

In total, 689 patients were randomized with 346 patients in the vaccine arm and 343 patients in the observation arm.

All treatment assignments were based on entry pathology. Centralized pathology and surgical reviews were conducted after randomization.

The data cutoff for the relapse free survival analysis was February of 2000. The cutoff was predefined. It was determined when a predefined number of event had occurred as per the SWOG Statistical Center. At that point 33 percent of the patients had either relapsed or had died.

The median follow-up for all patients was 4.1 years. The minimum time since registration of the last patient at that point was three years.

The vaccine and the observation arms were comparably distributed between the stratification

factors of tumor thickness, lymph node staging and gender. Ulceration is now known to be a prognostic factor. It turns out that the vaccine and observation arms were equally distributed between patients that had ulcerated tumor versus no ulcerated tumor.

There was a trend towards more tumors in the vaccine group on the extremity, but that did not reach statistical significance.

SWOG's analysis of the 2000 database demonstrated that all three stratification factors had a significant effect on relapse free survival, as expected and predicted, with thin tumors doing better than thick tumors, females doing better than males, and patients with lymph node staging doing better than patients who did not have lymph node staging.

Relapse free survival was the primary endpoint. SWOG's analysis of the 2000 database demonstrated that the vaccine had a significant effect on relapse free survival. It was significantly longer for vaccine versus observation, the Cox model, intent to treat population with a P value of .040; the hazard ratio of .76.

These relapse free survival curves point out the benefit for vaccine versus observation in all patients, again, with a P value of .40 adjusted for stratification factors. Again, this slide demonstrates vaccine significantly prolonged relapse free survival in all patients in the 2000 database.

However, upon the data sweep, there were an additional 27 events, and the relapse free survival benefit for the vaccine lost its statistical significance. The curves came together at approximately six to six and a half years, demonstrating again following a data sweep that the significant benefit for the vaccine was lost.

The next topic that I want to talk about is the association between HLA and Melacine benefit, but I first want to set the stage again for why SWOG looked at HLA and why they did the particular analyses that they did.

Mitchell's study, his analysis in 1992 demonstrated that five HLA were shown to be associated with Melacine benefit and disseminated melanoma. Mitchell demonstrated two things: first, a benefit

for Melacine in patients with two or more of these five HLA antigens; and, second, a benefit for Melacine was really strongest in patients that expressed either HLA or HLA-C3 or both.

Because of Mitchell's analysis and findings in advanced stage patients, the SWOG amended their trial in early stage patients in 1994 to examine whether similar benefits occurred in these early stage patients.

SWOG's distribution of HLA antigens was similar to the Caucasian population in general. This is the population that's at risk for this disease with 46 percent of the patients being HLA-A2, 29 percent of the patients being HLA-C3, and you can read the rest as well as I can.

The point of this slide really is that the combination of A2 plus C3 occurred in 58 percent of the patients. The 46 percent and the 29 percent don't add up to 48 percent, clearly. A number of patients expressed both A2 and C3.

But the point is this is a substantial subset of the entire population.

Mitchell's analysis demonstrated that patients that expressed two or more of these HLA antigens benefitted from the vaccine. The SWOG analysis demonstrated the same. In patients with two or more matches there was a benefit for vaccine over observation with a P value of .002.

By contrast, in the subgroup of patients with zero to one match, there was no benefit for vaccine versus observation.

Okay. Mitchell demonstrated that HLA-A2 and HLA-C3 were the two HLA antigens with strongest association with benefit from the vaccine. SWOG analyzed each one of the five predefined HLA antigens and demonstrated a benefit for HLA-A2 with a P value of .009; a benefit for HLA-C3 with a P value of .02; HLA-B44 was not statistically associated with benefit, and there were not enough HLA-A28 or B45 patients in order to appropriately analyze vaccine benefit.

SWOG went on then to analyze the potential correlation of the benefit with the A2/C3 population and demonstrated that the vaccine had significant benefit on relapse free survival with a P value of

.002 and a hazard ratio of .56.

These relapse free survivals are depicted on this slide of the February 2000 database vaccine versus observation in A2/C3 positive patients. The vaccine significantly prolonged relapse free survival with a P value of .002.

The next slide shows the same two groups, vaccine versus observation in the A2/C3 positive patients, but in the May 2001 database following the data sweep showing that the statistical significant benefit for the vaccine in the subset was not lost on the data sweep with a P value at .005.

The question was also asked whether or not the vaccine had a benefit in patients that were A2/C3 negative, and the answer, it did not. This is vaccine versus observation. In the A2/C3 negative patients, a P value of .77.

The question was also asked as to whether expression of A2/C3 was in and of itself a prognostic factor, and it was not. In patients that were A2/C3 positive and only observed, the outcome was the same as patients that were A2/C3 negative and were only

observed.

Therefore, A2/C3 expression without vaccine did not prolong relapse free survival.

The five year relapse free survival estimate for patients that were A2/C3 positive and received the vaccine was 75 percent versus 63 percent for the same category of patients that were observed only. Patients that were A2/C3 negative, five year relapse free survival was 62 percent irrespective of whether they were observed or whether they received the vaccine.

Following the data sweep with the May 2001 database, overall survival was also examined, and it was determined that relapse free survival was also reflected in overall survival in a subset of patients that were A2/C3 positive, with a P value of .003.

The same additional two questions were asked. The first question is whether or not there was an increase in overall survival in patients who were A2/C3 negative, and there was not.

And the last question was whether or not the expression of A2/C3 was in and of itself a

prognostic factor for overall survival, and it was not on the survival curves.

The summary of the follow-up analysis by Corixa of the May 2001 database then. The vaccine is effective in prolonging relapse free survival. A2/C3 positive patients, a P value of .005. The vaccine is effective in prolonging overall survival in A2/C3 positive patients with a P value of .003.

These analyses by Corixa were subsequently confirmed by SWOG and have been submitted for presentation at ASCO this year.

The trial also looked at vaccine safety in patients with early stage disease. Adverse events were evaluated in the treated population. They were assessed by SWOG toxicity criteria. They were recorded only for the Melacine patients. They were not recorded for symptoms that were certainly most likely due to disease or other nontreatment causes.

Ninety-six percent of the patients experienced at least one adverse event. The majority of the adverse events were mild to moderate. Twenty-three percent of the patients had a maximum of Grade 1

toxicity. Sixty-five percent of the patients had a maximum of a Grade 2 toxicity. Nine percent of the patients had a maximum of Grade 3 toxicity, and none of the patients had a Grade 4 toxicity or death. The adverse events were comparable in the A2/C3 positive and in the A2/C3 negative populations.

This slide lists the Grade 3 toxicities that were reported in three or more patients. This includes injection site reactions, malaise and fatigue, diarrhea, transient vision abnormalities and fever in the absence of infection.

The transient vision abnormalities were seen in three patients, less than one percent. In each case the vision abnormalities were associated with other symptoms, such as headache or nausea. In each circumstance the treating physician felt that the symptoms were minimal enough that all of the patients had additional doses of the vaccine; that transient visual abnormalities did not recur in any of the patients, and in none of the patients was there any evidence of retinitis.

The summary then of SWOG 9035 is that

Melacine significantly improved relapse free survival and overall survival in patients who expressed HLA-A2 and/or HLA-C3. The toxicity was minimal. These results are highly encouraging for patients with melanoma and for cancer vaccines in general; that the results are consistent with the prediction that in the post genomic era that we're in currently, therapies will be tailored to patients' genetic capabilities to respond.

And this correlation between HLA type and outcome makes biologic sense. HLA or human leukocyte antigens lay a central role in immune surveillance, immune response and immune regulation; that the role for HLA is to bind peptide fragments of antigens. HLA presents peptide fragments of antigens to T cells and activates T cells, triggers T cell responses.

The HLA antigens are highly polymorphic. Each particular allele, each particular HLA antigen binds a paritcular subset of peptides, and each HLA binds a different subset of antigenic peptides. It's the peptide binding of HLA antigens that governs responsiveness versus nonresponsiveness to vaccines.

The number of circumstances in infection disease vaccines where responsiveness versus nonresponsiveness is dictated by HLA or low responsiveness versus high responsiveness is dictated by HLA. The vaccines include Hepatitis B, influenza, as well as HIV.

