[Slide]

You might get something like this. You suddenly get something turning out to be significant and it looks way over and you start running it. It is all inappropriate because the overall test was not significant.

[Slide]

Now you say to yourself are you leading me to say we never can look at subsets? Well, you can look at subsets. You can start off by having a stated hypothesis that you are going to see some group effects or possibly subgroup effects. You can do randomization by stratification pre-randomization or you can do a post-randomized stratification. But you basically start off saying that I think the drug may work differently in the different subsets.

What is oftentimes done is to get the different subsets and perform an interaction test and see if they have an unequal effect on the outcome. In this case, if there is a significant interaction you don't pool. You look at the

subgroups differently. If there is no significant interaction you pool the data. If you have this latter case where you have no significant interaction, you may want to put a variable in your ultimate analysis for the subgroups, like you do with, say, centers.

You can avoid the interaction test if you want to start off saying I think subgroups are important and you test them separately so you don't need to do the interaction test. But if you do this business of saying that I don't want to do the interaction test, I want to look at subset one, treatment one versus treatment two, then you have to start doing something with your alpha level. You have to run each of these at 0.25 or do some other manipulation to make sure that your alpha level is still under control. You have this maybe for location, say brain cancer, to see an effect; for non-brain cancer you don't see an effect. So, you say I probably have an interaction type of thing.

[Slide]

You look at your data and notice there are no other subsets looked at here and you say, well, in fact, I have done my analysis very carefully. I started off with subsets so I can run with this case. Again, it is what you do a priori. It is not what you do in post hoc fashion.

[Slide]

What are some of the statistical properties of these analyses? If the primary hypothesis of the overall data is satisfied, is statistically significant, then secondary analyses can be examined and you can control the error rate, again, predicated on significance in the overall group. Even in this case it is very important to understand that when you move to the secondary analyses, the subgroup analyses, after you get the overall significance you have to know which groups you want to look at. If the number of subgroups is unspecified, then even in this case, the nicest case, you are basically looking at an exploratory analysis.

[Slide]

If the primary hypothesis of overall significance is not met, then basically we have lost control of the error rate. You have heard it already stated, but we have used up all the alpha and anything beyond this point is really exploratory.

[Slide]

If you move to the other situation I was talking about where you are going to start looking at subgroups separately, then keep in mind what the level of significance is. The level of significance is the probability of rejecting a false null hypothesis. You are going to be rejecting at least one null hypothesis that should be a true null hypothesis.

And, you have to worry if you start saying I am going to look at subsets to begin with, and this is where the multiple testing comes in. If you have a couple of subgroups that you are interested in looking at, then you have to realize that if you test each of them at a 0.05 level of significance that the overall level of significance

may be two times that 0.05. If you have a per-protocol analysis, metastasis/non-metastasis, you have basically three analyses and your overall level of significance is 0.15. If you are willing to look at other things you are up to some huge level of significance. So, even granted that you can look at subgroups separately you have to make sure you take into account the level of significance.

[Slide]

Now, my closing comment--I have two closing comments, one here and one I would just like to verbalize. The error rate can be controlled for looking at subgroups but you have to have a careful structure of the statistical approach--overall significance and then looking at subgroups; or subgroups to begin with and then control of alpha by some splitting activity.

We should not confuse the test of subgroups stated in a prespecified manner from this post hoc identification and test which can very easily happen. In the latter case we are basically

in the situation of not being able to really make any sense out of the statistics.

I want to make just one clinical comment to people who say at this point, okay, Ralph, that is wonderful. You have all this statistical significance but there is a clinical argument here. When I was young, and I am not young anymore, I did a subset analysis, a subgroup analysis and the subgroup that I thought was going to have significant differences didn't turn out. I was very disappointed. I presented it to the investigators and we spent half a day generating reasons why we should see significance in the subgroup. I went home feeling very comfortable but I got on the computer and did an analysis and I realized I made a mistake, that the subgroup I thought the significance was in was really not; it was the other subgroup. So, I went back the next day and said, I am sorry, I blew it. I gave you the wrong subgroup; it was this other subgroup. And the response was, well, that is even better and we spent the day generating even better hypotheses

on why that was explainable.

Once you start dealing with jumping with these analyses with the levels of significance and how you start talking about justifying I think we have a real problem in terms of how you justify further discussions when the statistical significance isn't there. It is too easy to generate hypotheses on clinical meaningfulness if statistically significance isn't there. Thank you, Madam Chairman.

DR. MARTINO: Thank you. As usual, we are running late. I need to introduce one more member to the committee who joined us, Dr. Rodriguez, please.

DR. RODRIGUEZ: I am Maria Rodriguez, M.D. Anderson Cancer Center.

Questions from the Committee

DR. MARTINO: The next portion of this are questions either to FDA or the representative from Abbott. Please keep your questions straightforward. I don't want to hear too many words because time is short but if there are

questions that are critical to you, this is the time, please.

DR. KAZMIERCZAK: Gene Kazmierczak, prostate cancer FDA consultant. I understand the FDA has granted Abbott permission to use expanded access from this particular drug. How will the outcome of this particular committee affect that particular ability for expanded access to patients who are in the latter stages with hormone-refractory prostate cancer?

DR. PAZDUR: Why doesn't Abbott answer that question? Really that is a question for the company.

DR. GORDON: Gary Gordon, Abbott Laboratories. At this time the outcome of the discussion today would not have an impact on the expanded access program, contingent upon FDA continuing to support that program.

DR. MARTINO: While you are up there, doctor, could I hear just some thoughts. I know you have other studies that are planned in this disease. Can you just summarize those briefly for

us?

DR. GORDON: Yes. Currently, as you know, there is an ongoing study in men with hormone-refractory prostate cancer that is not metastatic to bone. There are three pilot studies that are under way. Two of these are looking at atrasentan in combination with docetaxel. An additional one is a completed--all of these are small studies--looking at a combination of atrasentan with zoledronic acid. As many of you know, we are in discussions with the Southwest Oncology Group and have engaged in discussions with FDA regarding a large study of atrasentan with docetaxel. In addition, there are preliminary discussions with the Eastern Cooperative Oncology group.

DR. MARTINO: What are the patient populations for these?

DR. GORDON: The patient population for those are men with hormone-refractory prostate cancer with metastasis.

DR. MARTINO: Are there other questions?

Yes, doctor?

DR. MORTIMER: I am just curious in the future designs and if there is concern about cardiac toxicity and monitoring of lipid levels or beta-blockers?

DR. GORDON: So, let me try to take your question in three segments. One is are there concerns relative to the use of other vasoactive compounds in patients? So, in the Phase 2/3 experience we have looked at that and have not seen any increase in adverse events, for instance, in patients on digoxin or on Coumadin.

I think your second question was are there concerns in general about cardiovascular toxicity? As I already mentioned there will be more specific recommendations in the clinical trials to investigators and with regards to patient education.

DR. MARTINO: Dr. Levine?

DR. LEVINE: In the new trials you say the men with metastatic disease are enrolled. Is that metastatic disease to bone specifically or how did

you design that? Also, what kinds of pain assessments will be part of that?

DR. GORDON: I can't speak exactly to the pain assessments. I will ask Dr. Sleep to address that in terms of the Southwest Oncology Group trial. We have not finished the discussions with these groups regarding exactly which men. It is certainly our intention that it would be men with hormone-refractory metastatic prostate cancer with metastasis to bone.

I would ask the Chair if at some point there is an opportunity to address some of the statistical concerns that were raised by the FDA review.

DR. MARTINO: There probably is. Thank you.

