letrozole will not have an adverse effect on survival. Therefore, we think the committee can consider this application.

[Slide.]

In terms of safety, both treatments were well tolerated and with most adverse events being mild to moderate in severity. Cardiovascular or cerebrovascular events occurred infrequently, and fractures appeared to be largely disease related.

[Slide.]

Now only a single randomized trial really was submitted in support of this application. The FDA criteria for considering approval based on a single study is that substantial evidence of effectiveness be demonstrated.

The fact that this was a large multicenter study and that there was internal consistency of data helps support the substantial evidence of effectiveness because it suggests that these results might be generalizable to a larger population of women with advanced breast cancer, who are postmenopausal and receptor positive.

The facts that the results were clinically persuasive and statistically persuasive also validates that substantial evidence of effectiveness was demonstrated.

[Slide.]

Based on this, it is the review team

recommendation that letrozole be approved for first-line hormonal therapy in postmenopausal women with advanced hormone receptor positive or--and we probably ought to put this in quotes--"hormone receptor unknown breast cancer."

Thank you.

DR. NERENSTONE: Thank you very much for the presentation.

We now open the questions to ODAC. Are there any questions for the FDA presenters? Kathy, do you want to start with questions?

Questions from the Committee

DR. ALBAIN: Just a question on your last statement. ER/PR unknown you would recommend?

DR. COHEN: Well, we have heard comments about that earlier this morning, and I would agree with the comments from earlier this morning, that in the United States at least--I don't know what the situation is in, say, Russia or China--that patients should have receptor status performed before receiving this treatment.

DR. ALBAIN: Do you want more general comments at this time, Dr. Nerenstone? I can go ahead.

DR. NERENSTONE: Why don't we continue with questions. Dr. Blayney.

DR. BLAYNEY: Dr. Cohen, I enjoyed your briefing document. Since many of the patients or entrants on this

study were from, as you point out, Russia and China, what primary materials did you have to review to assure that the responses were indeed responses? Did you have x-rays?

DR. COHEN: No.

DR. BLAYNEY: Case report forms?

DR. COHEN: Minimal. It was primarily based on serial tumor measurements.

DR. BLAYNEY: Which were done at the center?

DR. COHEN: Which were done at the center.

DR. BLAYNEY: And presumably monitored by a Novartis monitor?

DR. COHEN: Presumably, yes.

DR. BLAYNEY: But you had no primary materials to verify such measurements?

DR. COHEN: No.

DR. BLAYNEY: And death certificates or some other evidence that indeed the patients died or some other official--

DR. COHEN: No, I had besides the electronic data, I had minimal other data to support any efficacy conclusions.

DR. BLAYNEY: Thank you.

DR. NERENSTONE: Other questions for FDA? Dr. Przepiorka.

DR. PRZEPIORKA: To really get a good idea about

the internal consistency and make sure that we don't have two studies with different outcomes neutralizing each other, did you have a chance to look at outcome by geographic area? Clearly, there is not enough numbers at one center to look for center effects.

DR. COHEN: Yes. Both the sponsor and I did analyses by geographic area, and the results were similar.

DR. FISHER: If I could make just one comment. Not only were the point estimates similar, but there was a preplanned analysis by geographic area. There was Europe, North America, and then the rest of the world. All three different analyses individually were statistically significant for the primary endpoint.

DR. NERENSTONE: Thank you for that clarification.

Dr. Temple.

DR. TEMPLE: Marty, the drug-drug interaction that was unexpectedly found in the third arm of the study suggests that that might be a concern more generally.

How much do we know--I haven't gone back to look at the label--how much do we know about the potential for a wide variety of drugs to interact with this one, and is there any work ongoing that you know of? Maybe the company would want to answer.

Also, it would be interesting to know whether it inhibits the metabolism of any other drugs, how much is

known about that.

DR. COHEN: I am really not familiar with any data to answer your question. Maybe one of the FDA pharmacologists might have information.

DR. NERENSTONE: Can anyone from Novartis respond? Please just identify yourself for the recorder.

DR. PFISTER: I am Christian Pfister from Clinical Pharmacology at Novartis.

Can I have slide No. PK17, please.

[Slide.]

For the first registration we have performed two interaction studies, one with cimetidine, which is a known inhibitor of Cytochrome p450, and also one with warfarin, and there were no interactions, pharmacokinetic interactions with these two drugs.

Then, we have this study research which has already been mentioned with tamoxifen, and on the next slide, No. 18, please, these are results from preclinical studies looking at the interaction at the Cytochrome p450 levels.

[Slide.]

As you see for the letrozole, it is metabolized, it is cleared mainly by metabolism, and this is by, or at least this preclinical experiment suggests it is done by two enzymes, the 3A4 and the 2A6, and for the 3A4, letrozole has

a rather low affinity, and also its inhibition constant is very high, and the plasma levels achieved at steady state are far below this inhibition constant, so we do not expect--

DR. TEMPLE: Is tamoxifen an inducer of 3A4? Is that what happened?

DR. PFISTER: This is not known. At least, to the best of my knowledge, I have looked at the literature. There are some preclinical studies which indicate that tamoxifen could be an inducer of Cytochrome p450, and, in fact, the major metabolite of tamoxifen, this pathway is catalyzed by 3A4.

DR. TEMPLE: I mean that does suggest there are other inducers in the environment.

DR. PFISTER: Yes.

DR. TEMPLE: Anti-seizure drugs, St. John's Wort, and other--

DR. PFISTER: Yes, and carbamazepine and phenytoin. It is possible that inducers of 3A4 may reduce the drug levels of letrozole and that is, in fact, the hypothesis we have for this interaction with tamoxifen.

DR. NERENSTONE: Dr. Kelsen.

DR. KELSEN: This is a follow-up to Doug's question. It is more of a general question. I am asking the concern about reviewing primary data from sites that are

very distant from the United States.

I don't think it applies so much to this study, because as I understand it, this is double-blinded and the investigators at the individual sites were not aware of the assignment, and so bias is not an issue.

But how about for a chemotherapeutic agent or cytotoxic agent where it is really hard to blind investigators, what is the approach to looking at primary data from sites that are very far away, do you do that, or do you accept the data from the company? How do you all approach that?

DR. COHEN: We site-visited one of the sites in Russia, and the site visitor reviewed the primary data from Russia, and the data was satisfactory. That was the extent of our review.

DR. KELSEN: I am not so worried about this trial because, as I said, it is double-blinded, and the bias I think is not an issue. I sort of asked a more general question as to it is very hard to blind investigators to agents in some settings.

Do you accept the data as presented, do you site visit each site? It is a general question.

DR. PAZDUR: No, the site visits are usually held at the largest accruing sites. So, in this case, the largest accruing sites happened to be outside of the United

States. But, in general, we don't discriminate against data coming from a foreign country and hold it into less esteem or greater esteem than that coming from the United States.

DR. KELSEN: It is same wherever--

DR. PAZDUR: Basically, yes, unless there is some reason to conclude--

DR. TEMPLE: Well, we are more familiar with some parts of the world than others, and the need to go check might differ between places like Western Europe where we have seen hundreds and hundreds of studies of all kinds, and parts of the world we are less familiar with. I mean that sounds xenophobic, but I think it is just a matter of experience.

The other thing is we can get some kinds of primary data. We could get x-rays and things like that if we really thought that was necessary without necessarily going to the place.

DR. KELSEN: I know you can. I was just wondering if you were.

DR. TEMPLE: We do sometimes.

DR. NERENSTONE: Other questions for FDA?

Ms. Zook-Fischler.

MS. ZOOK-FISCHLER: It is not really a question. It is a comment. As a patient rep., I am always struck when I heard words like "mild to moderate" for adverse effects,

and I just think it should be noted that from a patient's point of view, that has to be balanced with statistical significance.

It is not really a question. It is just playing devil's advocate.

DR. NERENSTONE: Thank you.

If there are no further questions, then, we have got to get to the committee discussion. We have two discussants from ODAC, Dr. Albain and Dr. Sledge.

Who would like to start? Dr. Albain alphabetically.

Committee Discussion and Vote

ODAC Discussants

DR. ALBAIN: Well, first of all, I would like to start out with commending the sponsor for an excellent presentation and discussion, and to conduct this trial in so many sites worldwide, and again, as I said earlier, in so many women over the age of 70. Women of that age group do not enroll in clinical trials in breast cancer, and I think this is a credit to this trial that that was done and that the effects are as strong in that subset.

Although I asked a lot of pointed questions to Dr. Fleming and the group about the survival and the statistics, it does not worry me that we don't have survival data or even if it should come out that there is no survival

benefit. In fact, I am reassured by the results for time to progression here in the context of the previous drug that was approved, anastrozole, very similar types of effects.

That brings us into the next area, are all aromatase inhibitors the same, and I don't think we know that quite yet. We have seen some intriguing data today, that there may be differences and that letrozole may have some superiority, but whether that results in a true clinical benefit, and in particular in the group of women where we are going to want to see where these drugs go in the adjuvant setting in that population, what will be the safety in, for example, a five-year duration.

I mean we are picking that because that is what we used for tamoxifen, but is that the right duration. These are all unsettled questions that we await new trials, this trial obviously can't answer, but the safety profile here is reassuring for shorter duration therapy, but what will happen to lipids, what will happen to bone density, for example, in the scenario of a longer duration in the adjuvant setting is not known.

I think that for future drugs, let's say this trial were to show a p 0.049 survival benefit when we eventually come down to it, will we then really need to see such a survival benefit for all new hormonal agents or new biologics.

I am more worried about that, and just a little tweak at the FDA that we need to continue to have some open discussion about time to progression as a realistic and viable primary endpoint as this trial has shown.

Those were basically my comments, very favorable toward this compound.

DR. NERENSTONE: Thank you.

Dr. Sledge.

DR. SLEDGE: I would agree with just about everything that my esteemed colleague has said. I think that this trial provides fairly compelling data that letrozole is at least equivalent to tamoxifen and quite possibly superior to it.

I think the clinical experience of physicians who take care of breast cancer is that the aromatase inhibitors in general, and letrozole in particular, are certainly safe and well tolerated medications.

So, I am certainly quite happy with this drug going forward.

I would like to focus a little bit on something we haven't discussed a whole lot, which is where do we actually use these drugs in the United States. Unlike in this trial where 80 percent of the patients had not had prior, what we consider significant adjuvant tamoxifen, say, two years or more of therapy, in the United States that number is I am

sure reversed, and it is probably more like 90 percent of patients have had significant amounts of prior adjuvant tamoxifen.

So, when we are talking about a first-line indication for metastatic breast cancer, in fact, what we are talking about is second-line, after having failed prior adjuvant hormonal therapy with tamoxifen.

So, I think in the United States, the clinically relevant group is that group of patients rather than the overall group. Here, I find the data quite compelling in that, if I am reading the numbers correctly, only 3 of 51 patients, or 6 percent of patients, who had had significant adjuvant tamoxifen, had a following response to tamoxifen at the time of progression versus 18 of 58, or 31 percent of patients.

I actually find this the most compelling data that is clinically relevant in the United States. I would actually look at that data and say that tamoxifen should not be used for a patient who has had significant prior adjuvant tamoxifen and then has gone on to progress, and certainly, to my mind, makes a superb case for letrozole.

I also found Dr. Ellis' data with regard to HER-2 and epidermal growth factor receptor to be very interesting data albeit preliminary data. This data suggests reasonably strongly that tamoxifen probably isn't going to work or not

work very well in a patient who has had a different growth factor receptor pathway, such as EGFR or HER-2 turned on, whereas, the preliminary data from the study that was presented suggests that letrozole certainly may work in this population of patients.

So, again, that could well be another clinically relevant observation with regard to this agent, I think certainly should be pursued in a larger database.