So it makes some sense that we would see the same correlation in cancer vaccines.

Despite the correlation of vaccine benefit with particular HLA antigens, the mechanism of the benefit from the vaccine is unknown. There are several possible explanations, including HLA-A2 and C3 or Class I HLA. They are known to present antigens that activate cytotoxic T cells. So A2 and C3 may preferentially present one or more of the Melacine melanoma antigens within Melacine to cytotoxic T cells.

Alternatively A2 and C3 may be linked to other polymorphic immune response genes that themselves are responsible for benefit of the vaccine, and the next slide basically lists the genes that are on chromosome 6 that are in proximity to Class I genes

that are polymorphic and have functions that relate to immune response, including the MICA, MICB genes, which activate gamma delta T cells, TNF heat shock protein which chaperons antigens, the complement components; Class II HLA, which is necessary for activating cytotoxic T cells, as well as generating antibody responses; the TAP genes that are involved in antigen degradation and presentation on T cells.

Nunley (phonetic) chromosomes are also other uncharacterized genes with as yet unknown function.

It also needs to be noted that there's a high level of linkage disequilibrium between HLA and these particular immune response genes, meaning that quite often they segregate along with HLA genes and define distinct immune response haplotypes.

Parenthetically even though we don't know what the mechanism of Melacine is, I would also contend that we aren't any closer to understanding the mechanism of interferon either.

The next topic are issues affecting further development of the vaccine. Since initiation

of SWOG in 1935, there have been a number of changes in standard care that in effect attempts to replicate and confirm the results of SWOG 9035.

Number one, INTRON has been approved as adjuvant therapy in patients with high risk for recurrence. Again, these patients are considered to be intermediate risk for recurrence.

The next AJCC staging system is in use with different cutoffs and parameters, and the lymphatic mapping of sentinel node biopsies is commonly employed.

I don't think we need to dwell on this slide. We talked about this extensively this morning, but I only want to make the point that the general assumption going into this morning's meeting and what I took out of the meeting is that INTRON-A is approved for lesions of greater than four millimeter without or with lymph node involvement, and the corollary is that INTRON is not approved for lesions of less than four millimeter without lymph node involvement.

Okay. The new AJCC staging system, which you have a copy of in Balch's manuscripts in the

briefing document, has thickness break points at one, two, and four millimeters as opposed to the old system, which is .76, 1.5, and four millimeters.

SWOG 9035 entered patients with lesions of 1.5 to four millimeters according to the prior AJCC staging system.

The new staging system also up stages patients with ulcerated primary lesions.

The standard practice now is to subject patients to lymphatic mapping and sentinel mode biopsy. The primary tumor is greater than one millimeter. This divides patients who are previously clinically staged as lymph node negative into pathologically staged lymph node positive patients and lymph node negative patients. Patients with pathologically staged positive lymph nodes are now commonly offered INTRON-A.

In SWOG 9035, 25 percent of the patients were pathologically staged, 75 percent only clinically staged. In the proposed trial, according to standard practice now, all patients will be pathologically staged whenever technically feasible.

As a consequence then, the proposed patient population will exclude patients with lymph nodes containing microscopic or occult tumor that was detectable only by biopsy. This may then lower the risk of the study population for recurrence.

Okay. The next topic is the proposed second randomized pivotal trial. The proposed trial will try to mimic or reproduce as closely as possible SWOG 9035. It will include Stages IIA and IIB. Again, this is not the IIB that was discussed this morning. Rather IIB by the new staging system, which we'll show in a moment.

These patients are deemed to be at intermediate risk for relapse. The higher stages will be excluded as being not represented in SWOG 1935, and they may be interferon candidates.

Lower stages will be excluded because they were not well represented in SWOG 1935, and the risk of recurrence in these patients will be to low.

Okay. The major eligibility criteria will be histologically diagnosed surgically removed Stage IIA or IIB cutaneous melanoma. All patients will be

HLA typed and will be HLA-A2 and/or HLA-C3. All patients will have lymphatic mapping and sentinel node biopsy if technically feasible. There will be no evidence of metastatic disease, and there can be no prior or planned INTRON-A chemotherapy, radiation therapy, or other biological response modifiers planned.

In SWOG 9035, patients were entered according to the old AJCC staging system. The patients on the trial were those with Stage IIA T3 tumors. These tumors are 1.5 to four millimeter.

In the new proposed AJCC staging system -- I say "proposed," but it's commonly being used today -- in this new AJCC staging system, the proposed patient population are those with Stage IIA. Those are tumors of 1.5 to two millimeter with ulceration. The five year survival in those is 77 percent or Stage T3A. These are tumors of two to four millimeter without ulceration. The five year survival is 79 percent.

And finally, half of the patients or the better half of patients with Stage IIB will be

included. Those are patients with tumors of two to four millimeter, with ulceration. The outcome in these, five year survival is 63 percent.

Excluded will be the half of IIB that have tumors of greater than four millimeter because these tumors were not included in the initial trial.

Patients will be stratified according to pathologic stage. They'll be stratified according to gender, and they'll be stratified according to the primary site of tumor extremity versus head and neck and trunk.

A total of 700 patients that are A2/C3 positive will be entered on the trial. They'll be randomized in a one-to-one ratio between vaccine and observation. Approximately 350 patients per arm.

The estimated five year relapse free survival based on SWOG 9035, as well as the AJCC database will be 70 percent in the observation arm versus 80 percent in the vaccine arm. Enrollment will take approximately three to four years.

The data cutoff date for the primary analysis will be five years after enrollment. This

will allow an 80 percent power to detect this ten percent difference.

The trial design will be essentially the same as SWOG 9035. Patients will have primary tumor removed. They'll be stratified and randomized between observation and vaccine. The vaccine will be given over two years, 40 doses. Patients in both groups will be evaluated equivalently for disease relapse.

Data points will be efficacy and safety. The efficacy will be in the intent to treat population. The primary endpoint will be relapse free survival. The secondary endpoint will be overall survival.

Patients will also be evaluated for safety by evaluating for adverse events. We will look for adverse events both in the Melacine and the observation arms.

Finally, the issues for ODAC and FDA. Our first question: is it agreed that treatment with INTRON-A is not necessary for the proposed intermediate risk patient population that includes patients with Stage IIA and IIB tumors?

Our second question is: can or should patients with Stage IIIA tumors -- that's N1a -- especially if less than four millimeters, but with one positive microscopic lymph node detected by sentinel node biopsy, be included in the proposed trial?

And this issue can be, I think, best pointed out by going back to this table which was taken out of Balch's manuscript in the briefing document.

The proposed trial as planned now will include patients in Stage IIA and IIB. The five year survival in those categories is between 63 and 79 percent.

This category of Stage IIIA, patients that have occult or microscopic metastases diagnosed because of virtue of the fact that they have sentinel node biopsy, have a five year survival of 69 percent, which is equivalent, and even though we don't have this data, if we look at only those tumors that are less than four millimeter, the five year survival is probably greater than the 69 percent.

So, in summary, adjuvant therapy for

intermediate thickness Stage II melanoma is an unmet medical need. In SWOG 9035, Melacine prolonged relapse free survival and overall survival in Stage II patients who expressed two or more of five predefined HLA types or expressed HLA-A2 and/or C3.

The mechanism by which Melacine provides a benefit is unknown, but is associated with immune response genes.

Finally Corixa needs consensus on the second Phase III trial design to replicate SWOG 9035 in order to confirm the benefit of Melacine in this patient population and for regulatory approval.

Thank you very much for your attention. We welcome questions from ODAC members and from the FDA, and to help field the questions we have SWOG representatives with us. We have John Thompson. Maybe you could just come up to answer questions up here.

We have John Thompson who is a Professor of Medicine at the University of Washington; Jeff Sosman, a Professor of Medicine at Vanderbilt University; and Walter Urba, Director of Cancer

Research at the Earl Childs Research Institute in Portland, Oregon.

And to help field questions from Corixa, we have Cindy Jacobs, who is Senior Vice President of Clinical Development; Monica Krieger, Vice President of Regulatory Affairs; Chuck Richardson, Senior Vice President and Manufacturing Site Manager; Ken Von Eschen, Medical Director; and Heather Tully, the Manager of Biostatistics.