DR. SLEEP: Thank you. Darryl Sleep, from Abbott. With respect to the patient populations, firstly, the two pilot studies that have been conducted with combination with atrasentan and docetaxel are PK, DLT type studies and that is including all patients with metastatic

hormone-refractory prostate cancer. As Dr. Gordon pointed out, the Southwest Oncology trial is targeting specifically patients with bone metastases and that was decided upon based on the science and the results that we have from Phase 3.

We are discussing with the FDA right now as to what is a primary endpoint. So, survival will obviously be included as an endpoint but with respect to pain and how to exactly measure the effect of atrasentan in combination on pain, we are working on that, whether we are using brief pain inventories or McGill pain, but it is likely to be a combination of pain assessments on a regular basis as well as appropriate analgesic use to determine the effect on pain.

DR. MARTINO: One more question from me, in the studies that are proposed what will be the primary endpoint? Is survival your ultimate goal here or is it something other than that?

DR. GORDON: That matter is currently under discussion with the Southwest Oncology Group, Abbott and FDA and has not been completely resolved

at this point.

DR. MARTINO: Are there other questions from the committee? If not, we will have a ten-minute break and we will be back at 10:15, please.

[Brief recess]

DR. MARTINO: The next portion of the program is the open public hearing. Those of you who wish to address the committee, you will need to come to the microphone and, before you do that, I need to read a statement to you.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor,

its product and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at this meeting.

Likewise, the FDA encourages you at the beginning of your statement to advise the committee if you do not have such a financial relationship. If you choose not to address this issue of financial relationship at the beginning of your statement, it will not preclude you from speaking.

Ms. Clifford will announce our speakers and introduce them to you.

Open Public Hearing

MS. CLIFFORD: Our first speaker is J. Waldenfelds.

MR. WALDENFELDS: Hello! My name is Jim Waldenfelds and I have no financial associations to report. Now, at age 62 I am a five-year, nine-month survivor of a challenging case of prostate cancer and I am in excellent shape. I am representing myself today but I am on the board of

the Virginia Prostate Cancer Coalition as a director, and I am also on the board of the Fairfax Us Too, Man to Man Support Group. I have attended three patient-oriented national conferences on prostate cancer and last April I attended the National Convention of the American Association for Cancer Research as an invited member of the scientist survivor program. I see several familiar faces.

Here are brief facts of my case and therapy that have affected my viewpoint and what I would like to communicate to the committee about Xinlay. I was diagnosed in December, 1999, Gleason-7, stage 3, confirmed by experts, with a PSA of 113. Fortunately, bone CT and later scans were negative.

My only therapy has been hormonal blockade which evolved to intermittent triple blockade, including Proscar complemented by phosimax and Celebrex, a standard supporting program of nutrition, diet supplements, exercise and stress reduction. I reached a nadir of less than 0.01 and

was off Lupron when I went into remission for 34 months for a total first cycle period of nearly five and a half years, including a six-month thalidomide boost at the end. I began my second full cycle of hormonal blockade in May.

In sum, I am a survivor, in my early 60s, of a challenging case who has responded, and is still responding very well to triple blockade and I am profoundly grateful that it has worked so well for me.

However, the cancer is still resilient and I am concerned that I am using up a silver bullet with each round of blockade, and I am concerned that I only have one to three more of these bullets and also that the periods will become shorter.

Therefore, like so many survivors with cases that appear to be currently incurable, I am highly in favor of drugs like Xinlay that will expand future therapy options. Past studies have demonstrated that Xinlay is effective for some men with so-called hormone-refractory prostate cancer. This is clear even though the Phase 3 trial ran

aground on early additional bone mets.

Unless Xinlay is approved soon, before definitive Phase 3 proof of effectiveness, oncologists will be unable to begin learning and communicating with each other about which patients are likely to respond and which will have responses that far exceed the median. They will be unable to apply their clinical expertise, experience and insight in considering Xinlay combinations of drugs and its use in less advanced patients, and many men with advanced cases will be unable to find out if they are good responders.

If I may use a military analogy, such early and off-label clinical use, perhaps use here where the proof is less than fully convincing, is like a Calvary foray to find and characterize the enemy. Probing weaknesses and opportunistically taking advantage and exploiting opportunities, doing this cheaply and inexpensively while the main forest, analogous here for example to elegant Phase 3 trials, has the truly vital role of conclusively addressing efficacy.

For instance, I mentioned thalidomide earlier, a drug carefully managed by the FDA--thank God. For me, a 50 mg low daily dose, supported by 300 mg of vitamin B6 to help prevent peripheral neuropathy enabled me to safely and comfortably extend my therapy maintenance period by six months. Such use is documented only by a 2002 letter to the general oncology.

This illustrates that such types of use, off-label clinical use in this case of a drug can produce significant benefit and provide leads to formal research. Approval of Xinlay will directly benefit men with hormone-refractory cancer who are running out of options. I have talked to some of them and they are highly in favor or it, to put it mildly. I asked my oncologist what he thought of Xinlay and he said that he would love to have it available. Clinical use of Xinlay will resonate with a much larger pool of patients than the target population. I might be one of them.

DR. MARTINO: Thank you.

MS. CLIFFORD: The next speaker is Mr.

William Blair.

MR. BLAIR: My name is Bill Blair and I am here as a citizen with prostate cancer. I have no vested financial interest with this drug or any other of its type.

I am here to speak in favor of the drug Xinlay for prostate cancer for those of us with advanced disease. My background is that of a retired cancer researcher and teacher. My current activities include efficacy chairman from Northwestern SPORE, chairman of the Inner SPORE Advocates, member of CTEP, grant reviewer for DoD, NCI, and I am particularly proud of being a reviewer for IDPH, Illinois Department of Public Health, where we have raised yearly over $200,000 for prostate cancer research and have funded a vaccine program which seems to be helpful.

I am daily in contact with prostate cancer patients around the country. I have traveled ten states in talking to prostate cancer patients on survivorship, which I am. I also mentor a metastasis group of men. I am a nearly ten-year

survivor of prostate cancer with D disease at inception, and a four and a half year survivor with skeletal metastases. I have benefited from the optimal treatment that I receive for my disease but there are few treatment options at this point.

I am here to represent the many thousands of men with advanced prostate cancer with skeletal metastases and HRPC. In my original group, which I started in 2001, there were 32 men. There are three survivors now.

I would like to pass two pictures around to the committee. I would like you to look at the first picture and look into the faces of these men. These are all friends. The ones with Xs on top are not with us anymore. They all died in a very difficult situation with a lot of pain and suffering. I was with each one of them when they died. It was not a pleasant experience.

The second picture is my new group. You will see in that first picture, by the way, that there are three without Xs on the left side. Those are the three survivors, of which I am one. One

has only a single metastasis to the sternum and is a ten-year survivor. I don't expect you will see the three within the next few years.

The second picture is a new group which is larger now, much larger and it is getting bigger and bigger. In this original group there were 32 men, three survivors. We would like to see it get better for the second group.

I would like to say we also fully subscribe to the challenge of the scientific director of NCI, Dr. Andy von Eschenbach--no more deaths and no more suffering from cancer by 2015. I believe it is achievable but I think we also have to understand that when you have ten men with prostate cancer you have ten different cancers sitting out there. Statistically, to think that you are going to be able to come up with a defined treatment for every patient with one drug, I really doubt.

Xinlay is a selective endothelin-1 receptor antagonist and it may help those of us with late stage skeletal metastases to relive pain

and extend survivorship. That is our goal. We state we want to die with this disease and not from it, and we intend to try this. It just may be another piece of the puzzle which is extremely confusing but still has to be done. I implore you to consider recommending approval of this drug for those of us with late stage disease. Thank you.