So, overall, I think this is a drug that we should give serious attention to approving for this indication. I would make one comment for the FDA going forward. I really don't think in the year 2000 that we should be approving trials that don't test estrogen receptor status in a significant percentage of the population.

I understand why, when one does a trial on a worldwide basis, in places where estrogen receptor may not be available, why it is convenient not to do that, but the clinical reality in the United States is that virtually everyone has had ER tested and that is the clinically relevant population for drugs that are being introduced in the United States.

DR. NERENSTONE: Thank you. Are there any more comments? Yes, Dr. Blayney.

DR. BLAYNEY: I also think and agree with the two comments that letrozole really is a pleasure to use now that

we have two aromatase inhibitors. I was intrigued by the data about the completeness of blocking of the aromatase enzyme.

I am concerned in the FDA briefing document, review document, Table 39 talked about the crossover responses, and I hear that the data is too preliminary. I am concerned that response to letrozole may prejudice a response to tamoxifen or another selective estrogen receptor modulator, so the paradigm that was presented earlier about how we treat breast cancer may deserve some modification as we go on.

I am also a little mildly interested that the clotting events, which is one of the reasons heretofore that we have used aromatase inhibitors in preference to tamoxifen were the same in this trial, whereas, in the two anastrozole trials, the anastrozole had about half the reported clotting events.

As evidenced by my question again to the FDA, I think in the future if there are a variety of offshore sites that contribute data, lately we have seen several paradigm shifting trials that have been not as what they presented, so I think it would be useful to let us know if indeed there is a lot of offshore, what monitoring activities you have undertaken. It would give me assurance or some measure of comfort that indeed the data is real upon which we are

making a decision.

Thank you.

DR. NERENSTONE: Other comments? Yes, Dr. Temple.

DR. TEMPLE: One of the things we do sometimes, and, of course, it is controversial because it is hard to know what to make of it if you see a difference, is to analyze data by region. I gather that was done in this case, and there was no difference. That sometimes provides some comfort. When there is a difference, you get into violent arguments about what to make of it, of course.

Could I just ask Dr. Blayney, how would one go about answering the question you pose about crossover? In other words, in this study everybody crosses over, I mean if they were crossing over to something not in the study, then, you could see whether one prior treatment had a greater impact on response to that other treatment than the other. In this case, they are crossing over to the one they didn't get. If, for example, in this trial you saw more response when they cross over to the aromatase inhibitor than to the tamoxifen, well, that was the result of the initial treatment.

So, how does one go about this? How can one get the answer to the question you are posing?

DR. BLAYNEY: Well, I think partly by survival, perhaps the survival is going to be the same, so it won't

make a difference, but in our treatment strategies, as we heard eloquently earlier on, in taking care of these women with long disease courses, it is great to have a variety of agents to use, but if it doesn't make sense to go to tamoxifen after letrozole fails or anastrozole fails, then, that is an useful piece of information.

DR. TEMPLE: That, you will see, of course.

DR. NERENSTONE: Other comments? Yes, Dr. Lippman.

DR. LIPPMAN: I would just like to follow up and underscore Dr. Sledge's comments and a couple others that came up regarding the findings in adjuvant tamoxifen and the relevance of this approach in this country.

Even though this is a small subset analysis, the differences in response rate and the other parameters are so striking that I think we can feel comfortable at least for the standard practice in this country where most patients are getting adjuvant therapy, that this fits into the sequential use of these hormones that Dr. Harvey presented very nicely, again following adjuvant therapy.

DR. NERENSTONE: If there are no further questions, I would like to get to the questions to the committee.

Rather than to read this all over yet again, I just point your attention to Table 1 where the large

randomized, multinational clinical trial results, response rates for Femara versus tamoxifen either evaluated by Novartis or by the FDA, significant at the p 0.0003 level, response durations were not done, median time to progression, which was the primary endpoint of this trial, significant at the 0.0001 level.

On the next page of our handout, the list of the toxicities which were not different between the arms, and then a reiteration of the discussion on page 2 about the indication for approval for new cytotoxics, and how that differs for the indication for approval of hormonal drugs for initial treatment of advanced metastatic breast cancer.

They do go on, remind you that updated survival data are required at the time of approval, but demonstration of statistical superiority or non-inferiority of survival is not required.

Then, they talk about how the hormone drugs in the past have not been shown to increase survival, and therefore, non-inferiority of survival is considered a safety endpoint, and not an indication of efficacy.

They talk about if a new hormonal drug is shown to increase survival, the FDA will probably require future new hormonal drugs to demonstrate a favorable effect on survival to gain marketing approval.

The first question to this committee: Does the

committee agree with the FDA's criteria for approval of hormonal drugs for initial treatment of advanced metastatic breast cancer? I guess I have to say at this point in time.

Discussion? Dr. Albain.

DR. ALBAIN: Do you mean by that question do we approve of the use of survival for future drugs?

DR. NERENSTONE: No. At this point, that is not being proposed. Right now it is just survival is just a safety endpoint, it is time to progression, and the other secondary things that they are looking at, but time to progression is really the primary endpoint.

Is that agreeable to the committee at this point? Dr. Simon, do you want to comment?

DR. SIMON: I would just sort of say that I find it a whole lot more convincing in a double-blind trial than I would in a non-double-blind trial.

DR. NERENSTONE: So, with that caveat that it be a double-blind trial, time to progression then would be an acceptable endpoint.

May we have a show of hands for the FDA? This is yes, we agree that the current recommendation of time to progression is a valid endpoint for approval for a hormonal medication.

[Show of hands.]

DR. NERENSTONE: Any opposed?

[No response.]

The second question. Does the single study comparing Femara with tamoxifen show that Femara is effective for initial hormonal treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown advanced metastatic breast cancer?

Comments? Dr. Albain.

DR. ALBAIN: Just to the FDA again. For the cytotoxics in general you have suggested that two trials is optimal, and I am noticing for hormonal therapies, one randomized trial. Is there a reason why that difference?

DR. NERENSTONE: Would someone like to answer that? Dr. Johnson.

DR. JOHNSON: There is no difference. We haven't suggested any difference in the number of trials.

DR. NERENSTONE: I would point out that this trial is very large and also multicenter, and I think maybe that is the weighted evidence, that if you had had two comparable trials, one in the U.S. and one in Europe, which is usually what we are presented with, you want them to be the same, and whether you call them two trials or one trial, this is so large that perhaps--

DR. PAZDUR: Marty did present a slide that showed why one trial might be acceptable, and it includes the fact that it was multicenter, it was internally consistent, it

was statistically persuasive and methodologically sound, so I think these things went into our feeling one trial would be sufficient.

DR. TEMPLE: In addition, there are trials in other stages of the disease that are also supportive. All of those are conditions in which we have relied on a single study.

DR. NERENSTONE: Other comments or questions?

[No response.]

DR. NERENSTONE: May I see a show of hands?

So, does this single study, does it show that this is effective treatment?

All those in favor?

[Show of hands.]

DR. NERENSTONE: Okay.

The third question. In view of the efficacy, is the safety of Femara adequate? Do you feel that we have adequate information at this time? Comments?

DR. SANTANA: How does the FDA deal with this issue of potential drug-drug interaction in the absence of conclusive data when you do the labeling? Can you clarify that for me?

DR. NERENSTONE: Dr. Temple.

DR. TEMPLE: Well, actually, to my knowledge, I mean this is my first thinking about it, but a plausible

explanation is that an inducer of 3A4 lowered the blood level in a way whose clinical meaning you don't understand, you put something in labeling about 3A4 inducers which are known, and there are other drugs that are labeled the same way. Then, you negotiate about getting some real data.

DR. NERENSTONE: Dr. Sledge.

DR. SLEDGE: For this drug, that particular interaction is perhaps not a great issue since certainly the standard of care in the United States is to use sequential hormonal agents rather than combination hormonal agents.

Now, the important qualifier there is that an important research issue right now might be, for instance, for a premenopausal patient who, for instance, say, got a drug like, say, xylodex [ph], an LHRH agonist, whether or not addition of an agent like letrozole on top of the LHRH agonist might give further significant benefit.

In that setting the drug-drug interactions would be of obvious importance, and certainly would be something you would want to look into.

DR. PAZDUR: But our major concern is other concomitant medications rather than combination hormonal therapy obviously, and that is why we may look at other studies, clinical data that needs to be generated.

DR. NERENSTONE: Dr. Albain.

DR. ALBAIN: I would like to add the caveat of the

safety, yes, in the metastatic setting where durations of use are shorter than noticing out in many settings a tendency to switch to an aromatase inhibitor in the adjuvant setting, and there are sometimes reasons to do that on a case-by-case basis, but with the very favorable safety profile of these agents in the metastatic setting, I think we need to be careful in the labeling or however this goes forward that this is in the metastatic setting and we await the data in the adjuvant trials for longer duration safety.

DR. NERENSTONE: I have a question for FDA. Do we know, is there any data yet about the effectiveness in the premenopausal ERPR-positive patients? No, just postmenopausal.

DR. COHEN: You wouldn't expect it either.

DR. NERENSTONE: We use tamoxifen in that group, and they respond to sequential hormonal treatment although probably not at quite the same percentage, but there certainly are subsets of patients you would think about using it in.

So a show of hands. Is the safety of Femara adequate? All those in favor yes.

[Show of hands.]

DR. NERENSTONE: Any no's?

[No response.]

DR. NERENSTONE: Is then Femara approvable for a

secondary NDA?

All those in favor, please raise your hand yes.

[Show of hands.]

DR. NERENSTONE: Any nays?

[No response.]

DR. NERENSTONE: I thank the committee very much. This was very nice and non-controversial. It was a good introduction for me, I appreciate that. At 1:30, please be back. If we could start at 1:15, I think it would be good for this afternoon's discussion.

[Whereupon, at 11:55 a.m., the proceedings were recessed, to be resumed at 1:15 p.m.]

A F T E R N O O N S E S S I O N

[1:15 p.m.]

Call to Order and Introductions

DR. NERENSTONE: I would like to thank everyone for coming. We are going to be discussing the histamine dihydrochloride injection NDA.

I would like to start by having the committee introduce itself again for the record and also for people who haven't been here for the morning session.

DR. TAYLOR: I am Dr. Sarah Taylor from the University of Kansas Medical Center. I am Director of Palliative Care and a Medical Oncologist.

DR. KELSEN: I am Dave Kelsen, Medical Oncologist from Sloan-Kettering in New York.

DR. SIMON: Richard Simon from the National Cancer Institute.

DR. SLEDGE: George Sledge, Indiana University.

MR. McDONOUGH: Ken McDonough, North Huntingdon Township, patient representative.

DR. LIPPMAN: Scott Lippman, Medical Oncology, M.D. Anderson Cancer Center.

DR. DUTCHER: Janice Dutcher, Medical Oncologist, Our Lady of Mercy, New York Medical College in New York.

DR. SANTANA: Victor Santana, St. Jude's Children's Research Hospital in Memphis, Tennessee.

DR. NERENSTONE: Stacy Nerenstone, Medical Oncology, from Hartford, Connecticut.

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

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

DR. PELUSI: Jody Pelusi, Oncology, nurse-practitioner at Phoenix Indian Medical Center, and I sit as the consumer rep.

DR. REDMAN: Bruce Redman, Medical Oncologist, University of Michigan Comprehensive Cancer Center.

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

DR. CARPENTER: John Carpenter from the University of Alabama at Birmingham, Medical Oncology.

DR. CHIAO: Judy Chiao, Medical Reviewer, FDA.

DR. GRIEBEL: Donna Griebel, Medical Team Leader, FDA.

DR. NERENSTONE: Dr. Templeton-Somers will read the Conflict of Interest Statement.