So I turn the forum back to ODAC.

CHAIRPERSON NERENSTONE: Thank you very much.

Are there any questions from the Committee to the sponsor?

I have a first question about the trial design. Being that it is going to be a relapse free survival and not overall survival endpoint, has there been any thought to a placebo controlled design?

DR. CHEEVER: There are a couple of issues with that. I have the lavaliere on.

Okay. First, it's certainly something that we have considered. There are a number of

issues. First of all, it's difficult to come up with a true placebo where the patient and their physicians don't know what it is. It will look different and will have a different local reaction.

The second is that we think that the findings in SWOG 9035 are very compelling and would like more than anything to absolutely repeat this trial as closely as possible so that we can either confirm that the data is correct or refute it.

I think that it's very important for melanoma patients and it's, I think, very important for the field of cancer vaccines to precisely repeat the trial as it was. Maybe you have a different answer.

CHAIRPERSON NERENSTONE: I guess I understand your concern that it's not going to look alike. I think your data would be that much stronger.

The problem of investigator bias in the endpoint when recurrence happens, I think, is going to be very important, and if the investigator knows that the patient is on observation only, the likelihood of investigating a cough that gets worse is probably a

little bit more in terms of looking to see if it's related.

DR. CHEEVER: John, maybe you can answer this.

DR. THOMPSON: Well, I was very involved with this study, as were my colleagues here from SWOG, and I think it's safe to say that as clinicians taking care of melanoma patients, that when we evaluated patients in follow up on the protocol which was done on a regular basis every three months during the first two years and then every four months in years three through five, that if patients presented with symptoms that were suspicious of recurrence, those symptoms would have been investigated regardless of which arm the patient was on.

DR. SOSMAN: Yeah, in terms of the adjuvant, which is a question, I think, that was referred to, I think Dr. Cheever made a very good point that we've discussed ourselves in that there's been a lot of mistakes made in vaccine trials in the past, and the real hope is that we really look at the whole product versus no treatment, and if there was an

adequate placebo, that may be an idea, but it would be very hard, and to look at the whole vaccine versus part of the vaccine I think just is fraught with problems.

And we've been down that road other times in vaccine trials.

CHAIRPERSON NERENSTONE: Dr. Blayney.

DR. BLAYNEY: I share the Chair's concern about the bias on the part of investigators who might know which treatment a patient is receiving, and you've heard the concern.

Second, what would happen if a patient had a sentinel lymph node dissection in IA, microscopic disesae, and that was discovered? Would they go on to have a completion lymph node dissection of that lymph node bed or do you project calling it a day and going on?

DR. THOMPSON: That was not actually described in the protocol, but I think most of the institutions participating in this study had that as their paradigm, that if a sentinel node was positive, that those patients did have a completely lymph

adenectomy.

DR. SOSMAN: Obviously that is a question, and even ACOSOG (phonetic) discussed looking at that question, but I don't think that's something we have to be concerned about. They're not going to do that study because it is so ingrained at least in 2002 that almost all patients who have sentinel nodes that are positive go on to completion node dissection.

So I don't think that's something to be concerned about.

DR. BLAYNEY: Even the microscopic?

DR. SOSMAN: Well, that's what --

DR. BLAYNEY: The immunohistochemistry staining that's done afterwards?

DR. SOSMAN: Well, I think our definition we haven't talked about in detail, but likely we're going to try to be as consistent as possible with defining what is positive sentinel node, and that gets into detail that we'll have to work out as we put the trial together.

CHAIRPERSON NERENSTONE: Dr. Przepiorka.

DR. PRZEPIORKA: Not to belabor the issue,

but just to go on with it, detox., has anyone looked at detox. alone as a vaccine in melanoma or any other malignancies? Does he have any activity?

DR. CHEEVER: No, we have not looked at detox. alone for activity alone.

CHAIRPERSON NERENSTONE: Dr. Kelson.

DR. KELSON: You're proposing to do the primary endpoint analysis five years after the last patient is entered into the study. So the data will be very mature, and the curves for both relapse free and overall survival clearly separated by five years.

Why is the primary endpoint RFS instead of overall survival if you're not going to do the analysis until that point anyway?

DR. CHEEVER: Heather, can you answer that?

MS. TULLY: We have --

CHAIRPERSON NERENSTONE: Excuse me. Please use a microphone and identify yourself.

MS. TULLY: My name is Heather Tully. I work at Corixa. I'm a biostatistics manager.

Let me give you a little background into

the way that we sized the trial. I think that might be helpful.

In the 323 patients in the SWOG study who were A2/C3 positive, we had about a 73 percent relapse free survival in the vaccine arm and about 64 percent five year relapse free survival in the observation arm.

We were concerned because that trial started in 1992, and there have been numerous changes in the standard practice that we should increase our estimates of five year relapse free survival to size the trial, and so we based the size of the trial on 80 percent for the vaccine arm and 70 percent for the observation arm.

And at that point after five years, we would have about 80 percent power for relapse free survival.

DR. KELSON: What would the similar numbers be for survival?

DR. TULLY: I don't exactly know, except it wouldn't be that high.

DR. FLEMING: I did those calculations.

Can I comment?

CHAIRPERSON NERENSTONE: Sure.

DR. FLEMING: I took the data as had been presented to us on pages 13 and 14 in the briefing document. There are also corresponding slides that would have been presented, and on page 14 in the briefing document, for example, the hazard ratios are given there for both relapse free survival and for overall survival in the A2/C3 subgroup.

And the reduction in relative risk is 44 percent for relapse free survival. It's 57 percent for survival. Essentially the 80 versus 70 corresponds to a 38 percent reduction.

If one takes a more cautious approach and says the overall observed reduction on page 14 in the A2/C3 subgroup for survival is 57 percent, you say suppose it's only 40 percent. If it's only 40 percent, given the actual survival curves and the amount of information that we have, by my calculation 687 patients would give us a targeted 120 events, which is exactly what you need to get 80 percent power to pick up a 40 percent reduction.

And in fact, if you have 80 percent power to pick up a 40 percent reduction, your observed reduction has to be 30 percent for statistical significance, remembering if you have 80 percent power for a given reduction, the observed has to be two thirds to three quarters of that to achieve significance.

So if the sponsor looks at these results and sees a 57 percent reduction in risk and thinks that a subsequent trial with 700 patients could reasonably be expected to achieve half that amount of reduction in risk, observe 30 percent, that would achieve statistical significance.

So I've wondered the same thing. Given that there are the uncertainties about the objectivity with recurrence free survival and all of the discussions from this morning about whether recurrence free survival truly reliably predicts survival, this study with 700 patients is adequately powered to achieve significance on survival if the observed reduction is only about half of what you observed in the SWOG subgroup analysis.

MS. TULLY: That's very conservative.

DR. KELSON: I particularly have that in mind because we spent the whole morning talking about an observation in a different stage of the same disease using a biologic where relapse free survival was clearly affected in one way or the other, but overall survival wasn't, and overall survival is a much harder endpoint, you know.

DR. CHEEVER: It was my understanding from this morning's discussion -- and correct me if I'm wrong -- that one of the problems with the interferon trials is that everyone goes on interferon at some point in time.

And I think you may find the same thing with vaccines, that following relapse, a number of these patients will go on other vaccines at the same time.

DR. KELSON: That would assume that they're effective.

DR. SOSMAN: I think that I'm not so sure that we can say with staging in 2002 that that many people will relapse in their regional nodes. However,

the patients who relapse will relapse systemically and almost uniformly die of disease.

In those cases, we're now projecting seven, eight, nine years from now, and while I think there were some very elegant comments about the lack of movement in the field, we're hoping eight, nine years from now we actually might have therapy for a subset for patients with metastatic disease.

So I think it is a little concerning that we might change that outcome and relapses may be salvaged way down the line.

DR. KELSON: That would certainly be a most desirable outcome in the future, but the reason I ask this is the way I read it -- and please correct me if I'm wrong -- you're going to spend three to four years accruing patients, and you don't plan to do your first analysis until five years from the end of accrual, and that's nine years.