DR. MARTINO: Thank you. Next?

MS. CLIFFORD: Mr. Jim Kiefert.

MR. KIEFERT: Madam Chairman, thank you for this opportunity to appear before you. My name is Jim Kiefert. I was diagnosed with prostate cancer in 1989, PSA of 39. When they did the surgery they found my Gleason went from 7 on initial diagnosis up to 8. So, for the past almost 16 years I have been fighting this battle. I had a radical prostatectomy, followed by radiation and it did not get rid of the cancer. So, I have been living with all the different ways that I can to have a quality of life through this process. I am on hormone treatment right now intermittently and I do have some bone mets. So, this affects me

personally.

I have a doctor of education degree. I retired from education in 2001, having been a math and science teacher, a university professor and a school district superintendent. I live in Olympia, Washington and I now serve as chairman of the Washington State task force for prostate cancer which is funded by the Centers for Disease Control. I also am on the SPORE advisory committee and our state coalition.

I am pleased to speak to you today as chairman of the Us Too international prostate cancer education support group. My disclosure--by policy Us Too does not endorse any products or services, although Us Too does receive unrestricted educational grants from pharmaceuticals, including Abbott but Abbott did not contribute to my expenses, either to me directly or through Us Too International.

Us Too International is a grassroots organization that was formed in 1990, a year after I was diagnosed, by cancer survivors. Their intent

was to provide education and support for men and their families who have prostate cancer. We have approximately 325 chapters across the United States and they are all over the world. Our intent is to give them clear, accurate, up to date information about diagnosis and treatment of prostate cancer.

We contact and communicate with approximately 50,000 prostate cancer patients every month. We do this through sending out newsletters. We have virtual sites and a web site and we send News You Can Use by e-mail. My wife Maureen and I decided that we wanted to do something about prostate cancer so we got American Cancer Society training in the Man to Man group.

We formed two groups, one in Washington, one in Oregon and now she and I are training facilitators for prostate cancer leaders and we have trained about a dozen of them. My name is listed so I get telephone calls from men or many times their wives, saying that their husband or this man has recently been diagnosed, or I get what we call the high risers, those who have had

treatment and it has failed and their PSA is going up. Those are the ones who experience the greatest amount of stress. When you look at the Internet and it says there are very few options once you have advanced prostate cancer, other than chemotherapy, many of them, and their wives will suffer from severe depression knowing that there aren't many options available to them. So, our message primarily is to see if we can do anything we can to increase the options for men with advanced prostate cancer.

As part of our strategic plan, we have gathered data from our constituents on bone health, on hormone treatment and now we are doing it on quality of life issues, and we have done this through next year and we have had a survey that was sent out through the Prostate Cancer Foundation, our web site on prostate pointers, the National Alliance for Prostate Cancer Coalitions and others. We have gathered information from approximately 550 patients and caregivers and physicians. This is not a scientific study but it confirms the

information that we get from our chapter leaders.

Tom Kirk, who is our new CEO, and I as new board chair as of January, we have been having quarterly telephone calls with our regional directors and we contacted all of our chapter leaders, and the question that keeps coming to us is what are we going to do for these men who have advanced prostate cancer, and how do we help the men who have bone metastases who are dying agonizing deaths? The questions get very hard to answer.

Our survey indicated that most of the men who have advanced prostate cancer, their greatest fear is bone pain and 74 percent of them said that they understand that there is a survival benefit to chemotherapy but two-thirds of them said that they would rather do anything else rather than have chemotherapy. They are concerned about the quality of life issues. We know that chemotherapy has benefits for prostate cancer but when we ask these patients whether or not they would use chemotherapy, 50 percent of them said absolutely

not. If the indication is you could have two or three more months to live, they would rather be alive and coherent than to go through the pain and suffering of chemo. So, that is their perception of it.

I listed in my handout some of the statements from men who have advanced prostate cancer and bone pain and I think I would rather just tell you about what happened yesterday morning when a member of my support group called and said, Jim, we are going to have to sell our house. My bone pain is so bad I can't make it up and down the steps of our two-story house. I can no longer cut the lawn and I can't maintain it.

The bone pain is excruciating and it is a horrible, humiliating way for a man to die. Our interest is to find some treatment, some medication that will extend their period of life without the bone pain so that they can have some quality of life.

The options for men, as I said, are currently very limited. I don't need to repeat the

statistic that 30,000 men are dying every year from advanced prostate cancer. But Us Too would like to urge ODAC and FDA to open as many options as you can for those of us battling advanced prostate cancer. Thank you.

DR. MARTINO: Thank you.

MS. CLIFFORD: My Harry Pinchot?

MR. PINCHOT: Good morning. My name is Harry Pinchot and I am the program director for the Prostate Cancer Research Institute. I am here today not in my capacity of the Prostate Cancer Research Institute but as one of tens of thousands of individual patients afflicted with hormone-refractory metastatic prostate cancer.

With the promise of a cure, we have endured multiple treatment modalities, including surgery which has left many incontinent and impotent, radiation which has damaged rectums and bladders, and what many consider the ultimate insult to their masculinity and their body, androgen deprivation therapy inducing muscle wasting, anemia, osteoporosis and reduced cognitive

ability.

After enduring all of these treatments plus second-line hormonal manipulations, many of us are told that chemotherapy is our only option. In light of our past experience, is it any surprise that we question the wisdom of proceeding with toxic chemotherapy drugs which offer little hope of remission and ongoing deterioration of our physical strength and quality of life? By the time most men have heard the dreaded words, chemotherapy is your only option, we have become students of our disease and have no expectation of being cured by any drugs available now or in the current pipeline.

We read the published study results and ask ourselves why subject our bodies to cytotoxic drugs which offer, at best, a 50 percent chance of extending our lives by a very few months and a 100 percent probability of needing additional drugs to offset the damage caused by chemotherapy? So, it comes as no surprise that almost 50 percent of men with advanced metastatic cancer say they would rather die from the cancer than endure

chemotherapy. Unfortunately, some men end their lives rather than undergo chemotherapy.

With the knowledge that no available drug offers the hope of a cure, quality of life becomes paramount in importance. What we need are drugs which can delay progression while allowing a decent quality of life, drugs which allow physicians to treat prostate cancer as a chronic disease much like AIDS. We need an arsenal of drugs like those that have allowed AIDS patients to live with the disease without destroying quality of life; drugs which can give us the opportunity to enjoy life with family and friends; drugs which allow us to spend time with our children and grandchildren.

Atrasentan is such a drug, without the cytotoxicity of chemotherapy and significant side effects that allows metastatic prostate cancer patients to delay beginning chemotherapy. I have been treated with Taxotere and other chemotherapy drugs and can attest to the impact they have had on my quality of life. Recently I began receiving atrasentan. It has allowed me to feel normal and

reduced the number of supportive drugs I was taking with chemotherapy. As you can see, I am even growing hair on my head and I hope to get eyebrows back one of these days.

Until the day that treatment offering a cure is available, we need drugs such as atrasentan that allow us to enjoy life while delaying the progression of our disease. If atrasentan and more drugs like it were approved, perhaps more men would seek treatment knowing they could live normal lives. On behalf of the tens of thousands of hormone-refractory patients, I urge you to recommend approval of atrasentan.

DR. MARTINO: Thank you. Next?

MS. CLIFFORD: Mr. Kuntz?

DR. KUNTZ: Thank you. My name is Joe Kuntz. I am a physician and a urologist. I don't have prostate cancer, thank God, but I treat it. Please be patient with me, I don't do this very often.