Conflict of Interest Statement

DR. TEMPLETON-SOMERS: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and information provided by the participants, the Agency has determined that all reported interest in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the following exceptions.

In accordance with Section 208(b)(3), full waivers have been granted to Drs. Lippman, Santana, and Sledge. In addition, we would like to disclose for the record that Dr. Blayney is excluded from participating in the committee's discussions and vote regarding histamine dihydrochloride. A copy of these waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

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

Thank you.

Open Public Hearing

DR. NERENSTONE: We are now going to have the open public hearing part of this afternoon's discussion.

Karen S. Graham from the William S. Graham Foundation for Melanoma Research has asked to speak.

MS. GRAHAM: Good afternoon. My name is Karen Graham and I am the founder and president of the William S. Graham Foundation for Melanoma Research. We are fondly known as the "Billy Foundation."

In past years, we have accepted donations to our public awareness and education programs from some of the pharmaceutical companies. However, I have paid my own expense here today, and if I might add, at a very dear cost.

Please, please, someone out there tell me that there is something that you can do to help. My loved one has by his doctor been given a death sentence, and I refuse to believe, I refuse to believe that there isn't something that we can do that won't be nearly as devastating as the disease itself.

Ladies and gentlemen, many times on a daily basis at the Foundation office, we hear these heartbreaking pleas from patients, their families, and their loved ones as they try to sort through the many different therapies and their options for what would be the best suited for their particular fight against this lethal form of skin cancer,

and we have had to answer these pleas with the same answers that were given to our son over seven years ago.

I personally was found in the same situation when Billy, at the age of 21, was diagnosed in Stage IV melanoma with liver metastasis and given three to six months to live. He was basically sent home to die. His only hope was to hang on with the chance that something would be developed in time to save his life.

In the past, the only options have been high-toxicity drugs that literally bring the patient to the brink of their human tolerance with little hope in the way of prolonged life expectancy, let alone addressing any of the quality of life issues or regimes that are known to do very little, if anything, for Stage IV melanoma.

We see the agony that this places the families and patients in as they are trying to make decisions on a subject that they probably didn't even know existed before their nightmare began. They have been placed in the throes of a decision-making process that, quite frankly, is not going to have a happy ending, not yet.

But this new drug may be that light at the end of the tunnel that every melanoma patient needs to be able to see to continue their fight.

Just the fact that this drug can be administered at home, outside of a hospital setting and all the trauma

that is involved with that, the physical, the psychological effects that an ICU unit stay has to entail, that alone can spark the flame of hope, and hope, after all, should be the right given to every patient, family, and loved one, the hope of hanging on just a little while longer, so that you can take that family vacation and make that one last memory or perhaps it is the hope of being able to watch your wife give birth to your first child before you die, or the hope of being able, able to graduate with your class. Yes, it is the hope of holding on just a little while longer because surely, surely that cure will be just around the corner.

We at the Billy Foundation are anxiously awaiting the opportunity to be able to refer patients to a drug that will take in some of the quality of life issues.

I would like to thank you for your listening ear, for your time and your kind consideration because I truly believe from the bottom of my heart that together we will beat this disease.

If you have any questions, I will be glad to address them at this time.

DR. NERENSTONE: Does the committee have any questions for Mrs. Graham?

[No response.]

DR. NERENSTONE: No. Thank you very much for your time.

Our next speaker is Mr. Joe Groebner.

MR. GROEBNER: I will catch my breath. That was a little too close to home, to be honest with you.

I am a patient advocate. I have gone through this particular treatment. I was on it for two years, three months. I want to thank the FDA and this committee for the opportunity to be here today, because I honestly believe that histamine, as given to us by Maxim, will make a difference to a lot of patients.

First of all, let me tell you why. I have a common story, it is much like many people that end up with melanoma. I am 45 years old. I am a husband, I am a father, I have a 2 1/2 year old. I am an ordained minister. I am a manager for a computer company, I am a supplier quality engineer living in Longmont, Colorado.

Twelve years ago I got a mole on my right leg. It looked suspicious. I went in and talked to my practicing physician, and he took the mole off and sent it in. It turned out to be malignant melanoma, Clark's Level III, I think, or I can't remember all the terminology.

Three months later, after surgery and removing the skin about the mole, three months later I went in for a routine physical. My practicing physician found a malignant tumor in my right groin. I had to have all of the right groin lymph nodes removed, and I was told at that time that

six months was the median time to live.

There was no treatment available, and I was sent home without any treatment. Every three months I went in for checkups, and as the time went by, we started to believe that the cancer was never going to return. Pretty soon it was every six months.

Nine years went by without any sign of the melanoma reoccurring. I moved to Colorado, I changed jobs, relocated my family. My wife was eight months pregnant when an x-ray showed that the melanoma had metastasized and moved into my lungs.

But this time there was a treatment at least available as a test, interleukin-2 with histamine. I was on this particular protocol, like I said, two years and three months, and the first three to six months weren't easy. I suffered from fevers. I woke up in the morning with my pillow soaking wet. Chills, I literally shook at night and had to take warm baths. Loss of energy. My wife wanted me to make certain I gave you that. Even what the oncology nurses called a "blush" headache. You take the histamine, you turn red. Since my color was light anyway, people just thought it was as normal blush.

I had to learn to give myself subcutaneous shots. They recommended 10 to 30 minutes for histamine. You can't give it to yourself too fast or, who knows, maybe a heart

attack will occur. I chose 20 minutes, and I was able to do the protocol at six o'clock in the morning, every morning, and then in the evening varied a little bit because I was never sure when I would get home from work.

Beyond the early symptoms, it was a wonderful thing because it was on a six-week cycle, and I always had weekends off, which means week one was high dose, week two was a low dose interleukin always with the histamine, week three was high dose, week four was low dose, and week five and six I didn't have to take anything at all.

It fit into my job. I have to travel to China and Japan, which means I could keep working. The fifth and sixth week I went to Japan and China. First, week one through four I was able to work back and actually do some domestic travel.

The fevers went away, the chills went away, the headaches went away. I didn't even have to take anything for headaches. The shots really became routine. I gave the interleukin-2 in my belly, big target, histamine in my legs, morning in one leg, afternoon in the other. It really did become routine.

The cancer was stable, it didn't grow for two years and three months. The shots were easy. The protocol worked for me. I had time with my family. My daughter is now 2 1/2 years old. My wife has been very thankful that I

have been around. It did stop working. I am on a different protocol, evidence of my bald head. I look around the room. I maybe could have got away with not wearing the hat.

For me, this treatment wasn't a cure, but it stabilized the cancer. It gave me time with my family and friends. The side effects became minor, and the protocol allowed me to work full time and live a full and almost normal life.

If the statistics shows--by the way, I am a rookie statistician--if the statistics show a lengthening of life, I strongly recommend you approve the drug and give other people the opportunity to extend life with very minor side effects.

Thank you.

Now, does the committee have any questions for me?

DR. NERENSTONE: Any questions?

[No response.]

DR. NERENSTONE: Thank you very much.

Our next speaker is Dr. Eric Whitman.

DR. WHITMAN: Good afternoon. I would like to thank the committee for the opportunity to speak during the public portion of this session.

My name is Dr. Eric Whitman and I am a surgical oncologist in St. Louis, Missouri. I will just give you a little bit of my background. After finishing medical school

at Pennsylvania State University, I was trained as a general surgeon at the Milton S. Hershey Medical Center in Hershey, PA, which is also part of Penn State. I was then a senior staff fellow in Dr. Rosenberg's Surgery Branch just down the street at the NCI.

Following six years as an Assistant Professor of Surgery in the Cancer Section at Washington University of St. Louis, I entered private practice in the St. Louis area. I am currently the director and actually the founder of the Melanoma Center of St. Louis, which is a clinical specialty center of excellence. We treat over 200 patients a year with melanoma. We see probably about 50 percent of all the melanoma patients in the area.

Just so we all understand, I have no financial or equity interest in Maxim Pharmaceuticals. I volunteered to be here today, and I paid my own way, and I hope my kids are having a good time right now.

I was, however, one of the initial investigators in the Phase III trial that we are talking about today. Our center is currently also one of the sites for the follow-up Phase II trial which is looking just at the combination of interleukin-2 and histamine dihydrochloride. All together I managed the care of about 25 patients on these two protocols, and currently we have about 10 patients who are receiving this treatment all on the Phase II trial.

After the emotional speeches that preceded me, we all know that melanoma is an absolutely horrible cancer. As oncology specialists, all of us, we know that many cancers currently have therapy even in the advanced stages that will at least offer some statistical benefit. I don't think that is true at all for melanoma.

Once melanoma has progressed beyond the local primary site, there are no generally accepted effective treatments. Patients with liver metastases do particularly poorly. Once the melanoma has spread to the liver, most people die within three to six months. There really is no treatment.

As the cancer within the liver progresses, they become emaciated, weak, often jaundiced. It is absolutely horrible to see as a physician, but I know, and I know from listening to the two people before me, that what I feel and what my staff feels is nothing in comparison with what the patient and their family and friends feel.

Unfortunately, from my perspective, there is no treatment that offers any benefit that is approved right now. The two agents that are approved, DTIC or dacarbazine or high dose interleukin-2 don't improve survival as far as I can tell, and whatever they do accomplish is at a very high expense in terms of quality of life.

Conversely, as you heard, the side effects from

interleukin-2 and histamine dihydrochloride are extremely low. We have never had to hospitalize any of the patients we treated. They give the therapy at home either by themselves, by a home care nurse, or by a caregiver.

Once every six weeks they come to our office and they are evaluated, and we make the decision whether or not to continue treatment. In comparison to my extensive experience with patients receiving other types of treatment for melanoma, whether it be chemotherapy, immunotherapy, or a combination, there is no comparison. They just do much better.

We have treated farmers who actively manage their crops, executives like the previous gentleman who are able to continue their busy schedules, traveling, meetings, even elderly retirees well into their seventies who no one in this room would ever treat with any of the other approved agents, who are able to continue their lives, enjoy their family, pursue hobbies and crafts.

Despite or more precisely, perhaps in addition to, its low toxicity, I believe that combination therapy with interleukin-2 and histamine dihydrochloride works.

When we first started putting our data together in the Phase III trial, we were astonished at the survival in the treatment arm, in the experimental arm. That was just for our site. We are very happy to find that the

multicenter data was consistent with ours.

I would say for the benefit of the committee that no experimental design is perfect, however, the most important fact to me is that I know of no other treatment for advanced melanoma that has shown any survival benefit when compared to any drug or observation.

Most of the patients who have been referred to me with advanced melanoma have been told the gruesome statistics about treatments for the disease, the toxicity of the therapy. They know the low likelihood of success, and they also understand that there will be an inevitable progression of the disease to death.

They arrive in my office often armed with printouts from the Internet because that is where you can get information nowadays, stacks and stacks of paper on color laser printer. Unfortunately, most of it is inaccurate or irrelevant to their disease or ineffective.

I believe that Maxim's drug for the first time provides hope for these patients, hope for survival, hope for more time with children and grandchildren, hope, as a melanoma patient once told me, for keeping this "beast" at bay.

In closing, I would like to say that I traveled from St. Louis to Washington not to avoid the foot of snow falling as we speak, but to urge the committee to approve

this drug, again, the first drug that on the bottom line has showed any survival benefit for patients with Stage IV melanoma.

Thank you very much. I will be happy to answer any questions.

DR. NERENSTONE: Does the committee have any questions?

[No response.]

DR. NERENSTONE: Thank you for your time.

Our last scheduled speaker is Laura Stover.