And, therefore, as you have designed your trial, we all, I think, would be delighted to see changes over the next nine years. You actually don't plan to do your analysis for the next nine years

anyway. So I'm still not quite 100 percent sure why you wouldn't be looking at survival under those circumstances.

DR. CHEEVER: Stuart, do you want to answer that?

MR. KROLL: My name is Stuart Kroll. I'm the Director of Biostatistics at Corixa.

I think we looked at the 57 percent difference that Tom was talking about and thought that being that this was a selected subgroup, that that would probably be too optimistic a difference.

And we also looked at the survival and felt that with this group where everyone is staged that the survival also would be higher than what we saw in the SWOG study, and given both of those facts, even though Tom says a 30 percent difference in survival our study is adequate powered for, a 30 percent difference in survival is a huge difference, and the way we worked it out, we still think that we would want additional follow-up for survival. So probably an additional two years, two or three years after the five year point, and to make sure that we're

adequately powered for that survival endpoint.

CHAIRPERSON NERENSTONE: Dr. Albain.

DR. ALBAIN: I wanted to commend you for a very educational, interesting presentation.

I wanted to change the subject a little bit. I find this very exciting data and am just concerned that it's going to be ten years before, if all goes well, that you will have an answer and would encourage us to think about expanding your eligibility a bit more even so that you can accrue more quickly because you mentioned this is 25 percent of the population, but that's not the A2/C3 or A3/C2 -- did I get it right the first time? -- A2/C3 subtype.

DR. CHEEVER: The A2/C3 would be half of that.

DR. ALBAIN: Right. So, in fact, I'm not convinced you're going to accrue as rapidly as you think you might in this very restricted appropriate population for this type of study and would have no problem with you expanding the eligibility a bit.

But could you comment on this long time?

DR. CHEEVER: John, may you or Walter

could talk about accrual.

DR. THOMPSON: The history from the previous study, 9035, is that patients began to enter treatment in 1992 and then accrual ceased in 1995. So the patients were accrued in that interval of years.

And the rate of accrual ramped up significantly toward the latter part of the study.

DR. ALBAIN: That wasn't the A2/C3 group.

DR. THOMPSON: Well, you're right, but that was all patients, and the A2/C3 group is 58 percent of the entire group that we'll enter on the study. So if you project a higher rate of accrual, the type of rate that we saw toward the end of 9035, multiply that by 58 percent; that would be the rate that we would have accrued in the mid-'90s.

Now, with the increasing interest, the A2/C3 equation to this, I think that interest in this trial and, hence, patients being referred for consideration of this trial has to go up. I don't know how much. That will remain to be seen, but I would predict that it would go up substantially.

DR. SOSMAN: Dr. Cheever speaks obviously

more as a representative of Corixa. I think your point is well taken in terms of expanding the indications for this trial. There are a lot of issues with that, but we don't have a cooperative group trial for any of those patients.

I think that this trial hopefully will -- SWOG 9035 was a single group study without intergroup support, and this trial will hopefully and almost has to be a multi-group trial.

And I think there is interest in the other cooperative groups. We have talked a lot about this, and I think there is an interest in this.

CHAIRPERSON NERENSTONE: Dr. Nelson

DR. NELSON: I have a follow-up of that question. I'm trying to make sure I get the twos and the threes and the ABCs correct.

But given the discussion this morning, why not establish a sort of parallel track with much the same design, including what looks to me under the new classification 2C, 3B, 3C, which would be basically those who would refuse INTRON and then be eligible for enrollment into a trial designed much in this same way

as a second population, not lumped together, but then analyzed separately.

DR. THOMPSON: You mean the node positive? Are you referring to the --

DR. NELSON: Well, I guess I'm following up. If, if, big "if," the conclusion was that someone who does not want to receive interferon could be eligible for a vaccine trial, you've excluded the groups that are currently eligible for interferon. So if you don't -- I'm not saying put them together for the purpose of analysis, but allow enrollment for individuals who then fit the new classification two and three that would be eligible, but are yet still HLA-A2/C3 positive. Would that then give you more and allow you to draw some conclusions that could address that previous question?

DR. THOMPSON: Well, we're going to bring up the slide that shows the new AJCC staging system again, and one of the powerful features of this is that it allows us to predict very accurately the outcome, the relapse free survival of patients in each category, and we're going to see in a minute here the

categorization of the patients who are in 1A, that is, that they have a single node that was clinically occult.

DR. NELSON: But I'm basically asking why not include those who refuse interferon in your trial rather than those who just aren't eligible for the current approved indication for interferon.

DR. THOMPSON: Well, maybe I'm not understanding, but one proposal would be to include these patients in the current study that Dr. Cheever has just presented because they have a similar risk of relapse as the patients who are in Stage II.

DR. NELSON: Well, I saw that for 3A, but I guess, again, this is not my field. So I'm asking in the sense as a -- there are others who would have 3B classifications that --

DR. THOMPSON: Well --

DR. NELSON: Am I asking a clear question? Maybe you should restate it.

DR. URBA: I think the answer to that is the goal is to replicate 9035, and getting too far away from that changes the interpretation of the

study, changes the patient make-up, and then the real question and the hypothesis behind this study is to repeat what was done before as closely as possible, to try and make sure that you don't make any mistakes in development of this vaccine so that --

DR. NELSON: Right. I understand.

DR. URBA: -- if it works as effectively --

DR. NELSON: I'm suggesting do that plus more, is what I'm suggesting.

DR. URBA: Well, there's no question that one would be interested in looking at what Melacine does in other stages outside of this defined study. I wouldn't argue that.

I think what you heard from the experts sitting over here was permission to do things like Melacine in those patients if they refuse interferon.

I would agree with the panel members from this morning that the answer is, yes, we should make that studies available.

Now, if you're talking about a separate Phase 2 study or something asking a different question and interferon refuseniks, I would agree.

DR. CHEEVER: I would say there are two competing factors. One is the one that replicates SWOG 9035 as closely as possible, but the other is the possibility of entering interferon refuseniks, if you will call them that, and that is a new concept which I think we really have to wait the FDA's final opinion as to what transpired this morning and the final conclusion before we can inculcate those ideas, I think, into our thinking and future plans.

DR. SOSMAN: I think, you know, just sort of to add to them and to add what Dr. Fleming and the other statisticians have said, I think it would be a real mistake to under power the group that made up 9035. So you could add a variety of other groups. I'm not saying that that -- you know, there are many issues with it, but if whatever study you design, power your study so that the group that were on 9035 are adequate, whether there's 700 or so, so that you can do the study and you don't lose the significance in that group.

And one of your primary objectives is that group has a better outcome. That way you won't have

diluted it with patients who may have a different immune response. There's so little we know and so many variables that we don't want to make that mistake, but there are many ways around it.

CHAIRPERSON NERENSTONE: We do have some time constraints, and I think maybe if the sponsor would like one of you to answer the question so that we can continue on because we're going to lose some of our committee members to flight problems.

Dr. George.

DR. GEORGE: I would like, first of all, to cast my vote with those who were suggesting that this trial should be designed at least partly with overall survival as the primary endpoint. I think that would be a very important thing to do.

The second part of my comments had to do with eligibility though. You stated numerous times that the goal is to replicate 9035, and what I think you mean by that is you're doing a confirmatory trial of a positive subgroup analysis in these A2/C3 patients, not really to replicate entirely 9035.

And my point about this is you could also

view this as you have an opportunity for a confirmatory trial of a negative subgroup analysis in the other patients. That is, how do you know that the vaccine doesn't work in these other patients? You had this subgroup analysis that says it's positive in one subgroup. You have the same kind of analysis saying it looks negative in the other, but is there some disadvantage with broadening the eligibility requirements to include those patients, not to change the numbers with respect to how many you need in the A2/C3 group, but why not do the other?

DR. CHEEVER: We'll have Dr. Jacobs answer your question.

DR. JACOBS: Hi. I'm Cindy Jacobs.

That's a good point. In fact, when we discussed with FDA SWOG 9035, the approval of that trial, the main problem was that the effect we saw in A2/C3, although it had been confirmed in the SWOG trial from Mitchell's prior data, it was the subgroup analysis, and that's why that accelerated approval was not an option.