I am at the other end of the spectrum from the panel. I am just a foot soldier. I am just a

urologist in clinical practice in a rural community. We have a small research company, Uroscope, and we were clinical investigators for this drug. I have no financial tie to any company. In fact, we lost money on this one so if you could do something about that, we would be most appreciative.

[Laughter]

I have a large prostate cancer practice. When I went into practice in 1985 PSA was just around the corner and we very early jumped on board and established ourselves as the big fish in a small pond so we have a large practice. Like all doctors that treat prostate cancer, we have had our failures.

I would like to just address three things. The first thing is that sitting here, I am just wondering if I am the only one listening to the statistical arguments that has an enormous headache. Benjamin Disraeli comes to mind. I just didn't understand all of that. But I do understand what Dr. Levine, my best teacher I ever had, by the

way, and my esteemed professor taught me so many years ago: It is not about statistics, it is about the individual patient. We would like to think we build a Ferrari for everybody.

So, we have used this drug and we are convinced the drug has efficacy. I think if you don't treat prostate cancer patients with bone pain it is very easy to sit there and look at the statistics and say, well, it doesn't work. But the fact is if it might work it is an effective drug.

The second thing is I was not the sharpest tool in the tool drawer. I am just a urologist and with all the stuff like congestive heart failure, and this and that, we have used mitoxantrone and we have used this drug and this drug is a very safe and effective drug. It is very safe. I mean, if you can afford a bathroom scale you can take this drug. One of our patients was one of the congestive heart failure guys and he still rides his bike faster than I do. He is 80-some years old. He rides three miles a day. His congestive heart failure is just as bad now as it was before

he started the drug and his ejection fraction is terrible, just like before he started the drug. So, we have found this drug to be very safe and easy to use.

I ask my patients--I have a few letters here--if they wanted more options because the perception in the patient community of chemotherapy is that it is highly toxic and not terribly efficacious. This is a letter from my patient in the trial that had congestive heart failure:

I am an 87 year-old prostate cancer survivor. I continue to bike five to ten miles a day and swim three times a week, 1,000 meters each swim, and I workout regularly at a gym. I have benefited from this medication unknowingly and I believe that FDA should make it available.

Having received what has been described as the best available treatment for prostate cancer, to be confronted with an ever-decreasing quality of life and the prospect of this disease ultimately killing me, I am worried. I am asking your committee to please make as many options as

possible available for prostate cancer patients.

I have a nice letter here from a psychiatrist: I continue to practice. My quality of life is very important to me. I urge the committee to make as many treatment options available.

Every letter is the same thing. It is not ultimately about how long you live but how well you live-- and I think Dr. Carducci might have said it--more normal days. So, just as somebody who is out there in the trenches, these guys are warriors and they are fighting for their lives, and we just urge you to make this tool available. Thank you.

DR. MARTINO: Thank you, and if you will allow me I would just like to make a comment. What has occurred to me as I have sat on the committee, and this is actually my fourth year, is that there is a general assumption that somehow those of us sitting here don't actually take care of patients, that we actually don't understand some of these very real, in the trenches, kind of issues. That is not the case. There are many of us on this

committee who do nothing but see patients day in and day out and who have for many, many years, who actually understand the day-to-day practicalities of taking care of patients with cancer. I apologize to those of you who think I am perhaps speaking out of turn, but you need to recognize who we actually are here. We truly do understand these issues. We are not all just highfalutin statisticians or professors who never get our hands dirty. That is not quite the case. Next, please.

MS. CLIFFORD: Ed Grove.

MR. GROVE: I am Ed Grove. I am a prostate cancer warrior of 13 years, and I have no financial arrangement with anybody. I am just a private citizen who runs a support group here locally.

I have been the chairman of the ANOVA Fairfax Hospital prostate cancer support group for 13 years, and during that time I have had numerous men come to me or come to our group to talk about advanced prostate cancer. It is clear, you know, that some of them were running out of arrows in

their quiver to deal with this disease and were in very, very difficult circumstances. Obviously, they need new options, as many options as they can get as they go on with this disease.

So, that is one thing from one side. Meanwhile, I have had an interesting journey with this disease myself. What I found in doing so, both personally and in dealing with other survivors, is that you can get good results in fighting this disease from experimental and exploratory initiatives which don't have formal FDA approval. I want to tell you I am a walking example of this right now.

My prostate cancer has slowly been coming back for the past ten years. I had a PSA of 6 plus, radiation therapy and then, in the mid-'90s, after a nadir point of 0.6 it rose last year to 18. Clearly, I had to do something about it. So, what I did was, in working with my oncologist, I started taking Leukine. I guess you folks all know that Leukine is a drug used for folks who have had chemotherapy to, you know, protect their immune

system and also for folks with Hodgkin's disease. However, Leukine has not been formally approved in the treatment of prostate cancer. What Leukine has done for me in the past ten months is it has dropped my PSA from 18 to 12 and it has bought me more time. I don't know where we are going or what is happening but it has bought me more time.

So, basically what I am saying, along with our other fellow survivors here, is that even though the FDA has some difficulties with Xinlay, I hope you continue to make sure that it is available as an option for hormone-refractory men with bone metastases because, you know, it is really important to us. Thanks.

DR. MARTINO: Thank you. Next, please?

MS. CLIFFORD: Katherine Meade.

MS. MEADE: I am Katherine Meade and I am here not as a survivor obviously but I am here as a widow. I know all of the men who spoke to you, and there are many, many, many men around the country who are in similar situations. Every year there are 30,000 men who are diagnosed with prostate

cancer and I heard an estimate recently that there are well over a million men living with prostate cancer in the United States.

As a widow, I have seen what prostate cancer is like at all stages. I work with men and women and children who are dealing with the effects of prostate cancer. It is very much of a family disease and there are young men and older men who are dying of prostate cancer. It is not a pretty death, as many of the men back here said. I am involved with the Virginia Prostate Cancer Coalition, the National Alliance of Prostate Cancer Coalition. I work with the Us Too minority and under-served outreach program. I am living in Tappahannock, Virginia. I came here today on my own. I wasn't planning to even speak but I think it is important that you realize that not only do men like this need you to do something--and I am speaking to the drug companies and to the FDA--to find something to treat prostate cancer but it is important to keep other women, like myself, from having to deal with widowhood and all of the issues

related to that because we have delayed finding something to deal with prostate cancer.

I just hope that you can think about the way that this can be done in a safe way. I don't want any men harmed in the process and I know you all don't either. But I also want to make sure that we don't become so concerned about issues that may or may not be vitally important that we forget the reality of the lives of the men living with prostate cancer and the lives of the women and children left after they die. You know, they don't have options. We need options. They are basically all on an untried clinical trial right now out there, you know, grabbing around, trying everything that they possibly can. So, please do what you can to make sure that we get something quickly and safely. Thank you.

Committee Discussion

DR. MARTINO: Thank you. Are there any other speakers? If not, thank you all. At this point we will turn to the committee's discussion on this drug and ultimately we have four questions

from the FDA that we have to answer. They have been provided to you. Before we start that, Mr. Kazmierczak, you had asked a question earlier. I wanted to be sure that you got an answer that you were satisfied with. If not, this would be a good time for you to re-ask your question.

MR. KAZMIERCZAK: Yes, I asked the question concerning expanded access for this particular drug for men with metastatic hormone-refractory prostate cancer, and whether or not the outcome of any action by this committee is going to impact that expanded access. I was told that that would not happen. Now, I don't believe that but I was told that by the drug company representative. I just want to make sure, triply sure, that that is the case.

DR. MARTINO: Dr. Gordon?

DR. GORDON: At this time there is no intent to change the expanded access program. If the drug is approved there will be a gradual phasing out of the expanded access program at some point. If the FDA decides that the expanded access

program cannot continue, it will not continue.