MS. STOVER: Good afternoon. My name is Laura Stover and I am a clinical research nurse at the University of Pittsburgh Cancer Institute, in our Melanoma Center there. I have worked for the Melanoma Center approximately five years, and I am happy to be here today and thank you for the opportunity.

I did pay my own way to come here and, as a nurse, that is sometimes burdening, but it was my pleasure.

The reason that I am standing up here today is because you have heard from a patient advocate, you have heard from a patient, and you have heard from a physician, and now you are hearing from a nurse, because part of this treatment, because it is so extensively outpatient, actually is anchored by nurses both in the community and at the institution where the patient is being treated, so nursing

is a very critical element for this type of treatment.

My past experience was actually giving high-dose interleukin on our Inpatient Oncology Unit at the University. Also, now, as a clinical research coordinator, coordinating the trials for high-dose interleukin-2, also being involved with this particular treatment since its inception at our center, what I can tell you is when we first started the histamine and interleukin treatment at our site, I was rather skeptical about the outpatient regimen that it entails.

However, as we became more and more familiar with the treatment, we found that the toxicities were so much less than the high dose experience that we had on the inpatient unit, we were able to treat these patients safely with constant communication between the patient, their support at home, the home care nurses that may have been involved, the nurses at the site, and also the physicians, it actually worked and it was working very well.

I think one of the biggest things to consider at this point is the patient's quality of life. When a patient is admitted for five days for an inpatient treatment that is very toxic, obviously, the quality of life is compromised substantially. So, that is one thing that really needs to be addressed, and I think in this particular trial, it was addressed.

These patients were able to maintain most of their normal activities at home. We had patients that had small children that were able to take care of them, and not be away from them for a week and make care inconsistent.

We had patients that were elderly, and as Dr. Whitman said, many of these patients would not be good candidates for high-dose interleukin-2 or other regimens containing interleukin. These are all important things to consider when looking at a patient's prognosis, which is very poor. They need to be involved with their care, and most of them are most willing to actually learn the subcutaneous injection of the histamine, although challenging, are willing to do that.

I think that education of the patient, education of the patient's family, and the nursing staff is also critical in this type of situation on an outpatient basis.

As I said, our patients were most willing to learn how to give this treatment, and the nurses also were willing to learn how to administer the drug safely.

I think that in this situation, that with the low-dose interleukin, that actually patients had a lower toxicity profile and a better quality of life, were able to maintain some of the normalcy of their life.

So, these are all things I wish that you would consider for these patients that are in the situation, that

have metastatic melanoma.

I will take any questions at this time.

DR. NERENSTONE: Any questions from the committee?

[No response.]

DR. NERENSTONE: Thank you.

On behalf of the committee, I would like to thank these four individuals for coming in and sharing their experiences. I know it is a cost of time and some expense for them, so thank you very much for letting your opinions be heard this afternoon.

We turn now to the sponsor presentation for the histamine dihydrochloride injection.

NDA 21-240, histamine dihydrochloride injection (1 mg/ml)

Maxim Pharmaceuticals, Inc.

Sponsor Presentation

Introductory Remarks

DR. GEHLSON: Thank you very much. It is an honor and a privilege to be here this afternoon. My name is Dr. Kurt Gehlson. I am the Senior Vice President of Development and the Chief Technical Officer for Maxim Pharmaceuticals.

We are honored to be here and we would like to thank Dr. Pazdur, members of the FDA, and, of course, members of ODAC for this opportunity to present our results with histamine dihydrochloride in combination with interleukin-2.

Before we get started, however, I would like to introduce a few of the guests that we have this afternoon that are available for your questions during the discussion session.

We have Dr. John Glaspy from UCLA. We have Dr. Sanjiv Agarwala from the University of Pittsburgh. We have Dr. Tom Fleming from the University of Washington, Dr. Michael Atkins from Harvard Medical School, and Dr. Alexander Eggermont who has come all the way from Rotterdam, but the person who has actually traveled the furthest, and maybe we have set a record here today, is Dr. Peter Naredi, who has come from the north of Sweden, from Umea, and he was actually the brave soul that actually injected the first person with histamine with melanoma.

[Slide.]

Now, we believe that the addition of histamine plus interleukin-2 significantly improves the survival of patients with liver metastases. What we would like to do this afternoon is provide you with an objective overview of the development of histamine dihydrochloride in this indication.

We would like to establish that this was, in fact, a prespecified subgroup. We would like to establish that this is, in fact, a compelling and significant result, and finally, we would like to show you that this result is, in

fact, reproducible.

Our agenda for this afternoon will be to give you an overview of the background of melanoma. Dr. Michael Atkins will do that for us. Then, I will come back up and give us the rationale for the combination therapy, we will discuss our clinical experience to date, our Phase III randomized trial, of course, we will spend most of our time on.

We will provide data from our supportive Phase II trial. We can give you an 18-month update on the efficacy results of the Phase III trial. We will summarize, and, of course, we will leave ample time for your discussion and your questions.

So, now I am going to turn this over to Dr. Michael Atkins.

Dr. Atkins, please.

Overview of Metastatic Melanoma

DR. ATKINS: Thank you, Kurt, and good afternoon.

[Slide.]

My task is to present background information on the prognosis and management of Stage IV melanoma.

[Slide.]

In the year 2000, there will be about 45,000 cases of melanoma in the United States, about 7,700 deaths. This represents about 3 percent of all cancers and about 1

percent of all cancer deaths. The estimated lifetime risk of developing a melanoma in the U.S. is now 1 in 74.

[Slide.]

Stage IV melanoma is synonymous with "metastatic" melanoma and as a definition, this is involvement of skin or soft tissue beyond the region of the primary tumor, involvement of distant nodal site, or the presence of visceral metastases.

[Slide.]

Metastatic melanoma is a bad disease. The median age is 45 to 50. Median survival is 6 to 10 months. Five-year survival in most series is less than 5 percent, and there are few, if any, effective therapies.

[Slide.]

This is a typical survival curve taken from the AJCC Staging Database involving almost 1,200 patients with Stage IV melanoma.

[Slide.]

A number of groups have looked at prognostic factors in State IV melanoma. Perhaps the first was a group led by Charlie Balch which looked at 200 patients and published their results in 1983.

In a multivariate analysis, three factors stood out - number of metastatic sites, remission duration, and site of metastases, as being independent predictors of poor

prognosis.

[Slide.]

Looking at sites more carefully, you can see that patients with visceral metastases at all of these time points had about half or less the chance of being alive compared to patients with non-visceral metastases, and patients with both visceral and non-visceral metastases fared even worse.

[Slide.]

Liver metastases carry a particularly poor prognosis.

[Slide.]

In the Balch data, patients with liver metastases either as the sole site or in combination with other sites, had a significantly poorer median survival compared to other sites or the group as a whole.

[Slide.]

Looking at the UCLA John Wayne Cancer Institute database, comprised of 1,521 patients, we can see that liver metastases have a median survival of 4 months on par with brain metastases, less than these other sites of disease and about half of the survival of the group as a whole.

[Slide.]

That is shown graphically here. About 20 percent of patients having liver metastases, and as you can see, at

each year time point, patients with liver metastases have a survival that is inferior to every other subset site of disease with the exception of possibly brain metastases.

[Slide.]

In the SWOG database of 649 patients treated on 11 chemotherapy trials, liver metastases was the third most important predictor of poor outcome, trailing performance status and number of metastatic sites.

[Slide.]

In a recently published ECOG pooled database, liver metastases was also the third most important predictor of poor outcome with a relative risk of 1.44.

[Slide.]

Why is prognosis so poor in patients with liver metastases? Well, in looking at all these patients, it is apparent that these patients aren't necessarily dying, by and large, of hepatic complications, therefore, liver metastases appear to be an indicator of more aggressive disease and/or impaired host defenses rather than simply an indicator of increased tumor burden.

[Slide.]

Other prognostic factors included an elevated serum LDH, which is also a strong negative prognostic factor.

[Slide.]

In the M.D. Anderson series, LDH was the most important predictor of poor outcome with a p-value of 0.001.

[Slide.]

In the ECOG pooled database in the three studies which incorporated laboratory parameters, LDH was also the most important predictor of poor outcome with a relative risk of 1.89.

[Slide.]

In summary, five studies found either the number of metastatic sites or visceral metastases to be predictive of poor outcome. In general, patients with one metastatic site do better than patients with multiple sites. Patients with skin, sub-Q and distant lymph node metastases have the best prognosis. Lung metastases are intermediate. Liver, brain, and other visceral sites have a median survival of 4 to 6 months.

Performance status greater than or equal to 1 is also associated with poor prognosis. Elevated serum LDH may be as important as the above factors.

[Slide.]

Taking this information into account, the AJCC recently proposed a modification to the staging for Stage IV disease, and that scheme is shown here where patients are separated into M1a, distant skin, sub-Q, or nodal metastases, and then normal LDH; M1b, lung metastases with a

normal LDH; and M1c, which is either all other visceral mets and a normal LDH or any distant met with an elevated LDH.

[Slide.]

Looking at that ECOG database that I showed you before, broken down by these categories, looking at all 1,362 patients, we can see that the median survival ranged from 10.6 months for the M1a group to 5.0 months for the M1c group, and incorporating LDH into this analysis, it is 12.8 months for the M1a group down to 7.8 months for the M1c group.

[Slide.]

What about systemic therapy? Well, the options include cytotoxic chemotherapy, immunotherapy particularly with cytokines or combinations of the above.

[Slide.]

The approved therapies are DTIC, which was approved in the 1970's, and high-dose interleukin-2, which was approved in 1998. It should be noted that no reproducible survival benefit has been established to date for these therapies.

[Slide.]

Looking at DTIC, the response rate is about 20 percent with a median response duration of 4 months, median survival of 6 to 9 months in most series, and 6-year survival of less than 2 percent.

[Slide.]

A number of Phase II and small Phase III trials looked at adding agents to dacarbazine, such as tamoxifen, interferon, vinblastine and cis-platinum or cis-platinum BCNU, and tamoxifen, the so-called "Dartmouth" regimen, and have reported promising results.

[Slide.]

Unfortunately, in Phase III trials, such as ECOG-3690, shown here, the addition of interferon or tamoxifen, or interferon plus tamoxifen to DTIC showed no benefit in terms of survival.

[Slide.]

This trial, also conducted by ECOG in conjunction with Memorial Sloan-Kettering randomized patients to the Dartmouth chemotherapy regimen or DTIC, and as you can see, the survival curves overlap.

[Slide.]

What about high-dose IL-2? Well, the standard regimen is shown here on this slide. It involves IL-2 administered at 600,000 units or 720,000 units/kg every 8 hours by a 15-minute infusion for 5 days, a 7 to 10 day rest period, followed by a second cycle of high-dose IL-2 also lasting 5 days with repeat courses being administered at 8 to 12 week intervals.

[Slide.]

This treatment was not shown to have a survival advantage. There was no Phase III trial done using this regimen, and it had a response rate of about 16 percent with 6 percent complete responses.

In my opinion, the reason why it received FDA approval was the quality of the responses produced with a median response duration of 8.9 months, and as shown here, the median not yet being reached for complete responders, and as you can see, there are no relapses in responding patients after the 30-month time point.

Unfortunately, this regimen is highly toxic, it is inpatient, it is expensive, and therefore impractical, and its use is limited to selected patients at experienced treatment centers.

[Slide.]

Patients who benefitted in terms of response to high-dose IL-2 were those who had a good performance status and not received any prior systemic therapy. There was no influence of any of these other factors on response.

[Slide.]

Even so, if your performance status was 1 or greater or you had received prior systemic therapy, your chance of responding to high-dose IL-2 was less than 10 percent.

[Slide.]

The median survival was 12 months with 11 percent of patients remaining alive at a minimum of 5 years follow-up.