For us then as a company to go and do

another eight to ten year trial, we need to have a study that we look at the intent to treat population of that entire study to confirm for approval those A2/C3 positive patients.

DR. SIEGEL: It is worth noting that the agency has permitted and does permit trials to be designed in which the primary analysis is based on a subset. In a case such as this, where the prior data suggests efficacy in a subset, if your trial is designed as it already is to assess efficacy in the subset, enrolling patients who don't belong in that subset on the same trial would not force you to have that larger set as a primary analysis. We have in the past and do accommodate that sort of approach.

DR. GEORGE: Well, just to be clear, I wasn't suggesting any change from that primary focus, but broadening the patients -- that is, still the main focus would be in this A2/C3 group. So just a comment.

Also, the other with respect to eligibility, I also don't see why you can't broaden it with respect to some of these other stages because of

the new definition. You've been toying with that, but it seems to me it would be better to include them even if your primary hypothesis focused on a smaller group.

DR. CHEEVER: Okay. Thank you.

DR. JACOBS: If you're referring to more general Stage III and Stage IV, we have done or RIBI has done trials with Melacine, including INTRON-A compared to INTRON-A plus Melacine, and those studies did not show or indicate any benefit or synergistic effect of Melacine with INTRON-A or in Stage III to date.

So really what we've seen is in Stage II patients, and that's why for us as a company to move forward for regulatory approval to focus on that patient population for this next trial.

CHAIRPERSON NERENSTONE: Dr. Brawley

DR. BRAWLEY: Three very quick points. I understand the point to expand -- well, first off, if more than three percent of melanoma patients went on the clinical trials, you could accrue a lot faster and finish this a lot faster. That just is a parenthetical remark.

I also understand that if you increase the stages available to the clinical trial, you're probably asking a different question, at least a different biological question.

So I understand why you want to stay with this low stage group of individuals.

And I also have made quite a career criticizing people for doing subset analysis based on race. So I'm not going to criticize you for not wanting to do a subset analysis based on something else now.

The one comment that I'd really like to make for the record in terms of overall survival versus disease free survival, when you have a treatment that has a very, very small impingement upon quality of life, and I really don't think you're -- except for some side effects at the injection site, I don't think you're interfering with the quality of life of these patients. Disease free survival actually to me becomes a much more important measurement.

You know, in the INTRON-A discussion where

you're giving people really, really harsh treatment, I'm just more interested in overall survival versus disease free survival, but if you don't push overall survival with a treatment that has very little effect on quality of life, but do improve disease free survival, to me you win on qualify of life points.

Did I blur that or did you understand what I was saying?

DR. CHEEVER: I understand that, and I appreciate your comment.

Do you want to comment, John?

DR. THOMPSON: Well, I would just second your statement regarding the toxicity of this regimen. I think my colleagues here will back this up, that the side effects of this vaccine protocol compared to other things that have been discussed this morning is fairly mild, injection site reactions primarily.

And I think that because of that I agree with your point that disease free survival assumed a greater importance, and perhaps that is another reason to look at that as the primary endpoint.

CHAIRPERSON NERENSTONE: Dr. Sledge.

DR. SLEDGE: I actually don't have any questions, just one comment. You know, listening here, this entire conversation is devolving rather than evolving, and that is to say we started out with a very general, almost philosophical question and now we're going into the "nitpicky" parts of designing your trial for you, for which I think this Committee should apologize to you.

There is probably nothing more dangerous than a group of non-experts trying to pretend that they know how to design a melanoma trial. So I guess my question would be either of you or the agency, I mean, is there some general important question that you want to hear from us rather than us writing your inclusion and exclusion criteria for you?

(Laughter.)

DR. SIEGEL: Yeah, you have printed questions, and I think from our perspective, you know, Question 3 which asks -- because this trial presumably will come back to this Committee. You know, fortunately most of you will have rotated off and won't have to stand behind your decision.

(Laughter.)

DR. SIEGEL: We've had this experience before, and that Committee is going to come back and say, "Well, geez, why didn't you bring us a trial with this endpoint when it clearly should have been with that endpoint?" or, "why did you bring us a trial with this entry criteria when it clearly should have been that entry criteria?

Well, ultimately, you know, I think companies and the FDA find it useful to get input before, you know, putting in seven or ten years and tens of millions of dollars and the sacrifices of hundreds of patients, of their time and effort and concerns into a trial to try to make sure that it is going to satisfy what not only those of us in the agency think would be appropriate, but what our expert advisors think would be appropriate.

So the questions do kind of focus on the areas that we think are most important, and I think the questions to you are closely parallel to the same questions. The inclusion of N1 patients, the nature of the endpoint.

DR. CHEEVER: We greatly appreciate your comments. As a company, there are certainly some people within our group that are hesitant to initiate a trial that will take years. In order to initiate that trial, we really need to make sure that the is consensus, that it's the correct trial, and that there is a clear path forward for regulatory approval if the study turns out to be positive as we predict that it will.

CHAIRPERSON NERENSTONE: Dr. Vanderpool.

DR. VANDERPOOL: Given some of my comments this morning, Jay, I may be rotated off this Committee after one meeting.

(Laughter.)

DR. VANDERPOOL: We are being asked to confirm whether the -- we're being consulted for advice concerning appropriate patient population to confirm the first pivotal trial results. I can understand, on the one hand, why you want to really control this, keep this trial to Stage II melanoma, because that's where the problem was, and you want to get on with the program and see if you can have an

effective drug.

I think the questions we have -- and I certainly entirely agree with Dr. Sledge that we can't -- I certainly have no wisdom as to how to design trials -- but I would hope that either interferon is beginning to show interest in doing research on Stage II melanoma or that, given the past success of your dealing with these patients with these particular A2/C3 genetic profiles, that you might be able to do something that the interferon trials are doing.

In other words, I can see why these trials need to be cleanly separated out in their own worlds, but at the same time would it be possible for the sake of faster drug development to have some crossovers between interferon, on the one hand, and your treatments, on the other?

That's my only open question.

DR. SOSMAN: Referring to that and a number of other comments, there's been lots of discussion with ECOG, and one of the thoughts has been that the A2/C3 negative patients would go on the ECOG 1697 study because SWOG is not active in that trial,

and they very badly need our involvement.

At the same time, ECOG would enroll their A2/C3 patients onto this trial and I think that would benefit everybody.

DR. CHEEVER: One last comment, to make sure it's clear that interferon in the standard high dose as proven to be effective is not currently being tested in this disease category by any of the cooperative groups.

DR. VANDERPOOL: I understand that. I mean, my question is given the effectiveness on the later stages, I didn't know whether Dr. Siegel would have any comment as to whether the makers of interferon are also interested in this earlier stage of melanoma or not.

CHAIRPERSON NERENSTONE: Dr. Carpenter.

DR. CARPENTER: Since there's been so much discussion about the choice of endpoints and it's inevitable that depending on who the committee is that this comes to in however many years, that there may still be discussion, and since it won't apparently cost you any more patients, if you can structure this

so that both overall and relapse free or disease free survival are primary endpoints, you would be prepared at that point to deal with the agency and with the Committee no matter which way they come down on the question.

And it would be relatively easy at this point to incorporate that design point in.

CHAIRPERSON NERENSTONE: What I'd like to do now is turn to the questions because that will engender a little bit more discussion.

The first question, skipping all the way down towards the end: please comment on the adequacy of the proposed development plan based on SWOG 9035 and the proposed trial to support the approval of Melacine for the adjuvant treatment of melanoma in this defined population, the HLA-A2 and/or HLA-C3 phenotype and Stage IA and IB melanoma.

Further discussions to that specific point? Dr. Nelson?

DR. NELSON: I have a question. Do you think that the stage is more important or the HLA type is more important as the underlying factor relative to

efficacy, not that I would design it any differently at this stage?

DR. CHEEVER: I mean, we think that both are important, that the vaccine will work best against patients with small tumor burden, but we also have the test evidence that it works in A2/C3 positive patients. I think they're both important.

DR. KEEGAN: Could I just clarify the intent with the question? The proposal is really one of given all of the data available with Melacine, including the two randomized controlled trials in metastatic disease that failed to meet their primary and secondary endpoints, a very intriguing finding on the subset analysis of one trial and one additional confirmatory trial looking to confirm that subset finding.