MR. KAZMIERCZAK: What if the drug isn't approved? Will expanded access continue?

DR. GORDON: The program would continue until some point in the future, the exact date I cannot tell you.

MR. KAZMIERCZAK: Thank you.

DR. MARTINO: Dr. Gordon, I believe you requested for someone in your group to deal with statistics. If you can do that briefly, I will allow it.

DR. GORDON: I believe it will take us about four minutes to run through. So, what I would like to do is try to bring us back to why we are here and what population we are dealing with, and how did we get to the point that we are at.

We are dealing with a disease that, as you have heard, has a prognosis, whether you look at the docetaxel data or you look at our data, that has a survival of 18-20 months. The types of benefits that were outlined by Dr. Sleep are in the range of 2-3 months, which represents a significant

portion of these patients' life span.

How did we get to this point? We got to this point because there was evolving science that spoke to the importance of the endothelin axis in drugs like atrasentan and the interaction between prostate cancer cells and osteoblasts.

The timing of the decision to look at this group of men was integrally related to the actions of the IDMC. The science was evolving. The decision was made. The IDMC recommended that the study be closed. It seemed to be inappropriate to modify the statistical analysis plan at the point in time when the IDMC was saying close the trial. The analysis of the men with metastatic disease was originally presented to the FDA in October of 2003, not four months ago or five months ago. There were discussions with the FDA. So, the notion of looking at this group of men and when was this done, the decision to do this was made before the blind was broken and the analysis was done when the blind was broken.

The next question was how do you make

adjustments for that? That is something I am going to turn to Dr. Emerson to talk about how you would make adjustments for this sort of analysis.

Then the other piece that I would like to come back to is the interpretation of the median in this group of men because, as Dr. Darryl Sleep pointed out, when you look at that ITT curve, it is an unusual shaped curve. It is a curve that had lots of events that occurred but, in fact, one has to look at the hazard ratio to see the full benefit. I will now turn the podium over to Dr. Emerson.

DR. EMERSON: Scott Emerson, biostatistician from the University of Washington. A major aspect of the subgroup analyses, as described by Dr. D'Agostino, is the question of when was the subgroup identified? Was it identified after you analyzed the data and were you looking for which one gave you that subgroup, or was it analyzed before you were looking at the data? That statistically is the issue. I understand the FDA also asked the question when you

documented that that was the issue but statistically the issue is was this subgroup identified before analyzing the data or not.

Then, a second issue is supposing that it were identified before analyzing the data, what is the proper way to analyze this data? Dr. D'Agostino gave some examples of how this might be done but I would like to describe a method that I think is a more appropriate analysis of subgroups that have been specified and I would like to talk about the way that this would be handled, and has been handled by me in the past on protocols that were submitted to the FDA.

This is the ITT analysis in which, as we talked before, the p value is 0.136; estimates of the survival summarized by the hazard ratio, 0.885; and a confidence interval that overlaps 1. In terms of the subgroup which comprised approximately 85 percent of this ITT population, the p value is 0.16; the hazard ratio is 0.813.

Now, a major aspect of this is if you were going forward and identifying the subgroup in

advance, the key point is that you can build on the exact same methods that we use in sequential monitoring of studies which is, in fact, my area of expertise and how I got involved in the study from the start which is doing the monitoring for the study. But in the sequential monitoring we recognize that if you do an analysis when you are 75 percent of the way through the study and if you do an analysis when you are 100 percent of the way through the study you have a multiple comparison issue. But we do not do the Bonferroni analysis that was being sort of suggested by Dr. D'Agostino as an example where he said this is one approach.

There are others. I am speaking to the others. In fact, this subgroup is a major element of that total subgroup. The results are highly correlated. The Bonferroni adjustment assumes that they are mutually exclusive, that you could not get a significant result in the subgroup at the same time you got one in the major group and that is obviously not true when you have a high correlation.

So, one approach that I have used in the past is to use the familiar O'Brien-Fleming adjustment, but now I am looking at using the O'Brien-Fleming adjustment on the 85 percent of the subgroup, being very conservative in that subgroup, and then doing an adjustment again at the end. You can see that these p values change very, very little. This is a hazard ratio now of 0.818 and this p value is very little changed from the one before. Of course, this we know well. The O'Brien-Fleming boundary is fairly conservative. We could have used other boundaries but the results stay the same. The high correlation between the outcomes in the subgroups in the final analysis would argue that very little adjustment is truly necessary.

So, just to recap, this is the ITT population that was clearly prespecified and documented. We do not have statistical significance on that primary endpoint. We did have secondary endpoints that were biologic rather than clinical and these had statistical significance in

the ITT population but, again, without the clinical endpoint. They were intended to be more supportive. Note that also on the quality of life endpoints which were tertiary, again, we have the statistically significant results in the ITT population.

We then go forward to the bone metastasis subgroup in which we have so far presented unadjusted analyses, and that was more from the standards. This adjustment that I said that I used in other trials to do the group sequential was also not documented beforehand, and these were the p values that were presented.

If we carry that then on this primary endpoint in the subgroup but adjust for the multiple comparisons, you see that the aspect of the multiple comparisons from a subgroup analysis is not truly an issue in the statistical significance and instead it hinges on the prespecification endpoint. Thank you.

DR. GORDON: So, the other point I would make is that, in terms of the indication we are

here to discuss today, the data that was presented shows that the primary endpoint that was defined in the protocol and subject to the special protocol assessment was met in the group of men with bone metastasis. That is the primary basis for the discussion. There were a number of secondary analyses presented, including effects on markers of either disease, PSA and bone alkaline phosphatase, drug action, bone alkaline phosphatase and, as you heard from the discussion, issues about patients reporting their own assessment of their quality of life. The study was blinded. The data collection was extensive, particularly with regard to those measures, and there is no reason to think that, given the blinding, there was any particular bias in how patients would selectively report their quality of life issues.

DR. MARTINO: Thank you. Go ahead, Dr. Cheson.

DR. CHESON: One of the concerns about the study that was presented by our FDA colleagues is that it was terminated early because of a futility

analysis by the data safety monitoring committee. Yet, you are presenting these data here, which you propose demonstrate that the study was actually positive. Were you not able to convince your own data safety monitoring committee that the study should be kept open for these reasons, and if not, why not?

DR. GORDON: So, we are fortunate to have Dr. Emerson with us who was the statistical consultant to the data safety monitoring committee. If we can put up slide VE-86 first?

[Slide]

Just to remind people that the study was powered to detect a difference at 650 events. The study was initiated in June, 2001. In September of 2002 the IDMC suggested that enrollment stop. I just want to correct the time line that was presented. In January of 2003 the IDMC actually formally made a recommendation regarding futility. At that time they were looking at 343 events. They had some other events at the point they made the final recommendation that had not been fully

entered into the database and within six weeks of the IDMC making a recommendation the study was closed. At the time we were able to bring all the data, in March, there were 610 events.

As you saw from the shape of the curve, there was an unusual number of events that occurred early. I am going to ask Dr. Emerson to talk about how the IDMC functioned and how they made their decision.

DR. EMERSON: Again, Scott Emerson from the University of Washington. It is best to go back to the design, and I just want to make clear that I aided in the design of this study and the stopping rule and I served as a consultant to the IDMC. I was not on the IDMC. I helped them interpret how the stopping rule went.

In the planning of this study we were going on the results of the Phase 2 study in which the key parts that were noted were that survival curves were quite coincident through the first 90 days of treatment and then they separated. This is clearly a non-proportional hazards sort of picture

if this is the truth and the planning of the Phase 3 study took that into account.