[Slide.]

This is the survival curve for those 270 patients that were presented to the FDA three years ago.

[Slide.]

High-dose IL-2 has a lot of toxicity, as we have heard alluded to. Over 50 percent of patients experienced hypotension requiring pressors, or severe GI toxicity, such as diarrhea, nausea and vomiting, or hyperbilirubinemia; 25 to 50 percent of patients experienced chills, malaise, anemia, thrombocytopenia, skin or CNS toxicity or capillary leaks manifest by weight gain, dyspnea, or renal dysfunction.

In addition, 6 out of these 270 patients had treatment-related death all attributable to infection in the era prior to routine antibiotic prophylaxis.

[Slide.]

Unfortunately, low-dose IL-2 has limited activity in Stage IV melanoma.

[Slide.]

In this table which I compiled for a chapter in a Rosenberg textbook, looking at alternative IL-2 regimens including low-dose IL-2, which were primarily subcutaneous

IL-2 regimens, you can see that only 1 out of 95 patients experienced a response to low-dose IL-2.

[Slide.]

What about biochemotherapy? Well, there have been a number of Phase II trials looking at cis-platinum based chemotherapy, IL-2 based immunotherapy in metastatic melanoma, which have shown response rates in the 40 to 50 percent range, and complete response rates in the 10 to 15 percent range with a median survival of 11 to 12 months.

In meta-analyses, it appears that the biochemotherapy regimens have higher response rates than immunotherapy regimens alone or then would be attributable to chemotherapy.

[Slide.]

There has been a Phase III trial which was reported at ASCO, looking at sequential cis-platinum and vinblastine, DTIC, IL-2, interferon, biochemotherapy versus CVD alone, which showed a doubling of the response rate and a doubling of the time to progression for biochemotherapy, as well as approximately 3 month prolongation in median survival, which was of borderline statistical significance.

Unfortunately, there are problems with this regimen. It is inpatient and also very intensive with 19 out of the first 31 treatment days being in the hospital. It is highly toxic with 90 percent of these patients

requiring blood pressure support.

In contrast to what is seen with high-dose IL-2, there are few durable responses, and as I mentioned before, the survival benefit is only borderline. Finally, there are no confirmatory trials as yet.

[Slide.]

The other Phase III trials are shown on this slide, and they include a trial from EORTC, which looked at IL-2 and interferon plus or minus cis-platinum, which showed an improved response rate, but no survival benefit; a trial from the NCI Surgery Branch looking at cis-platinum and DTIC plus or minus high-dose IL-2 and interferon, which also showed an improved response rate, but no survival benefit; and a recently reported trial from the EORTC looking at platinum/DTIC/interferon plus or minus IL-2, which showed no response or survival difference.

The value of biochemotherapy is going to rest on the results of the intergroup trial comparing CVD alone to CVD plus concurrent IL-2/interferon, which is nearing completion.

[Slide.]

In summary, with regard to metastatic melanoma, specific features are associated with poor outcome. These include performance status greater than or equal to 1, visceral disease particularly liver metastases, multiple

sites of metastases, or elevated serum LDH.

Single agent chemotherapy, particularly with the carbazine, produces 5-year survival in 1 to 2 percent of patients.

Combination chemotherapy or the addition of tamoxifen or alpha-interferon have not proven to be superior to DTIC alone.

[Slide.]

High dose IL-2 produces durable responses in a small percentage of patients, mostly previously untreated, performance status zero patients.

Low dose IL-2 alone has limited effectiveness.

Biochemotherapy increases the response rate and the toxicity, but its effect on survival remains uncertain.

In addition, improved tumor response rate has yet to be correlated with improved median survival.

[Slide.]

In conclusion, metastatic melanoma truly is a bad disease. Patients with liver metastases comprise a group of patients with especially poor prognosis. Finally, no treatment to date has an established survival advantage.

Thank you very much.

Questions?

DR. NERENSTONE: Why don't we save our questions for the end of the presentation.

DR. ATKINS: Thank you.

DR. GEHLSON: Thank you very much, Dr. Atkins. That was very helpful.

Efficacy and Safety of Histamine Dihydrochloride for Injection as an Adjunct to Interleukin-2 in Patients with Metastatic Melanoma

[Slide.]

I could imagine your reaction the first time that you heard that we were going to inject patients with histamine in combination with any kind of therapy because I can tell you our first experience at the initial PI meeting was rather remarkable, but there is in fact a rationale for the use of histamine in the treatment of certain cancers and other diseases in combination with immunotherapeutics.

[Slide.]

We have known for years that many tumor types are immunosuppressive. In fact, there are a number of hypotheses that try to describe this particular immunosuppression that these various tumor types can cause.

What our principal scientists have been working on over the last 18 years is a method by which tumors recruit large numbers of phagocytic cells like monocytes and macrophages, and it has been shown that monocytes and macrophages in and around the tumors can actually suppress significantly human lymphocyte functions.

In particular, monocytes and macrophages will actually block natural killer cell-mediated tumor cell lysis, it will block natural killer cell anticell proliferation and activation, it will also block natural killer cell and T cell cytokine production.

What happens? We have cytokines trying to stimulate cells that can't be activated. So, histamine was actually developed to reverse the immunosuppression and to protect NK cells and T cells from this induced inhibition caused by monocytes and macrophages and restore the responsiveness to interleukin-2 or other cytokines.

[Slide.]

There is a very simple illustration here of how dramatic this suppression really is. If you mix Daudi cells, which is a human B cell lymphoma cell line, with human natural killer cells, you can actually see that the natural killer cells can kill these Daudi cells and without any activation, but when you add interleukin-2 or interferon alpha, you can see you can dramatically stimulate their killing activity. This is a very interesting result.

[Slide.]

But if you look at the literature, you will notice that in certain tumor types, like colorectal cancer, breast cancer, and melanoma, the more monocytes that you have in the tumor, the worse the prognosis is for the patient.

This didn't quite make sense intuitively, but if you will take the same experiment and you add monocytes with the natural killer cells and the Daudi cells, you will see that the monocytes completely suppress the ability of the natural killer cells to kill the Daudi cells and you can't overcome the suppression with interleukin-2, a vaccine, or any other cytokine.

So, we need to solve that problem, and that is the goal of histamine is to solve that particular problem.

[Slide.]

What we have learned is that monocytes and macrophages, through an NADPH oxidase, they convert oxygen to the reactive oxygen metabolites. Well, it turns out that these reactive oxygen metabolites can rather significantly induce apoptosis in the NK cells and T cells, and, of course, if you are apoptotic you cannot respond to interleukin-2 or other cytokines.

[Slide.]

Now, if you want to restore that function and reverse the effects caused by monocytes and macrophages, you do a similar experiment. You have Daudi cells now in the presence of natural killer cells and monocytes. Again, interleukin-2 is ineffective at stimulating the killing activity, but as you can see here, histamine can response that killing activity.

[Slide.]

You can also restore their proliferative activity both in T cell and NK cells. Interleukin-2 is ineffective in the presence of monocytes. Again, that is reversed by the addition of histamine.

[Slide.]

Finally, if we look at a secondary cytokine production like interferon-gamma, we see the same thing. Now, what we have done here for a control is we actually added an H2 receptor blocker ranitidine, and that eliminates the effect of histamine, so this is an IL-2 alone control. It also proves that this phenomena works through the H2-receptor on these cells.

Again, the addition of histamine restores cytokine production.

[Slide.]

Now, if you look at apoptosis--and this is key--if you look at the percentage of cells, T cells or NK cells, that are apoptotic, that means they are going into program cell death in the presence of monocytes, you can see that 60 percent of T cells are apoptotic and 90 percent of the NK cells, however, as you increase the concentration of histamine, you can actually restore their normal function.

[Slide.]

So, what we have actually learned over the last 18

years is that histamine, through the H-2 receptor on these cells, will disrupt the NADPH oxidase enzyme, so these cells cannot make the reactive oxygen metabolites that are downregulating T cells and NK cells.

By doing that, you offer some favorable characteristics for these cells. One, they are viable; two, they can now respond to interleukin-2 and other cytokines in and around the tumor, and that is where they need to respond, and we maintain their function.

[Slide.]

Now, we have also done a series of animal studies, and I won't go into great detail on the animal studies because I know we need to get to the clinical data, but just as an example, in a B16 mouse melanoma model, if you inject 100,000 of these tumor cells by tail vein into these mice, within about four weeks you are going to get a significant number of lung tumors.

After the injection, if you actually wait three days for the tumors to establish, and then you treat those animals with either one dose of histamine, one dose of interleukin-2, or the combined, you can see you can dramatically reduce their tumor burden in this experimental model. But let's get into the clinical trials.

[Slide.]

We have been doing clinical trials for quite some

time, actually, for the last 11 years. Histamine has been tested in combination with interleukin-2, alpha-interferon, or both together in a number of patients, in metastatic melanoma, acute myelogenous leukemia, renal cell carcinoma, and even in hepatitic C.

We have ongoing or completed 15 clinical trials to date in a total of 1,253 patients. 817 of those patients have been treated with histamine. We have completed or have ongoing six, Phase II or III advanced melanoma studies. 413 of those patients have been treated with histamine, 162 of those patients actually have liver metastases.

We have completed two pharmacokinetic studies and two special population PK studies, as well, and all of this information has been provided in our NDA. But most notably, all patients that have been treated in any study with histamine are included in our safety summary.

[Slide.]

Now, I would like to spend a couple minutes on the early studies that got us here in the first place. These studies were initiated by Dr. Peter Naredi in Sweden. They are single center studies.

The first study we call MM1. The goal of this study was to take a continuous IV infusion regimen of interleukin-2 plus alpha-interferon plus or minus histamine in patients with advanced metastatic melanoma.

As you can see, there was an improvement in survival for the patients in the histamine group, but more remarkable to us, and because Peter is a liver surgeon, he noticed that the three patients in the control group that had extensive liver metastases had absolutely no response in the liver in particular, but anywhere else, but of the two patients that had extensive liver metastases in that first study, in the histamine group, they both had very extensive liver metastases. In one case, the patient had more than 200 tumors in the liver alone, and they were both CR's in the liver, and they both exceeded a 16-month survival duration.

The difficulty with this particular regimen, though is the high dose cytokines come with significant toxicity, and so it was proposed, if our hypothesis was in fact true, we might be able to lower the dose of the cytokines, maintain the survival benefit, but reduce the toxicity, and that was the goal of MM2, our second study.

Now, we weren't allowed to do a control arm, so this is a single-arm study of course in 27 patients. These patients had failed all prior therapy. Thirteen of these patients had liver metastases.

Now, when we look at the patients combined from the two studies that had liver metastases, they have a median survival of 10.8 months. That is a survival duration

that is unexpected for a population like this, as you have just seen from the results that Dr. Atkins has shown.

[Slide.]

If we look a little more closely at these patients, we see that if we look at the number of metastatic sites and their overall response, we see that there were 5 patients with one metastatic site, 5 patients with two metastatic sites, and 5 patients with greater than two, and we had 5 PR's, 4 stable disease, and 6 progressive disease.

If you look specifically in the liver, you can see we had 2 CR's in the liver, 3 PR's in the liver, 6 patients with stable disease, and 4 progressive disease. Again the median survival was unexpected.

[Slide.]

So, we conclude from our earlier work, and this also includes our conclusion from our AML studies and other studies we have done, that histamine can, in fact, be safely administered in combination with interleukin-2, alpha-interferon either together or alone.

We also noted that patients with liver metastases experienced a longer survival duration than would be expected.

So, we came to the conclusion that patients with liver metastases certainly should be explored and analyzed in our subsequent studies.

[Slide.]