Does that as an approach look like an acceptable development plan to lead towards licensure? And that's really the essence of the question. So I want to make sure I clarified that as you discussed that.

CHAIRPERSON NERENSTONE: Well, just a

point of clarification then. Assuming that this subset secondary trial was positive, would the indication then be broad or would it only be in the HLA subtypes that are being evaluated here?

DR. KEEGAN: I think it would be limited to the subjects that were studied in which the positive effects were found. So, yes, I think it would be limited to those HLA subtypes.

CHAIRPERSON NERENSTONE: And correct me if I'm wrong, but I believe that in the analysis there were other HLA subtypes that also looked promising. The effect was strongest in these two subtypes, but there were two subtypes that looked like they were positive, but there weren't enough patients to make it statistically significant.

And do you really want to eliminate those from your study group so that those from your study group so that those patients are not going to be treated?

DR. CHEEVER: Mitchell predicted -- pardon me. Go ahead.

DR. SOSMAN: There were two analyses, and

one led to the next, and that's exactly how Malcolm Mitchell initially did that.

The initial analysis included -- the initial analysis centered on the five and HLA antigens, serologically typed, and of which really two are very infrequently expressed in the public in melanoma patients.

E44 is not infrequently. It's about 25 percent of patients, but we saw no relationship at all with that separately, and since that really limited the number of patients and was a complex, hard to understand, and we really tried fairly simply. We didn't do complicated statistical analysis pulling one HLA type out and looking at the analysis. We simply looked at A2/C3 after we looked at each one independently, and that seemed like the simplest way to develop it and to try to support the finding.

CHAIRPERSON NERENSTONE: Dr. Kelson.

DR. KELSON: This may be semantics. I'm not really sure. The way I was looking at this is they have a hypothesis generating trial from a subset analysis. They're not confirming really that.

The trial that they're going to do is a pivotal trial in a defined subset, it will be the registration trial, and the supporting evidence for this single pivotal trial would be the retrospective sort of look at the subset from the main trial.

So the question to me sort of is a single pivotal trial with supporting evidence retrospectively adequate for approval. I mean that would be how I would sort of think of it.

DR. KEEGAN: Yes, I think you have the sense of it.

DR. SIEGEL: Exactly. That's the question, and that is, you know -- by our standards that can be in some settings, but each setting has its own nuances, but in many adjuvant settings the agent is also already approved for treatment of widespread metastatic disease. In this setting, you know, the issue of how strength -- that exploratory analysis was not entirely retrospective and it has some support from Mitchell's observation. So it has its own nuances, and that was the --

DR. KELSON: That's why I was asking for

an overall survival because to me, if you if you did a single trial prospectively designed based on a very valid hypothesis, I agree. I think it's a very valid issue to look at, and the overall survival was improved. There was no, you know, relapse free and dah, dah, dah, dah, with supporting evidence from another prospective trial, minimally toxic drug, boy, I would think that would be very compelling.

I would like to hear overall survival personally.

CHAIRPERSON NERENSTONE: Seeing the nods around the room, and I know people are worried about overall survival, the drug company is worried because of secondary home run hits that have not yet been postulated as what we're going to do in terms of metastatic melanoma.

I think a word to the wise is that overall survival is felt to be a very strong indicator and one that you can take to the bank. Relapse free survival is going to be much more problematic with any sitting ODAC.

Dr. Albain.

DR. ALBAIN: I was just going to say the same thing. Unless you could come up with a placebo, then I think relapse free survival could be very powerful in a single pivotal trial.

CHAIRPERSON NERENSTONE: Dr. Fleming.

DR. FLEMING: I've been waiting to make some of these comments because they relate to survival in Question 3, but Dr. Kelson has so beautifully articulated my own thoughts that I'm going to jump in and fold in my answer to three into one.

My own sense about the answer to one is, in fact, very significantly tied into whether the endpoint is recurrence free survival or survival, and I think Dr. Brawley made a very relevant point that if you have a very benign therapy in terms of its toxicity profile, one might set the bar lower in terms of efficacy.

And even if relapse free survival doesn't reliably predict survival, does it predict some type of quality of life benefit that because of the low toxicity profile is still net benefit. My sense about that is it may well, but then again, if that's what

we're trying to prove here, I have more reservations about not having two independent, well designed confirmatory trials.

I am more concerned about the issue of subjectivity and potential bias in an open label trial. As a result if one is proposing to do two such studies, it might be from my perspective more acceptable, but I do find the strategy the sponsor has put forward here as appropriate exactly for the reasons Dr. Kelson indicated, if in fact survival is the endpoint.

And when we were talking about -- at least Dr. Kroll was responding from the sponsor's perspective about a reason to go with relapse free survival instead of survival, and he made two very valid points. One is even though the estimated effect was 57 percent reduction in relative risk for survival in the very kind of trial we're trying to replicate, one should be cautious about expecting too high a bar, and then I think he also pointed out there may be fewer events than what had been seen in the previous study.

My responses to that are first you're already being cautious, assuming five to six years' average follow-up. It's a three or four year recruitment trial with five additional years. So we're probably more along the lines of seven years' follow-up. So I think you're probably covered there.

The other is the way you did your calculations you were targeting relapse free survival for an 80 versus 70 that corresponds to a 37 and a half percent reduction in risk that will require an observed 28 percent reduction in risk.

If you have an observed 30 percent reduction in risk in mortality, you achieve statistical significance, and you're trying to replicate the SWOG trial that, in fact, showed a larger reduction in risk in survival than it did in relapse free survival.

So the argument that you want to not overshoot is the rational one, but I could say that it's just as plausible that you're overshooting based on relapse free survival if you believe your results. If you believe that there, in fact, is substantial

evidence in this subgroup for benefits on both relapse free survival and survival.

As a result, I concur with the thought of being cautious, but it seems that if you believe the data and assume that you could achieve even half the level of estimated reduction that you achieved in the SWOG subgroup analysis, you will have significance on an endpoint that then I would accept.

If they show survival in this study, they will have one pivotal trial where supportive evidence will be obtained from a subgroup analysis that are notoriously unreliable, but it certainly could serve as supportive evidence for a survival endpoint.

DR. SOSMAN: Just one point, and it isn't in counter to what you just said, but the survival benefit was evaluated by Corixa after the data sweep to see if -- really just to look to see if the disease free survival would equate with overall survival.

SWOG did not do that initially and weren't planning to, but SWOG repeated all of the statistics to make sure that they were consistent with what they had, and they looked again and saw the overall

survival benefit.

And what's interesting is that overall survival benefit was much less significant earlier when the first analysis was done than in the later analysis.

So as opposed to all of the discussion this morning about separation, at least in this study it doesn't appear that there's a separation.

CHAIRPERSON NERENSTONE: We could go on to the second question, which is a little bit different.

Comment on the acceptability of inclusion of patients with pathologic N1 disease. If acceptable given that the SWOG 9035 trial did not include such subjects, please comment on whether there would be a requirement to enroll a sufficient number of subjects with no involvement to assess for size effect in this subset.

I sort of think this is getting back to what Dr. Sledge said was micro management, and I don't know if other people have thoughts.

DR. SIEGEL: Well, I'm trying to understand the question. So let me ask to understand.

The question says patients with micro nodal disease were not included, but I gather from the presentation that diagnostic procedures were different so that you anticipate that those patients may have been there, but were less likely to have their microscopic disease diagnosed.

So in part that's one of the questions, and part, I guess, this question rests on the issue that this is a population that falls within the category for which interferon efficacy was demonstrated.

Now, we have discussion from this issue this morning. It's a higher -- well, it may not be a higher risk. It falls within the population that was included in the study. So that raises the question as to whether they are appropriate for a placebo controlled trial.

And I believe I understand form your data that one of the points that you're making, however, is that whether by categorization or classification, they fall into one category. Their prognosis is actually a relatively favorable one with 70 percent five year

survival not very different from the other populations that you're including.

Am I getting the nuances of the issue here?

DR. THOMPSON: I think so. I think it's worth repeating that a relatively small number of patients actually had sentinel lymph node biopsy on the 9035 study, about 30 patients. So the remainder of the patients were clinically staged, not pathologically staged.