Now, I need to point out a couple of things that are statistical things, and I have sympathy for the speaker who didn't like statisticians, but the statistic that we eventually were going to use was one which is designed for looking at later occurring differences. This is a key point where, unfortunately, statistics too often looks at the wrong axis. Our statistic is looking very much at this axis and so we were designing the statistic that was going to do well at picking up differences that occur at the 75th percentile to the 25th percentile of the distribution. As the FDA pointed out, such things as the hazard ratios don't incorporate time, it is time that matters to people. I will argue that the median can often fall in that same category, that the median does not matter to people necessarily but I will come back to that.

So, in this case we went forward and designed a clinical trial stopping rule that was

designed to tell us, with high power, if this sort of pattern was seen again but then the futility rule was to say and when we have ruled out this sort of pattern, we might as well stop the study. So, we chose a stopping rule that was a one-sided symmetric design, as proposed by Tom Fleming and myself in '89. It was a type 1 error of 0.025, power 90 percent. Due to those later occurring differences we were actually more conservative than the O'Brien-Fleming boundary in this particular design.

So, efficacy was to reject the null hypothesis of no treatment difference; futility to reject an alternative effect similar to what we have seen before. It is very hard to go forward with non-proportional hazards and be able to describe what you want. So, that was using this G1-1 statistic which, again, is not focused on time; it is focused on quartiles of the distribution.

During the monitoring of the study, as was said, when the IDMC saw 344 confirmed events in

clean data they said stop. In fact, there were up to about 509 events that were known in a dirtier database. We didn't have all the safety data but did have the endpoint. And, it was confirmed at that point. But over-running of clinical trials always happens. We know how to handle that statistically.

But these are the final results based on 610 events. What you see clearly is that we weren't observing the pattern that was seen in the Phase 2 study. My personal bias is that it is more due to looking for subclinical measures on serial radiologic scans, not scheduled according to symptoms, that moved many of the clinical endpoints detected earlier. But the end result is that between 75th percentile and, say, the 40th percentile that occurred at the first scan. The G1-1 statistic was not going to be optimal in that setting and the study showed this.

I do want to comment that when you have this picture and when we look at what the hazard ratio is, the median isn't telling you this.

Imagine this were the truth. If there were no uncertainty in these curves, how many people would rather be on atrasentan than placebo if we knew this absolutely? The median doesn't pick this up any better than the hazard ratio does sometimes. In fact, tarring all ratios is sort of interesting because most often parametrically we analyze median ratios. It is not the ratio, it is the median. Had we had large separation, that the 20 percent of people who died first and those where we could extent their life is clinically important. The people who come out here--if I had made these people immortal, it is clinically important. Seizing on the ratio by itself is not necessarily the issue.

So, this aspect of picking out this effect where we are looking at what this difference is--if I might have the bone scan score?--the issue of the area between these curves does have a common statistical interpretation. It is the difference in the average number of days that somebody could be expected to benefit from over the period of

treatment. Because these curves don't go down to the bottom we can't estimate the mean absolutely; we can get the restricted mean. And, this rough 10 percent difference--and this is in the bone metastases, this rough 10 percent difference translates to roughly a 24-, 25-day difference in the average number of days over the first year of treatment.

DR. MARTINO: Does that answer your question? Are you okay at this point? All right. Next, Dr. Eckhardt, please?

DR. ECKHARDT: Well, just looking at this data, you know, I think one of the problems is that the hypothesis was really shifting during the course of the study. You know, when I look at the data I think of this as being more of a mechanism-based supportive care agent in a specific population. So, the question I have is how one can really look at the data currently and really assess its best use because, in fact, if you look at the patient selection parameters I think what we have seen is that there is a subset of patients that

probably do have a benefit from the drug, those with bone metastases. But I think then the secondary question is what is the best kind of endpoint to be using in this kind of study.

My concern is that the clinical endpoints of things such as time to disease progression may have been ones that would have been better as secondary endpoints, and certainly could have supported some of the other patient-reported outcomes with regards to pain. So, you know, in trying to salvage the study and salvage the data, I think the problem I am struggling with is that I can actually see that this data has generated some very testable hypotheses and the question is are we actually able to salvage this to get at the real question? I think the two main issues are patient selection and appropriate endpoints for those kinds of mechanism-based supportive care studies.

DR. MARTINO: Dr. D'Agostino?

DR. D'AGOSTINO: My comment is very similar. We have a lot of adaptive, adaptive, adaptive activities going on here and trying to put

them altogether and say, well, the data monitoring committee stopped the study but they stopped it too soon because it wasn't looking at the right thing--and even when you have the full set of data, the variable they were looking at still isn't significant, but if we looked at some other thing which we think is interesting, important, we can make an adaptive procedure to handle that. I think it is going to be a great example in textbooks, and so forth, but I think trying to go back now and say, yes, we can really feel comfortable about pulling the subgroup in this analysis--I think it is very, very hard to try to move in that direction.

DR. GORDON: Can I make one comment?

DR. MARTINO: Very briefly, yes.

DR. GORDON: So, I would just make the point that, in fact, the endpoint as defined wasn't looking at a different endpoint. It was looking at the endpoint as described in the protocol, albeit in 85 percent of the patients.

DR. D'AGOSTINO: Well, the original design

said all the patients and it wasn't significant in the original design. So, the third adaptiveness is to go to a subset.

DR. MARTINO: Dr. Brawley?

DR. BRAWLEY: I would like to ask Abbott if I accept that there is a subset, and I have seen a number of subset analyses this morning and I hate subset analyses--if I accept that there is a subset that actually responds to this drug, what work are you doing to actually identify that subset? If we were to vote for approval of this drug--and I want the advocates who want options available to hear me very clearly--if this drug is approved right now, we tell these very honorable men from Abbott that they can sell their drug to all men with metastatic prostate cancer and we take away all incentive for them to find the 15 percent of that population that actually ought to be taking the drug. That is a very important point. So, what are you doing to try to figure out the subset that actually responds to the drug?

DR. GORDON: So, I think the cleanest

answer to your question is we already have identified a group of men who are more likely to respond to this drug than others. So, consistent with the NCI initiative and the FDA initiatives to try to say across all men with hormone-refractory metastatic prostate cancer is there a group of men that are more likely to benefit, we are saying it is that group of men who have metastatic disease involving bone. As we discussed earlier, there are other studies now that are either conducted, in the midst of being conducted or ongoing.

DR. MARTINO: But if we assume that that is a correct statement, that as long as you have bony disease you are likely to benefit from this, that actually would encompass pretty much every patient with prostate cancer because sooner or later the overwhelming majority will have bone metastases. So, that sort of gets to the general population being treated and, again, results in the same problem that Dr. Brawley I think is pointing out.

DR. GORDON: Well, I mean, clearly the

indication we are discussing is much narrower than that. Right? The indication that we are requesting is in men with metastatic disease who have documented evidence of bone metastases. As I have already alluded to, we are conducting studies in other patient populations. We have two studies that are in that population of men, one of which had 85 percent of the participants having bone metastases at baseline, the other having 90 percent, which is the 594 study.

DR. MARTINO: Is this a drug that at this point you know is of benefit only in patients who have bone metastases that are asymptomatic versus bone metastases that are mildly symptomatic versus bone metastases that are horribly symptomatic? That is a wide range of patients. Do we know where this fits? Do you know? Clearly, I don't.

DR. GORDON: So, we are going to ask Dr. Nelson to help answer your question.

DR. NELSON: Madam Chair, you bring up the issue of this disease having a clear spectrum. The data that has been presented would target the

middle of the spectrum, those are men who have hormone-refractory disease that is initially, at the time of presentation, asymptomatic. They are easy to detect because you simply send them to nuclear medicine and they get a bone scan and it is positive.