Now, the question always comes up why do patients with liver metastases do worse. Well, we really don't have an answer to that, and Dr. Atkins has alluded to that, but there are a couple of things we do know, and it may be that the liver is a unique organ for several reasons.

One, it is not a favorable environment for a tumor, and it is certainly not a favorable environment for your immune system when the liver is diseased, because the liver is an organ that has significant oxidative stress. It not only has the macrophages and monocytes, but it also has an endogenous cell, the Kupffer cell that makes free radicals.

We know it is part of the reticular endothelial system, and so it has an abundant pool of lymphocytes actually that could be activated to fight off disease. It is an ideal situation for us to prove that histamine is an adjunct to cytokines because of this environment of oxidative stress, but also, most importantly, and this was also highlighted in our discussions with the FDA, it is very, very difficult to prove a survival benefit in a very heterogeneous population like melanoma.

You are going to have patients that are not going to do very well, they are going to die in a matter of weeks, and you have other patients that are going to do quite well

and live for a number of years regardless of treatment.

The liver metastases population is a very homogeneous population. They are typically going to live four to five months, there is no effective treatment today for these patients, and so it sort of homogenizes the population down, and if we can see a treatment effect for histamine, we should see it in this patient population.

[Slide.]

So, our objective in our Phase III trial was to prove that the addition of histamine to a subcutaneous regimen of interleukin-2 will improve the survival duration of patients with metastatic melanoma over treatment with IL-2 alone. We wanted to do this, of course, with an improved quality of life and without any added toxicity by the histamine.

[Slide.]

This was a multicenter, randomized, prospective, open-label, parallel group study to evaluate this combination in advanced metastatic melanoma patients. It is a very simple study. We tried to keep it simple. We wanted to randomize patients. All patients were randomized to interleukin-2 and one-half of the population got histamine.

Because survival was the primary endpoint, no crossover was allowed.

[Slide.]

Survival was prospectively then defined or the endpoint with survival applied to two prospectively defined populations, the overall intent-to-treat population and the intent-to-treat population of patients who had liver metastases at baseline.

We, of course, adjusted for multiple hypotheses. We also, of course, looked at traditional secondary endpoints, as well.

[Slide.]

Now, there is some speculation about whether or not this was a prespecified subgroup population. In our original protocol and in our original IND, we actually stated in two places, on page 33, that "Patients will be stratified in subgroup analyses accordingly: (a) presence with liver mets or not..." and on page 64, in another section, "Results will also be displayed stratified by patients presenting with liver metastases versus patients with no liver metastases."

I agree that this is not a very good description of what it is our intent, but actually it was very clear what our intent was, and that is to look at the patients with liver metastases.

[Slide.]

Now, the FDA, we have been discussing this for some time, and they acknowledge this subgroup actually in

the April 23rd dissertation on page 6 of the briefing document, where we decided not to prestratify for liver mets, but we would perform subgroup analyses based on the presence or absence of liver mets.

What we really wanted to do is defer to a statistical analysis plan because we did not know how we were going to divide up our alpha in this particular study. So, the statistical analysis plan actually evolved over a period of time in collaboration with the FDA actually, and our final statistical analysis plan, which was submitted November 18th, and finally accepted by the Division on December 17th of 1999 was very clear.

[Slide.]

We were able to clarify that our intent, the null hypothesis will be tested in two patient populations within the framework of the study. All randomized patients and all randomized patients with liver metastases at entry, on an intent-to-treat basis, and again we would adjust for multiple hypotheses.

Now, also regrettably, there was no prestratification for liver metastases, and there was no prestratification for any other prognostic factor. In hindsight, I will take that one to my grave.

But we did a lot of good things. All site, medical and data monitoring was done by the CRO. The

sponsor had no access to the data, in fact, we were completely embargoed from any efficacy data until a month after the data cutoff date, which was March 8th, 2000.

We did have a Data Safety Monitoring Board in place that monitored safety and efficacy in one closed interim analysis, so we were not privy to the results of that efficacy review, but on a monthly basis they did, in fact, review safety. But at the end of the day, there was no data available to either the CRO or the sponsor that could have influenced the final statistical analysis plan.

[Slide.]

Now, there is a rationale for a treatment regimen using interleukin-2. You have to remember we designed the study to show that histamine is an adjunct to interleukin-2. We weren't trying to show that sub-Q IL-2 and histamine is better than high dose IL-2. That would have been the wrong question. That wouldn't have been one we could have answered anyhow because most of the patients available today are intolerant or are ineligible for high dose IL-2, so to run a randomized study with that patient population would be very difficult in this kind of a disease.

What we wanted to do is observe a histamine effect. We also wanted to make sure that we were paying attention to receptor of biology, and we also wanted to make sure we were paying attention to the current practice of

sub-Q IL-2 in the clinic today because still many investigators use subcutaneous regimens of interleukin-2.

So, on weeks 1 and 3, days 1 and 2, we gave 9 milli-International units per meter squared twice a day. Then, on alternating weeks 2 and 4, we gave 2 milli-International units per meter squared twice a day, days 1 through 5.

Histamine was given on weeks 1 through 4, 1 mg, as we have always done in our Phase II trials, BID, 5 days a week. As has been mentioned, we actually gave our patients a rest on weeks 5 and 6, and each treatment cycle was 6 weeks.

[Slide.]

Our entry criteria are not remarkable. This is a trial where we wanted to include as many advanced melanoma patients as we possibly could. I think the only notable exceptions are that we actually allowed the patients who have had any prior therapy except for prior interleukin-2, which would have been, of course, unethical.

We also allowed patients to have brain metastases if they were controlled by surgery or gamma knife, and the patients were required to be scanned by MRI to make sure that they didn't have brain metastases.

I think also notable and different from any other trial that I have seen in advanced melanoma is we allowed

patients who had ocular melanoma with systemic metastases also in this study.

[Slide.]

We enrolled 305 patients in 56 centers all in the United States between July 1997 and March 1999. The analysis cutoff date was 12 months after the last patient was enrolled. That was March 8, 2000. We also would evaluate survival until all patients had died, and our next survival update was actually September 8, 2000, and we have provided that data, as well.

[Slide.]

If we look at the patient characteristics, this was, in fact, a randomized trial, so we have similar numbers of patients between the two groups, and as one would expect for age, gender, male, performance status of 1, albumin, or LDH, there are slight imbalances between the two groups. None are statistically significant, but those that you would expect in a randomized trial.

[Slide.]

If we look at prior chemotherapy, anticancer therapy, number of organ sites 1 or greater than 2, and disease sites, essentially, there is no real significant difference between the two groups except for 1, and it is unfortunate and we were unlucky because we didn't pre-stratify, it was, in fact, in the liver met population, but

we can test that.

[Slide.]

If we look at the demographics for the liver metastases population, there is an imbalance in the "n," however, if you look at the trends for any imbalance in the demographics between the group, they are actually consistent with what we saw in the intent-to-treat population, so they carried over. Notable, however, though, LDH actually favored the interleukin-2 group.

[Slide.]

The same thing for prior chemotherapy and some of these other demographic factors, they are actually balanced between the two groups. There is one also that we need to explore further, and that is the number of organ sites 1.

[Slide.]

Now, this is the Kaplan-Meier survival distribution curve for the intent-to-treat population at 12 months of follow-up. As you can see, there is a trend for improved survival overall for the histamine and IL-2 group, but it did not achieve statistical significance.

If we look at the number of patients at risk, there are more patients in the histamine and IL-2 group than in the IL-2 alone group.

[Slide.]

However, when we look at the patients that had

liver metastases at baseline, we see that there is a dramatically statistically significant improvement in their survival, and even when we adjust for multiple hypotheses, it is still statistically significant. Also, again, there are more patients possibly alive in the histamine and IL-2 group over the IL-2 alone group.

[Slide.]

Now, this asks the obvious question, what happened to those patients who did not have liver metastases. That is a fair question. As you can see here, there was no difference in the survival between the two groups for the patients that did not have liver metastases.

[Slide.]

So, we can summarize for median survival. As we improve median survival from 245 days to 272 days by the addition of histamine, it was not significant, but for the liver metastases patients, we actually improved their survival by 84 percent, and it was statistically significant.

[Slide.]

Now, we have to test because we do have a number of imbalances and we actually had prespecified in the statistical analysis plan those covariates that we would actually test in the Cox proportional hazard model.

[Slide.]

This is looking at the univariate of treatment effect for the intent-to-treat and for liver metastases intent-to-treat, and you see there is a reduction of risk of about 18 percent with the treatment of histamine, but is not statistically significant, but there is a significant reduction in risk for patients treated with histamine in the liver metastasis population.

[Slide.]

Now, the covariates that we have prespecified, of course, are those that are actually typically used as prognostic factors. We did include age greater than 65, gender of male, prior chemotherapy, prior anti-cancer therapies, LDH, and we used a dichotomous form of LDH because we had to normalize all of our values to the upper limit of normal, which is the way it is typically done, and baseline performance status, as you can see, those two are actually significant predictors of outcome.

[Slide.]

We also looked at number of disease sites, 1 versus greater than 2, and 2 versus greater than 2. We looked at race, and then we listed each one of the disease sites individually.

When you adjust for all of these covariates, the treatment effect for histamine and IL-2 is still significant.

[Slide.]

Now, the FDA in their analysis, of course, they should do this. They actually identified several new covariates from our database, and these are listed here. Notably, albumin has been identified as a prognostic factor in certain cancers. We haven't picked it up as a consistent one in melanoma, so we excluded it from our model.

They listed visceral and non-visceral, which is a little bit different. We listed each metastatic site individually. The two that are actually somewhat problematic are disease-free interval. They are not problematic because they can't be used as covariates, but problematic because the literature suggests that the disease-free interval is, in fact, a significant prognostic factor, and that is time from diagnosis to time or recurrence of the first metastatic disease.

Now, we don't have that data in our database. The data we have in our database is time from diagnosis to time of diagnosis of Stage IV melanoma. So, by a traditional definition, we don't know what our data really means, so we will call that covariate Q.

Now, time from initial metastasis to randomization, our database doesn't support that one either, and so we call this one covariate X as we don't have the data from time of initial metastasis to randomization, but

we do have time from Stage IV disease to randomization.

Finally, in some of their Cox proportional models, they transformed LDH using a log transformation whereas we have used the dichotomous form because we did not use a central laboratory in our studies, so we actually had to normalize everyone to the upper limit of normal because it is abnormal LDH that is the significant prognostic factor.

[Slide.]

Now, the FDA also did a very good analysis. Their Table 11b on page 17 of the Statistical Review Section allows us to look at their selection of covariates, but also add an interaction term.

Actually, the ICH guidelines suggest that if you have a prespecified subgroup, you actually can use a statistical model that has an interaction term as a confirmatory analysis. So, since this was a prespecified subgroup, this analysis could be quite useful.

What this analysis tells us is that at first, if you look at disease site liver, now, this is the intent-to-treat population, and what it is saying is that the imbalance, namely, the patient imbalance between 74 and 55 patients was not a significant predictor of survival or outcome.

If you look at treatment by liver met interaction, this is also very interesting because this has a ratio by a

definition for an interaction with a significance level of 0.1, which suggests that, in fact, there is a differential between patients with liver metastases and patients who don't have liver metastases.

Finally, and most notable in this, is the treatment arm, because this treatment arm represents those patients who do not have liver metastases. This is not the treatment effect in the patients with liver mets, but this is what we expected, and I have already shown you in the Kaplan-Meier estimates that there is no effect in patients who did not have liver metastases.

[Slide.]

So, if we take that same table and we change this interaction term to treatment in the patient population who have liver metastases, we see that, in fact, there is a significant effect for those patients when we add the appropriate parameter.