Given the depth of the primaries, 1.5 to four millimeters, we could predict that approximately 15 percent, 20 percent of those patients would have had occult nodal metastases that would have been identified by sentinel lymph node biopsy and would have fallen into the N1a category in the new staging system, but we didn't have that methodology at that time.

And then as a follow-up to your question, I think the important thing about the new staging system is though it tends to segregate patients out by prognosis differently than anatomic staging, so node

positive if they're in the N1a category actually have a risk five year relapse free survival risk that's very similar --

DR. SOSMAN: It won't go up.

DR. THOMPSON: I'm sorry. I was just looking at it here and thinking that everyone else can see it.

DR. CHEEVER: No, it's not up there.

DR. THOMPSON: But that's 69 percent, very similar to the risk categories of the Stage II patients that are already being proposed for the trial.

So although it seems a little bit discrepant in terms of anatomic staging, in terms of risk taking, it's very consistent.

DR. SIEGEL: So you believe including those patients actually comes closer to replicating what's logged in in the 90s than excluding them?

DR. THOMPSON: Well, I think from a biologic point of view having to do with risk of recurrence as the question mark, it would be very consistent to include those patients, and we have no

reason to think biologically that they would be different.

However, we could be missing something, some different biology that we just are not aware of, but strictly on a recurrence risk basis, they could fit in.

Then the question becomes because that is node positivity, does that require a different control group and that would be an issue that I think would be open for discussion.

CHAIRPERSON NERENSTONE: I think again I'm going to take the Chair's prerogative. On the basis of all the discussion we had today, I think the feeling is if you wanted a no control arm even in those patients who were offered interferon and the subgroup that it's licensed for, most of use felt that even though there is some activity, it is not a home run and, therefore, it is not unethical to have a placebo controlled or no treatment control.

You just have to be careful what you wish for because at the end of the day, you include these patients in your trial and your trial is negative. If

you don't have enough patients who are node negative, you don't have enough power to stand up on your own in that subgroup.

You can't then come back and say, "Well, it was still positive in the node negative group," but the node positive group is the one that made it not significant, and therefore, you want to come and have it licensed for the node negative group.

So I don't think it matters to us who you want to include in your group. You have to be able to analyze it and to justify that analysis when you're done with the study.

DR. CHEEVER: Thank you very much.

CHAIRPERSON NERENSTONE: Dr. Vanderpool.

DR. VANDERPOOL: I second your comments enthusiastically. It seems to me, just to summarize what I've been hearing, that we are under two imperatives. One is to do the trials right, but the other is to find better treatments as soon as possible.

So if the trial base can be expanded to the effect of finding better treatments for other

types of patients as soon as possible, we'd be for that if it can be justified on the basis of good analysis.

CHAIRPERSON NERENSTONE: Dr. Nelson.

DR. NELSON: This may be a question more for the FDA folks than the sponsor, but I mean, the history of innovation in medical care is that often if you have something that's more preferable in terms of decreased toxicity, that once it's approved for one indication, we use it off label for other indications.

So from a policy point of view if one of the questions ultimately you might want to answer would be the efficacy of this product in those with more extensive disease, a higher tumor burden and the like, would you lose that window of opportunity if you didn't do it now as opposed to when it's approved for those with lower tumor burden to the point where I could imagine after approval, let's say, six years from now instead of ten years from now if you have good enrollment, off label use would be such that any further trial to demonstrate efficacy from a policy point of view would become impossible.

And so people with melanoma would be taking potentially an ineffective vaccine based on toxicity and rejecting more toxic but more efficacious alternatives potentially.

Is there precedent for that kind of thinking?

DR. SIEGEL: It's funny. When you started the question, I thought you were going to say the exact same question, except about people with different HLA classes instead of with more advanced disease.

There is a lot of precedent for us urging, as Dr. George's question suggested earlier, companies to study broader populations because of concern about off label use in those populations. As to whether we can require a broader study within our regulations has to do with a lot of complex issues, but in part whether the population that's being defined represents a defined indication with a medical acceptance and scientific rationale.

So you can't just, you know, out of the blue say, as we once add a proposal, "I'm only going

to study men with multiple sclerosis because that's the only people based on the ten I've treated already that it's going to work in."

But I would say where we're talking about well defined disease stages that are used to guide how patients are managed, that are used in interferon therapy or whatever, that we are probably in a position where we could talk with a company and say, "Look. We would anticipate off label use. We would anticipate difficulty studying more advanced disease. We think it would be extremely wise in the interest of the patients and the public health, and we would urge you to study more advanced disease."

But if a company came back to us and said, "Well, you know, we only have so much money and interest, and we have reason to believe this is where it's going to work," I doubt we have the authority or ability to say, "Well, you can't limit it this way if it is a well defined and appropriate limitation," which I think is what we're looking at here.

DR. SOSMAN: I'm speaking not as a representative of Corixa, but as a representative of

SWOG who have worked with Corixa, and this is a very fragile association that we've tried to develop with this data, and this data came from SWOG, not from Corixa.

And I think that what we're trying to d is move forward so that in six to eight years we have a therapy to offer patients that is beneficial. Obviously that will give them a product that they can sell, and my concern is that if we start pushing for much larger trials, this fragile relationship will become more fragile and we will lose this opportunity which is really a unique opportunity.

And I can tell you most of the people who were associated with this study initially, except maybe some of the people at RIBI had a very open mind, nearly skeptical mind about this, and so the data has come around to convince us that we need to reproduce it.

And I don't think you'll have any problem convincing Corixa to allow us to do a study in Stage III patients if they have a product they're selling to Stage II patients.

Now, it's not the company's problem to convince medical oncologists to do the right thing. It's medical oncologists' problem to do the right thing.

Thank you.

CHAIRPERSON NERENSTONE: I just have a question to FDA. Sort of a different tact to get back to something that was asked before, as a non-vaccine person what do you think about the problem of you have two components to the vaccine? You have the melanoma lysate and you have the detox. Is there any data that this is at all detox.?

DR. KEEGAN: I don't think we have data that would assure us that we could rule out that it was detox. alone that was the active agent.

There are some data along the lines that I think you probably heard from other people talking about other vaccines about responses to the vaccines, immunologic responses, how responders do better than nonresponders, but those are responder/nonresponder analyses. So they're difficult to do much with.

But we don't have any trials, and I don't

believe that Corixa has ever conducted any that have segregated the affected of the adjuvant alone.

DR. CHEEVER: I mean, in general, all vaccines are given with adjuvants. Antigens don't work by themselves unless you add adjuvants.

I'm not aware of other vaccines where one has had to test the adjuvant to prove that it doesn't work before one can go ahead and test the vaccine. We've all -- you know, every kid has 20 vaccines. They all have adjuvants. The adjuvants have not been tested for efficacy in and of themselves.

DR. SIEGEL: Well, when you say adjuvants don't work by themselves, it's worth noting that in this particular disease, melanoma, that non-antigen specific immune modulators, whether you call them adjuvants or not, but some people would call Interleukin-2 an adjuvant. Some people might even call interferon in some settings an adjuvant.

In any case, they change the immune response in a non-antigen specific way, and they do in different stages and different settings each have activity in this disease.

The question you ask is a subpart of a broader question, which is when somebody develops a combination therapy and shows it to be effective, when do we require that they show the combination of two new agents, if you will, offers something beyond the individual components of, you know, each agent.

Do we require a factorial design with one or both of the individual agents? And that is an extremely complex question that rests in significant part not simply on empiric clinical data, but also on preclinical and plausibility data for the combination.

And if there is a strongly plausible reason for studying the combination, we will not strictly require showing that each component is contributory, at least in the premarketing phase. Sometimes we go back in post marketing.

Also it rests on the additive toxicity of the individual components, and in part that's an answer to the question Dr. Nelson raised, too, in terms of our leverage and what we do regarding off label use. If there are important safety issues that we're concerned about in off label use, we are more

apt to take a more aggressive approach in terms of its study.

I think the general anticipation here -- I don't think we have definitive information, but based on what we know to date is that we're probably not looking at tremendous additional toxicity for adding the vaccine part to the adjuvant part, and so that probably figures into the equation.