I would just like to mention that 15 percent of patients who die of prostate cancer in fact do not have bone metastases. So, to say it is inevitable that they would have bone metastases is simply not clinically supported. In that group of men that are asymptomatic, they will become symptomatic and the data I think is speaking to that population of men. For the men who are already symptomatic the data does not support the use of this medication or this drug in that setting.

DR. BRAWLEY: A real quick question, is there any work on the molecular target for that subset of individuals who actually will have a response to the drug? The group of people in that intermediate group is still fairly large.

DR. NELSON: Dr. Brawley, I would love to tell you that we can identify clearly those men who have endothelin receptor expressed at some particular level, but one of the benefits of this approach is that we are targeting the part of the body which would not expect to be heterogeneous. So, we would expect in general that osteoblasts will have roughly the same number of receptors, unlike cancer cells which, as you know, will lose all kinds of things which they would normally express. So, in some ways, the beauty of this approach is to target the stroma, not necessarily targeting the cancer.

DR. MARTINO: I want to get back to my argument which is if somehow this committee decides that this agent can be used in patients that are asymptomatic, how will we then behave towards patients that are symptomatic? Are we going to say, no, they don't get it? No, they shouldn't get it? How are we going to deal with them?

DR. GORDON: Dr. Sleep is going to help answer your question.

DR. SLEEP: Thank you. Darryl Sleep, from Abbott. Dr. Martino, I think what we are trying to do at Abbott really is to get to that question. Partly, that is why we initiated those trials at Columbia University with Dr. Petrylak to evaluate the effects of atrasentan, both DLT and PK, with docetaxel, and moving forward with SWOG to determine what happens to patients because that study will include patients who are asymptomatic and symptomatic and will actually look at the treatment effect in the two different groups and actually stratify ahead of time. The idea is to see if adding chemotherapy to atrasentan helps patients maintain a better quality of life once they become symptomatic. So, we are trying to address that in future studies really to determine whether it is appropriate or not to continue with atrasentan therapy in combination with docetaxel. But I think, as Dr. Nelson pointed out, right now data supports that these patients should be asymptomatic on atrasentan.

DR. CARDUCCI: Can I just add one comment?

I think clinically you ask an incredibly important thing when this drug gets reduced to practice. With hormonal therapy patients progress on it and we keep them on hormonal therapy. When patients are on zoledronic acid, they have a skeletal-related event and we keep them on the drug. So, the data gap that we have really is what are the benefits for that patient who becomes symptomatic because the trial design has stopped the drug at that time point. My sense is this drug is probably like those other agents that we already currently use, that the benefits are going to continue and persist based on the biology. Do we have data that shows that? No. Do we have data that says that there are no drug interactions if you started docetaxel, if you started the Zometa? I think there would be very few safety concerns from that perspective but we do not have that data.

DR. MARTINO: Are there other questions? Dr. Mortimer?

DR. MORTIMER: Yes, I guess both the committee and the company is sort of seeking to

find out a group of individuals who are clearly going to benefit from this agent which does seem to have some activity from the fact that BAP decrease leaves one to believe that this is clearly an osteoblast activity. I guess my question is, is there a variability similar to what you see with radio-pharmaceuticals to people who have hyper-positive bone scans so the more blastic the disease, the more likely they are to respond or to benefit from this in a subgroup analysis?

DR. GORDON: We have tried to look at issues such as that and there is not a clear-cut baseline characteristic, other than the absence or presence of bone metastases, that predicts this is somebody who is going to do particularly well or not do well. There is the beginning of a suggestion that looking at individuals' bone alkaline phosphatase changes may in the long run turn out to help us identify populations, but that is work we are exploring at the moment.

DR. MARTINO: Miss Haylock?

MS. HAYLOCK: One of the concerns that is

among the questions that we are asked to discuss is the issue of cardiovascular toxicity. If this is a group of men with a median age of 72 there is already significant risk of cardiovascular disease, and I don't see anything in the inclusion or exclusion criteria in the study that relates to that. So, I am wondering if you could speak a little bit to the issue of co-morbidities and risk factors.

DR. GORDON: We described that a little bit during the main presentation, showing that men, in fact, particularly in reference both to congestive heart failure and MI, were older and, in the case of MI, had underlying ischemic disease. But I am going to ask Dr. Eliopolis to address that a little bit more broadly for you.

DR. ELIOPOLIS: Helen Eliopolis, Abbot Laboratories. Following the Phase 2 study, 96-594, we did recognize there was a signal for heart failure. So, in study 00-211 patients with New York Heart Association Class II or greater were excluded, as were other patients with instable

conditions. Based on our clinical experience from 211, going forward in future studies we will be implementing more specific advisories, including exclusion of unstable angina, and focusing early monitoring of weight, hemoglobin and blood pressure, as well as advisories to physicians and patients regarding immediately reporting signs and symptoms and also cautioning against abrupt discontinuation of cardiac medications.

DR. GORDON: What I would also like to do is ask Dr. Lang to sort of address this question as a cardiologist who can help us understand the management of these patients and what one normal expects.

DR. LANG: My name is Roberto Lang, cardiologist at the University of Chicago. When you think about heart failure and you first think about the preclinical studies, I think it is clear that this drug does not have any negative inotropic effects. I think we are left with the fact that this drug is a vasoactive compound. In this regard it is not different than many vasodilators that I

use in my cardiology practice every day, like lodipine or nifedipine. Many of the sort of minor events of heart failure could be treated easily by monitoring the patients. It is imperative that we exclude patients with unstable angina, patients that do not have stable heart failure, and if you monitor simple things such as blood pressure, weight and levels of hemoglobin we will be able to exclude the vast majority of these case.

Another important thing is that of the cases that had heart failure, they responded, you know, just by adding an ACE inhibitor or a diuretic. These are the most simple things that physicians do to take care of heart failure and the vast majority of these patients responded well.

DR. GORDON: What I would also like to do is ask Dr. Carducci who, as he indicted, has treated in excess of 85 patients, to just talk to his experience using this drug in this population and other populations.

DR. CARDUCCI: I think, first, you pointed out a great fact about the prostate cancer patients

tending to be older groups overall. When you look at other studies you have had before the panel the groups tend to be younger. So, already we are starting with an older group of patients.

So, treating the men that I have had over the last five, ten years as well as being the PI of the ECOG study 6800, which is in advanced renal cell carcinoma, even though it started in 00, it didn't actually launch until the end of 2002. In that study we did see patients with extensive pulmonary metastases who had early dyspnea, about three, four percent of the patients. We instituted the guidelines that were described with the safety memo into that study, suggesting that patients be seen early, have monitoring of weight gain, have evaluation of changes in baseline symptoms and the early use of diuretics. With that, we were able to reduce that effect back to the baseline that we saw before so we were very encouraged that we were able to manage these symptoms by putting in education to the physicians, the other healthcare providers as well as to the patients.

DR. MARTINO: Dr. Bukowski, did you have a question?

DR. BUKOWSKI: Yes. I am wrestling with the issue of bone scan positivity in an asymptomatic patient and what that represents. I know you had a definition in the protocol regarding what a positive bone scan was. Could you just review that for us, and was there any requirement to further study a positive bone scan with, for example, an MRI to document that, indeed, these were metastatic lesions?

DR. GORDON: Dr. Sleep, do you want to talk to the study inclusion criteria?

DR. SLEEP: Thank you. Darryl Sleep, from Abbott again. There was no protocol-specified requirement to confirm the metastases seen on bone scan with CT or radiographic evaluation. However, I would like to point out that this was subject to an independent review by a central radiologist. In the event that the radiologist required additional confirmatory evidence of metastatic disease or not, as can be said for baseline and/or advancement of

progressive disease, he requested and was given appropriate confirmatory studies as required.