So, this data, in fact, is supportive of the Kaplan-Meier estimates that I have already shown you in the Cox proportional hazard model that we had done.

[Slide.]

Now, the Statistical Review Group also suggested possibly that the overall benefit may have been restricted to a subpopulation of patients, and I think that this is a good analysis because our objective was to show that when

you add histamine to interleukin-2, you can improve the efficacy of interleukin-2.

It shouldn't matter whether the patient has one tumor or five metastatic sites because once it metastasizes to the liver, it is probably the pacing organ that represents really this overall status of the patient, and that is evident here because if you look at the patients that have only one disease site liver, their median survival is only 3.8 months, however, in the histamine group for those 13 patients, their median survival is 16.6 months, 4 times more than one would expect.

Now, the study wasn't powered for such subgroup analyses, but if you look at patients with greater than one metastatic site, we do see a nice trend for improved survival from 5.5 months to 7.7 months.

[Slide.]

We can look at this in the Kaplan-Meier curves. The purple line is the histamine group with one disease site and the blue line is the IL-2 group with one disease site, and we improved survival, as I mentioned, from 117 days to 508 days, and was dramatically significant.

If you look at the green line, that is histamine with more than one site versus IL-2 in the red line with more than one site, you can see that there is, in fact, a strong trend for improved survival even in the

subpopulation.

So, we would conclude that the addition of histamine to a sub-Q regimen of interleukin-2 significantly improved survival in patients with liver metastases.

The Cox Proportional Analyses adjusting for significant covariates further supports the treatment effect of histamine in the liver metastases population.

In fact, these data met the pre-established criteria by the FDA for a compelling survival benefit, which was defined as a greater than 50 percent increase in the median survival duration, so a single trial with this compelling benefit could be supportive for approval.

[Slide.]

Now, we also did secondary endpoints, and I will go through those briefly. Time to disease progression in our study was defined as time from date of randomization to first observation of progressive disease or death due to melanoma.

We also noted that this was also called time to first progression. I don't want to confuse anyone. It really is time to disease progression.

Time to treatment failure was also highlighted as time to last progression, but it is really time to treatment failure. That is time from date of randomization to the last observed progressive disease resulting in removal from

study or death due to melanoma.

Now, we had a caveat, of course, in here, because this is immunotherapy and if you really think about it, response rates may not be that reliable in immunotherapy. This is not a cytotoxic drug. We are not going to see immediate response rates.

In fact, if you think about it, if you have a tumor with a billion tumor cells, what are we asking that tumor to do? We are asking it to take out another billion lymphocytes to kill the tumor. So, early on it actually could look larger, it could look like it has progressive disease.

[Slide.]

So, we asked that the investigators not evaluate for a response because it was a secondary endpoint until after two cycles of treatment, and if they looked like they had progressive disease, but there wasn't a significant deterioration in the Karnofsky status or their performance status by WHO, they could actually continue on the treatment with progressive disease and be reevaluated at each cycle.

So, our disease progression is slightly different because it is based on changes in tumor dimension plus performance status.

[Slide.]

As you can see here, when we do the Kaplan-Meier

estimation here, we see a significant improvement for patients in the intent-to-treat population for time to disease progression.

[Slide.]

For time to treatment failure, we also see a statistically significant improvement for the intent-to-treat population.

[Slide.]

For the patients with liver metastases, we also see a significant improvement in time to disease progression.

[Slide.]

We also see a significant improvement in time to treatment failure for those patients with baseline liver metastases.

[Slide.]

We also looked at response rate. Traditionally, as Dr. Atkins said, we have seen good response rates with a number of trials, but it hasn't correlated to survival. We are going to ask you to think a little bit differently. We are going to show you a survival benefit, but it doesn't have the corresponding response that you might expect, but maybe we have to look at it a little bit differently because again this is an immunotherapeutic, this is not a cytotoxic drug, so CR and PR rate may not be as important to these

patients as actually stable disease or minimal regression.

[Slide.]

So, if you look at patients that have a lack of disease progression, this is something that we are going to have to evaluate for patients with immunotherapy or anti-angiogenic factor so some of the other biologics.

If you combine the CR, PR, and stable disease, you see that there is a trend for improved response rate in these patients, and that may explain in part the survival benefit.

If we look at the liver metastases population, we look at lack of disease progression, we see the same thing, that there is a trend for improved responses in these patients or a trend towards improvement in lack of disease progression.

[Slide.]

Now, we need to look at safety, of course.

[Slide.]

Again, you can imagine Dr. Agarwala when he first injected his first patient, he actually had a crash cart there because he thought every patient was going to go into anaphylactic shock, and after now more than 1,000 patients or nearly 1,000 patients treated with histamine, we can tell you that the majority of adverse events were expected based on the physiological side effects of histamine, and they

were mild to moderate in severity.

These histamine-related adverse events were, in fact, transient. They lasted 30 to 60 minutes. They didn't require any treatment by the patient and they were without any sequelae. What you would expect happened actually. Patients would flush. It is a vasodilator. Because it is a vasodilator, you get a slight drop in blood pressure, which can cause the heart rate go up.

Patients do get an injection site reaction, a slight pulsatile headache, of course, dyspepsia, which we ask that they actually pre-treat with a proton pump blocker, of course, not an H2 blocker like Prevacid or Prilosec, dizziness, and rhinitis.

[Slide.]

If we look at the incidence of severe adverse events, Grade 3 and 4, what I have done here is selected out those that mirrored what Dr. Atkins actually had in his paper, looking at high dose IL-2.

Now, I don't want to compare high dose IL-2 to our treatment, but I want to show you that the addition of histamine to this regimen of IL-2 did not increase the incidence or severity of Grade 3 or 4 adverse events when we talk about cardiovascular events, GI events or neurological events.

[Slide.]

The same is true for pulmonary serious adverse events, hepatic adverse events, or renal adverse events. There is no difference when we added histamine between the two groups.

[Slide.]

Finally, if we look at the hematological, the skin, or in general, there was no increase in the number or severity of adverse events that are Grade 3 and 4 by the addition of histamine.

[Slide.]

If we look a little closer at the overall population of patients that were enrolled, we look at Grade 4 toxicity, the majority of patients that had Grade 4 toxicity, it was due to progressive disease of their melanoma. There are very few patients that had Grade 4 toxicity that was related to study drugs.

If we look at Grade 3 toxicity, we have fewer patients where Grade 3 toxicity is related to melanoma, and those are related to study drugs.

[Slide.]

If we look at the number of patients who died on study or within 28 days of receiving study drug, we see that in the intent-to-treat population, in the IL-2 group, there were 15 patients and 16 patients in the histamine group, and there was identical numbers of patients in the liver met

population. The patients that actually died were scored as dying due to melanoma was mostly the majority of these patients. Very few patients died within 28 days due or related to study drugs.

[Slide.]

So, we didn't observe any adverse events that were unexpected. Most AE's were mild to moderate in severity. The differences between the two treatment arms were mostly due to expected physiological side effects.

The addition of histamine to sub-Q IL-2 was safe and well tolerated in these patients with advanced melanoma in an outpatient setting. This also could provide a significant cost benefit for these patients, as well.

[Slide.]

Finally, we also built in quality of life into our study, and we used a Quality of Well-Being instrument, and our hypothesis early on was the addition of histamine would not negatively affect the patient's quality of life.

[Slide.]

Now, we chose the Quality of Well-Being scale because it is a perfect test for the study that we were trying to do. It is an outpatient therapy and the symptoms and the problems that this instrument actually identifies are exactly those related to the histamine side effects.

It is a 76-item questionnaire and it is

administered by the patient at the start of each cycle. The other important characteristic for this instrument is the fact that it also includes death. It includes mortality and morbidity into a common unit, so it scores zero for death and 1 for optimum health.

[Slide.]

So, if we look at the median predicted mean Quality of Well-Being scores for patients in the intent-to-treat population, we see that the addition of histamine did not adversely affect the quality of well-being of these patients in the intent-to-treat population.

[Slide.]

If we look at the quality of well-being scores for the liver metastases population, however, we see a different picture. We see, in fact, that patients had a significantly improved quality of well-being in addition to improving their quality of survival.

[Slide.]

Now, you can take the area under those two curves and you can actually do median quality-adjusted survival, and you can see that for all randomized patients, if you look at their median quality-adjusted survival, it was improved by 31 days, and it was statistically significant.

If you look at those patients that were randomized with liver metastases, we improved their median quality-

adjusted survival by 50 days. That was also statistically significant.

[Slide.]

So, we conclude that the addition of histamine to sub-Q IL-2 is safe and significantly improves survival of patients with liver metastases without added toxicity or a decrease in their quality of life.

[Slide.]

Now, I am going to touch on the interim efficacy update. We actually updated our Phase III study, the MO1 study, on September 8, 2000, which is 18 months of follow-up, and I also will now, after that, show you the Phase II study. I can give you interim results on that one, and we hope that that will be used as a confirmatory study.

[Slide.]

If we look at the survival in the intent-to-treat population at 18 months, we still see that trend for improved survival, but now the p-value is 0.0526.

[Slide.]

If we look at the survival distribution curves at 18 months for the liver metastases population, we see what we saw earlier, a very significant improvement in survival even when adjusted for multiple hypotheses.

[Slide.]

If we update Table 11b with the 18-month data, we

see that the treatment effect in the patients with liver metastases at 8 months maintain the same level of significance using this set of covariates.

[Slide.]

Now, our single-arm study was in direct response to wanting to do a confirmatory study, when we went out to do the feasibility on a confirmatory study using the same dose of regimen of interleukin-2 and histamine, we found that in the melanoma population, because of all the clinical trials that are going on, many of those being single-arm, Phase II studies, it would be very difficult to continue to do a randomized study with this treatment regimen.

So, we actually went out and did a Phase II study as a single-arm study using the same treatment regimen as the Phase III. The only notable difference is that also patients who had prior interleukin-2 therapy were also eligible for this study.

At the time we submitted the NDA, there were 39 patients evaluable for the NDA, and as of September 8th, we actually had 88 patients that would be evaluable with a median of five months follow-up.

Today, we actually have 125 patients enrolled because our clinicians have asked that we keep this protocol going while we wait for approval of this drug.

I can tell you also the patient demographics are

very similar to those between the two arms in the Phase III study. The only difference is 30 percent of the patients had actually received prior interleukin-2 therapy in addition to their other prior therapies.

[Slide.]

Now, really all we can do in this particular series is overlay the old Phase II data for the histamine and IL-2 group on top of the data for the Phase III trial, so this is the exact data I showed you at 12 months for the Phase III trial, and in black, tracking nicely the treatment arm are those 39 patients in the intent-to-treat population from 0103.

[Slide.]

We can do the same thing for the liver met population although this is a very small number, there were only 10 patients at the time, but again they tend to track the survival curve for the histamine group.

[Slide.]

Now, at 18 months, we have updated the MO1 study at 18 months, so this is the curve I just showed you earlier for the 18-month survival data for the Phase III study.

What we have done now is we have 33 patients that had liver metastases of those 88 patients, and we have overlaid those as an interim analysis on top of the survival distribution curves for MO1. Again, they seem to confirm

the benefit seen in the Phase III trial.

[Slide.]

So, to summarize, I think we have actually reproduced this result three times. In MM1 and MM2, if we look at the 15 patients that were treated with histamine, we have a median survival of 10.8 months.

In our Phase III trial, our MO1 control had 74 patients, and the median survival was 5 months. It is very consistent with the literature which shows that the median survival regardless of treatment today for advanced melanoma with liver metastases ranges from 2.4 to 4.7 months.

This last reference represents only ocular melanoma patients with liver metastases. If we look at the 55 patients from MO1 that had liver metastases, their median survival is 9.1 months, and if we look at the median survival at the interim efficacy evaluation for this Phase II study for those 33 patients, the median survival is 10 months.