But I'm not saying I know what the right answer to that question is and should we require or insist on or should this Committee insist on receiving the adjuvant alone or, for that matter, the vaccine alone are interesting questions.

CHAIRPERSON NERENSTONE: Dr. Fleming.

DR. SOSMAN: There is actually a precedent in vaccine therapy. Dr. Wallach did a trial with viral oncolysate plus he used an adjuvant versus the adjuvant plus vaccine.

There was no difference, and from that trial he basically thought the data showed that the adjuvant alone worked, and we don't want to get into that position.

And secondly, no one made Dr. Fleming and others go back and prove that it was Levamisole that added to 5 FU, not that I want to say that this data is as good, but many people after the 5 FU/Levamisole data said that it wasn't the Levamisole, if I say correctly.

It's not an issue now, but I think in this case it would be an awful lot of effort for a little bang.

DR. JACOBS: I guess as far as Corixa is concerned, we're looking at the Melacine as a whole vaccine. We have no intention even if the adjuvant suddenly miraculously did something to market that.

So at this time in the clinical development plan, we're really looking at developing vaccines as a whole.

CHAIRPERSON NERENSTONE: Dr. Fleming.

DR. FLEMING: Before I get to my comment, just quickly to follow up on that previous thought, it was an important question as to whether it was the Levamisole in the 5 FU/Levamisole, and at least there was a 5,000 person meta analysis of previous FU trials

that seemingly at least provided some considerable suggestion it wasn't the 5 FU alone.

But moving ahead just to question number two, and I just wanted to reinforce a little bit what Dr. Siegel and some others have said about the potential of looking at additional patients at this point in time or additional -- a wider array of patients. I just want to say, first off, I'm very pleased to see the commitment by the sponsor and SWOG to mounting this trial to determine whether or not this exploratory subgroup effect is real.

And there always will be judgment as to how inclusive to make eligibility criteria where making them more inclusive gives us more generalizable conclusion, more timely enrollment.

The disadvantage though is if you truly believe that you have, in fact, modifiers here so that these HLA subgroups and these subgroups of stages are far and away the most likely to have the most favorable benefit to risk. There's a rationale for doing what you are proposing to do.

And, again, in my view, it's your judgment

as to how you want to play off that generalizability against increased plausibility of effect in your more targeted group.

If, in fact, you do go with the more restricted group, which by my calculation I think might be ten to 12 percent of the overall population because you're taking the 25 percent and cutting it in half by looking at these HLA subgroups, I do think there is at least some wisdom to be thinking about whether mounting additional concurrent studies either as extensions of this study, but not part of the primary analysis or as separate studies, would be something wise to do.

And I just go back , and you were talking about SWOG, and I'll just talk about the wisdom that SWOG had in 1984 in the 5 FU/Levamisole setting. They were building off of the North Central Group trial, and there was, in fact, a decision made to concurrently study Stage III and Stage II so that when the Stage III results were in and were as positive as they were, there were data in hand that were placebo controlled for Stage II that might have been very

difficult to mount in the early 1990s if that study hadn't been started in Stage II at that time.

And those data did, in fact, suggest that the effect was very different in Stage II than Stage III.

I'll also point out that there was wisdom at SWOG in not believing the subgroup analyses entirely from the North Central trial that showed that all of the effect in the North Central trial of 5 FU/Levamisole was in the female populations in the younger patients.

The subsequent trial confirmed that gender and age were, in fact, modifiers, where in the larger, confirmatory trial almost all of the effect was in the males and the older patients.

So we've learned to be very cautious about subgroup analyses. I guess the bottom line here is it really is your judgment. There is an investment in resources to do the complementary groups outside of your targeted population, where from the targeted population if we don't see an effect, maybe those resources weren't well spent.

On the other hand, if we do have the success that you're hoping to have in our targeted subgroup, by HLA subgroups and by state subgroups, it will be very beneficial that we will have mounted studies over this eight year period looking at broader populations because it might be awfully difficult in the year 2010 to mount such studies.

CHAIRPERSON NERENSTONE: Dr. Blayney.

DR. BLAYNEY: Yes. I also think it's commendable that you're committing to a seven year trial on behalf of your company. That's important.

I would like to echo, I think, what the Chair said in her comment a few minutes ago, that in eight years when you come before this Committee if the question is asked, is this a breakthrough medicine, and the answer because of intervening developments may be no, that then the FDA is going to make you go back and prove that the lysate was the important part rather than the adjuvant.

So I think and for my money you ought to be able -- I would put this mix together and say it is biologically and scientifically plausible that all of

this is important for the effect and not make them go back, you know, in eight years and say improve each part of the mix as the important part.

Because it may be by that time one of those antigens that you showed on the board is available and useful, and you may get stuck with having to prove what was the active part of your thing.

So I think you would be advised to get a commitment in advance that this is the important -- that this comes as a package because other companies have stumbled in this regard.

DR. VON ESCHEN: I'd like to make a comment to this question about contribution of the antigen and adjuvant. My name is Ken Von Eschen. I have been involved in Melacine's clinical development since the turn of the century actually.

(Laughter.)

DR. VON ESCHEN: I kind of joke. I was with the ole RIBI and immuno-chem. when the first IND for Melacine was filed, and, Dr. Keegan, I believe that was even before you were at the FDA. So I've got

you beat, Pat.

Just a couple of quick comments. We have conducted a series of preclinical studies in a variety of animal species looking at the immune response to melanoma antigens in animals treated with lysate, with detox. or the complete vaccine. Categorically, animals treated with only the adjuvant never make immune responses to melanoma antigens.

Secondly, the very first initial clinical trials of detox. were done under a separate IND in the early 1980s in which the adjuvant was used as intralesional therapy in patients with cutaneous melanoma.

Those studies, uncontrolled, always showed that detox. administered intralesionally, while they may have had an effect on the single lesion that was injected, had absolutely no effect on any systemic metastases and objective responses.

Finally, some initial trials done by Dr. Malcolm Mitchell in which he treated Stage IV patients with the lysate alone showed absolutely no objective clinical responses.

I think as we debate this issue, it's important to remember those baseline facts, and as we look at the future trial, as Dr. Cheever said, we perceive or recognize Melacine as a total package of antigen plus adjuvant as giving the necessary immune boost to elicit positive responses in these patients.

Thanks.

DR. SOSMAN: I just wanted to add one thing. I'm sure some of you appreciate where Dr. Cheever comes form in terms of immunology and his prior involvement in the field at University of Washington.

I think all of us are also committed to do a corollary study in these patients so that we hopefully not only learn whether it works or not, which is the ultimate, the only important question, but why or when or how it works.

So there's going to be, if this trial is mounted, a lot of effort, hopefully from the intergroup mechanism, to study patients immunologically pre and post vaccine.

CHAIRPERSON NERENSTONE: Dr. Keegan, Dr.

Siegel, do you have any other questions, any other comments?

DR. SIEGEL: I guess I have a question regarding the observation that there weren't responses to detox. alone intralesionally in distant sites.

Were there in the same study then responses to detox. with tumor lysate in other sites that were significantly different from those in detox. alone?

DR. VON ESCHEN: Dr. Siegel, in those trials, only detox. was used. There was no combination of detox. and lysate, and those studies were done under an IND, and the number is 1888, which was detox. only.

DR. SIEGEL: You don't have any particular model or any particular -- or advanced disease where you do see a different response or you have seen, I should say, a different response of detox. plus lysate to detox. alone?

DR. VON ESCHEN: We've never done a controlled trial in advanced patients with detox. by itself compared to the intact vaccine.

DR. SIEGEL: I, for one, have found this entire day quite intriguing, stimulating, and also fatiguing. And I'm very appreciative of the efforts of all the presenters, of the Committee, the public participants, and yourself, Madame Chairman.

I think our questions are very well addressed on these issues. We're quite pleased. Thank you.

CHAIRPERSON NERENSTONE: Dr. Pelusi, do you have any comments?

(No response and laughter.)

CHAIRPERSON NERENSTONE: Okay. Well, I want to thank everybody, and we do get to adjourn a little bit early.

Our next meeting will be June 6th. Thank you.

(Whereupon, at 4:16 p.m., the Advisory Committee meeting was concluded.)