So, we think and we believe that this result is, in fact, reproducible in three separate studies.

[Slide.]

Our overall summary would be that the combination therapy with histamine plus IL-2 significantly improved survival of patients with liver metastases, it significantly improved time to disease progression, it significantly

improved time to treatment failure, it significantly improved meeting quality-adjusted survival, and we believe the interim results actually confirmed the favorable survival benefit seen in the randomized trial.

[Slide.]

We think we have addressed the key concerns that have been raised, that the liver metastases population was, in fact, prespecified. This is a very large, well-controlled trial for advanced melanoma and survival was the primary endpoint. This had not been done before we had started this study.

We did have a Data Safety Monitoring Board involved monitoring safety, and they did one interim efficacy evaluation that was closed to the company.

We also had the outside CRO monitoring the data and monitoring the sites and medical monitoring this study.

We believe that the Cox models do, in fact, support the treatment effect.

So we believe that treatment with histamine plus IL-2 in the liver metastases population does, in fact, provide a compelling result.

[Slide.]

So, as you heard earlier from the patients and Dr. Atkins, there is no established standard of care today. The treatment options are rather limited for patients with

malignant melanoma.

We think that the addition of histamine plus IL-2 did provide a significant clinical benefit by the definition that we improved survival and we did so with a quality of life, in an outpatient setting that could be cost effective, for patients with liver metastases.

There is absolutely minimal risk to this patient population by adding histamine to sub-Q IL-2 with a huge potential benefit.

[Slide.]

So, we ask that you consider proposing that histamine be approved as an adjunct to interleukin-2 for the treatment of adult patients with advanced melanoma that has metastasized to the liver.

[Slide.]

We have a number of people to thank. We couldn't have done this without all these people listed here especially our patients.

Thank you very much.

DR. NERENSTONE: Thank you, Dr. Gehlson.

What I would like to do now is to open up questions from ODAC to the sponsor.

Dr. Dutcher.

Questions from the Committee

DR. DUTCHER: Could you please clarify a few

things in terms of the conduct of the study. Maybe I just missed it, but I didn't get a sense of where were the ocular melanoma patients in terms of the two treatment arms and how many were ocular melanoma metastatic to the liver?

DR. GEHLSON: Thank you. That is a very good question.

Ocular melanoma patients were allowed and they were equally distributed between the two groups. There were 15 patients in the histamine/IL-2 group that had ocular melanoma and 14 patients in the IL-2 alone group, and those patients with liver metastases was equally distributed with 13 patients in each arm.

DR. DUTCHER: Could you also comment in terms of the treatment management how long were patients were kept on study, in general, what was the median time, and also who made decisions about dose reductions, how were the dose reductions done, were doses skipped, you know, how much treatment did these patients actually get?

DR. GEHLSON: That is a very good question. Of course, it ranged from zero to beyond the 12 months which was specified in the protocol, as you heard, Joel, one of our patients, actually went into two extension protocols and beyond.

On average, the average number of cycles was I believe three--is that correct--three cycles for both arms,

and the decision about whether or not there was a dose reduction and how long a patient would actually remain on therapy was the decision that was made by the clinician and the nurse and the patients themselves.

In fact, if you would like, I would actually like to have Dr. Agarwala comment on those decisions on whether or not to keep the patients on or not.

DR. DUTCHER: [Off mike.]

DR. GEHLSON: We asked in the protocol, of course, that the patients receive a minimum of two cycles of therapy before they would be evaluated for a response. After that evaluation, of course, it was their determination if they had progressive disease whether or not to keep the patient on study or to remove that patient.

If they did keep that patient on study with progressive disease, they were to monitor for response at every cycle. Again, that decision was really made by the clinician and the patient themselves.

For dose reductions, the same thing took place. If there was a dose reduction for interleukin-2 or for histamine, those decisions were made by the clinicians themselves and we had prespecified for toxicity in the protocol the kinds and types of dose reductions depending on the type of toxicity.

DR. DUTCHER: Could you also comment on your

slides 98 and 99? It seems to be that a fairly large number were considered not evaluable for tumor response.

DR. GEHLSON: Yes. The patients here that are listed as non-evaluable were those patients that actually had died or had not completed at least two cycles of treatment, so they never made it to their first evaluation.

DR. NERENSTONE: A question about those patients, the ones who were not evaluable. Were they followed for survival, are they included or excluded on your survival data?

DR. GEHLSON: That is a very good question. All patients, because it was an intent-to-treat analysis, all randomized patients are included in the survival analysis even those patients that were not evaluable for a response by the first evaluation period.

DR. DUTCHER: One more question and then I can let someone else ask questions.

In the FDA evaluation, they found a fair number of people that they would consider performance status 2, and clinically, that is quite different from performance status 1, so could you tell me, first, if you agree with that, and second, if you do, where were those patients in terms of distribution in the two arms?

DR. GEHLSON: I would have to actually defer to see if we have that data broken down that far.

The question was for patients with performance status 2, how many were there, and were they equally distributed between the two treatment arms.

Dr. Dutcher, if it's okay, we will see if we can find that data for you.

DR. DUTCHER: One more question. When you are talking about response, you are talking about all sites of disease?

DR. GEHLSON: All measurable disease, yes.

DR. NERENSTONE: Dr. Redman and then Dr. Simon.

DR. REDMAN: To ask a similar question in another way, despite the time on treatment, do you have the median number of cycles in each of your arms that the patients received?

DR. GEHLSON: Yes, we do. Actually, the median number of cycles for the interleukin-2 group was 2.8 cycles, and the median number for the treatment group was 3.0 cycles.

DR. REDMAN: Thank you.

DR. NERENSTONE: Dr. Simon.

DR. SIMON: I am very puzzled by this data. I guess the thing that is most puzzling to me is that initially, it looks like the FDA suggested that you stratify by liver involvement. The company did not want to do that, stratify the randomization.

Then, you go ahead and do the study and you wind up with a very extreme difference in the number of patients on the two treatment groups in the liver involvement subset, a difference that is actually statistically significant at like the 0.01 level.

So, that raises three concerns for me and maybe you can address at least a couple of them. One is whether it was a valid randomization. So, I would like to hear details about the randomization and who did it and how it was carried out.

Secondly, it raises a concern for me as to how was the assessment made that a patient had liver involvement and who made that assessment.

Thirdly, to me it puts in question all of your analyses of the liver subset, liver involvement subset, because given that imbalance in overall numbers of patients in the two treatment groups, and to me which other very substantial imbalances in the prognostic factors for the two treatment groups within that subset, you have dismissed that there are imbalances, but I believe there are serious imbalances.

I don't believe that adjusting for those imbalances adjusts for the unknown imbalances that probably exist given the overall imbalance in numbers. So, at least I would like to hear some details about how the

randomization was done and how the assessment of liver involvement was done.

DR. GEHLSON: Thank you very much. I appreciate that question. The CRO that we used actually used a central randomization procedure, and each site had randomization codes in blocks of four, so the investigator, once a patient was identified, the investigator would call the central randomization desk, they would be given a treatment code. That code would then determine which treatment arm that patient went into.

So, everything was done--none of the investigators, it was not specified in the protocol what the randomization blocks were in or anything like that, but it was done by a site, a center basis, and it was done through a central procedure, not by the sponsor, of course.

The patients with liver metastases were actually evaluated at baseline because in order to determine what the extent of their disease was, liver metastases, of course, if they were there, would be captured in their baseline assessments, and that is why it is patients with liver metastases at baseline before randomization, so then once they are randomized, they go into either treatment arm and no one could actually select patients to put into either one of the arms.

All the patients, of course, would have had CT

scans for those disease sites, so they would have been assessed at pre-study before they were randomized.

DR. LIPPMAN: I have a question that gets to the biologic plausibility of the histamine finding specifically in the liver.

Since we are basing a lot of this obviously, even if it is preplanned, a subgroup analysis, it would be helpful if we had very strong biologic plausibility, not for the fact that liver disease does worse, but for the histamine effect specifically there.

I may have missed this, but you mentioned some work with reactive oxygen species, oxidative stress, I think. Well, there is a lot of oxidative stress in the lung, as well, so I think that if we are really looking at this subgroup, it would help to feel confident about the biologic plausibility of the finding with this drug.

DR. GEHLSON: That is an excellent question. Unfortunately, we are not able to appropriately measure free radical production in these cells, because they don't last very long and it is very difficult.

We have been in our scientific study, this Phase II study that I showed you the results on, we actually have been looking at specific markers like CD3 zeda, which is a marker of lymphocyte function, of the viability of the lymphocyte, and in cancer patients and even in patients

treated with interleukin-2, we have seen--and this data was just presented at ASH from one of our investigators--that we actually see that the lymphocytes are, in fact, suppressed. We see a dramatic decrease in CD3 zeda, and when you add histamine, you actually restore CD3 zeda, so we have a number of markers that do suggest that the oxidative stress is, in fact, affecting the lymphocytes.

In this particular study, we didn't do any tumor biopsies or we didn't do any science to further prove that we were, in fact, dramatically expanding the lymphocyte population in these patients.

DR. LIPPMAN: Right, and one could do preclinical studies to look at that, as well, not only in the clinic, but I was really trying to get at the specific activity in the liver. Is there some biologic plausibility for why histamine should work more in these tumors when they are in the liver?

DR. GEHLSON: I think it would be more the slide that I showed earlier of why patients with liver metastases may have a poorer prognosis. The liver is certainly an organ with extreme oxidative stress because of the disease in there, so we know that there is a lot of oxidative stress, and, in fact, we know from our hepatitis C studies, in fact, where you have a lot of inflammation in the liver.

When we add alpha-interferon in that case, we get

a dramatic reduction in viral load in a situation of oxidative stress. In the melanoma patients, you have melanoma tumors, you have abundant lymphocytes that are in the tumor, but they seem to be anergized or nonfunctional because of this oxidative stress.

So, it is an ideal organ for us to prove that our drug does, in fact, work because the lymphocytes are actually there, they could be activated, but with the cytokine alone we don't see any of this activation, and we do see this response in the liver, and we do see the survival advantage that we have seen consistently in all of our studies.

DR. LIPPMAN: I understand, but just one follow-up. Wouldn't there be a lot of oxidative stress in the lung? It certainly has a high oxygen content, and that has been used as an argument for lung tumors in different settings.

Do you have evidence that there is a higher oxidative stress in the liver, in these tumors, than in the lung?

DR. GEHLSON: I can't say that we have definitive evidence in either the lung or the liver that there is significant oxidative stress suppressing the immune response. This is really a hypothetical at this point in time unless Peter--I could ask Dr. Peter Naredi, who has

actually done a lot of the scientific work. He may actually have a little bit more insight than could be helpful.

DR. NAREDI: We have to look at preclinical data. We have done microdialysis, so I cannot directly answer your question.

DR. NERENSTONE: Could you please state your name for the record.

DR. NAREDI: Peter Naredi from the University of Umea, Sweden. So, I have to relate to preclinical data. We have today no measure, to in vivo measure within the liver the oxidative stress.

But if we do inert measures to measure the function of the reticuloendothelial system by giving technetium-labeled albumin, for example, the absolute vast majority is taken up by the liver. It is like 90 percent, 4 percent to the spleen, some to the bone marrow, so you are right concerning the lung and the number of macrophages, but as a complete system, I think that the liver holds the vast majority of these cells and also of the specialized lymphocytes.

Coming back to why can histamine work effectively in the liver, we have done microdialysis of different tissues, and there is a significant lower concentration of histamine in the liver compared to sub-Q tissue, for example, and we have also then done the pharmacokinetics and