DR. MARTINO: One last question.

DR. CHESON: A very quick one, was this independent review blinded as to the treatment arm?

DR. GORDON: There were two aspects to independent review. There was a baseline independent review that was conducted prior to the patient being enrolled in the study so that was documenting baseline presence of bone metastases. Then the independent review process during the course of the study was conducted blinded not only to treatment but to PSA levels as well. And, there were two radiologists that reviewed each scan and needed to agree on it, and if the two didn't agree there was a third radiologist. Then, to document clinical endpoints there was an independent oncology reviewer who had to agree that there was progression.

DR. MARTINO: I am now going to turn you to the questions but, just before I do that, Dr. Gordon, I want you to, in two or three sentences,

summarize for me the following: Not in your entire population but in the population that you prefer, the patients with bone metastases--and I don't want to hear any statistics--I want you to summarize for me what you think you have demonstrated in that subpopulation.

DR. GORDON: Okay, I will try it and if it is agreeable I will have a clinician who takes care of the patients sum it up for you as well. I think what we have shown, and because you don't want statistics I won't put up the slide--I think what we have shown across the studies in a primary endpoint that included both radiographic and clinical elements, and the clinical elements being those types of effects or disease progression events that patients fear--as we have heard pain and the development of pain--that we have had a positive effect in reduction in the risk of developing those.

I think the other part of our story that is compelling is the science and how the science ripples through that. This drug is predicted to

work on the osteoblast-prostate cancer interface. If that is true you would expect that we would decrease the elaboration of bone alkaline phosphatase not only as a marker of disease burden but of drug action. The drug does that. If that were to be true, you would expect to see changes in the amount of bone scan progression. You see that. If you believe that bone scan and the development of osteoblastic disease is important and translates ultimately into symptoms, we see that. All of those are objective measures.

On top of that, if you believe that these are things that matter to patients, then those aspects of the protocol-specified quality of life measures, FACT-P and the domain that is most relevant to prostate cancer patients in fact does change and shows benefit for those patients.

I will ask Dr. Nelson to address what does this mean to patients.

DR. NELSON: I recently had a patient who had been on atrasentan and he was asymptomatic and then he progressed and became symptomatic. I sat

with him and he said, you know, I knew I was going to die of prostate cancer and now I am dying of it because I am feeling the symptoms of my disease. And, he thanked me for the time that he had when he knew his disease was progressing but he was not suffering from it. That is what this drug does.

FDA Questions to the Committee

DR. MARTINO: Thank you, Dr. Gordon. If someone can put up the questions, I will direct the committee's attention to the fact that we have four questions. Rick, do you want actual discussion or do you want votes on each of these four? Yes, you want votes on each of the four? Okay.

Question number one, in study 211 in the intent-to-treat analysis of time to disease progression and progression-free survival atrasentan did not show an advantage over placebo. Multiple subgroup analyses were done which the FDA considers exploratory. The applicant now requests approval based on an unprespecified subgroup analysis in hormone-refractory prostate cancer patients with bone metastasis. Are the time to

disease progression results in study 211 in the bone metastasis subgroup statistically persuasive?

Is there discussion on this issue? Again, the question is are they statistically persuasive, not clinically. Dr. D'Agostino?

DR. D'AGOSTINO: From a statistics point of view, for all the above description, I would definitely say no. It is a subset analysis; it is a post hoc analysis, which leads us to being unable to interpret it from a statistics point of view.

DR. MARTINO: Other comments? Seeing no other comments, I will take a vote and we will start on my left, please, and please state your name before you vote.

MR. KAZMIERCZAK: Eugene Kazmierczak, statistically, no.

DR. BRAWLEY: Brawley, no.

DR. D'AGOSTINO: D'Agostino, no.

DR. BUKOWSKI: Bukowski, no.

DR. CHESON: Cheson, no.

DR. ECKHARDT: Eckhardt, no.

DR. PERRY: Perry, no.

DR. RODRIGUEZ: Rodriguez, no.

DR. MARTINO: Martino, no.

DR. MORTIMER: Mortimer, no.

DR. LEVINE: Levine, no.

MS. HAYLOCK: Haylock, no.

DR. REAMAN: Reaman, no.

DR. MARTINO: The vote is unanimous and the answer is no. Question number two, in study 211 the difference in median time to disease progression between atrasentan and placebo is five days in the intent-to-treat population, four days in the per-protocol subgroup and seven days in the bone metastasis subgroup. Is the size of the atrasentan time to disease progression effect in study 211 in the intent-to-treat, per-protocol subgroup or bone metastasis subgroup clinically important?

Discussion on this question, please, clinical significance of these differences. Please?

MS. HAYLOCK: Just a comment, I am concerned that it is the wrong question, that the

time to disease progression doesn't seem to be the right measurement, as I think you pointed out earlier, in terms of supportive care questions. The time to disease progression isn't the question but it is, rather, the time to symptoms.

DR. MARTINO: Mr. Kazmierczak, did you have a comment?

MR. KAZMIERCZAK: No, I don't have any comments.

DR. MARTINO: Dr. Rodriguez?

DR. RODRIGUEZ: I think several comments from the group suggest that that is, indeed, the case but, unfortunately, I did not hear any data that time to symptoms was accurately, consistently and reliably measured.

DR. MARTINO: Are there other comments?

DR. PAZDUR: Silvana, I have one. We usually talk about a finding that is statistically positive and then talk about the clinical relevance of that. For example, something may be associated with a very low p value and then the difference might be in a matter of days. Okay? And then one

could question whether this is clinically relevant.

In reading this question over again, we are kind of asking the opposite question and I kind of want discussion on the question in a sense, especially from Dr. D'Agostino. You know, the purpose that we have statistics is really to determine whether something is a true finding, to give us credence that this isn't just happening by chance. Does it make sense really to discuss the clinical importance of a situation that you are unsure of? I would like discussion on the question I guess somewhat.

DR. MARTINO: Dr. D'Agostino?

DR. D'AGOSTINO: I think in this very committee I have in the past become red-faced arguing over and over again that you really shouldn't talk about clinical significance if you don't have statistical significance. My vote is going to reflect that I think that the question is inappropriate. That is, if we say no to one then we shouldn't really move on to clinical significance. I thought maybe you were just trying

to get at a sense of was seven days a meaningful thing, whether or not it relates to the data or not. I think the study is a failure for the endpoint that they had and the statistical significance ends the discussion about the usefulness of interpreting the measurements here but, again, I thought that the question was really trying to get at are these numbers meaningful and my answer would be no.

But from the statistics point of view, the way you just phrased it, I don't think we really want a discussion about clinical significance if the statistical significance isn't there, and I think that is a very important scientific step that, again, we have argued about over and over again in the past, and I think we should argue it here and make sure that we understand that you can't really talk about clinical significance from the data if you don't have statistical significance.

DR. MARTINO: Dr. Brawley?

DR. BRAWLEY: Dr. D'Agostino made my

point.

DR. MARTINO: Rick, do you have something else you want to say?

DR. PAZDUR: I just wondered if others on the committee have other opinions. If we take a vote and people do feel that it does not have statistical significance yet clinical significance, if they could explain their reasoning. I would be interested in hearing people's opinions.

DR. BRAWLEY: In that case, may I?

DR. MARTINO: You can answer.

DR. BRAWLEY: The way I look at it is that the finding in study 211 is not statistically significant. Therefore, any numbers that we get are a fluke. Question number two that I read is, is four days versus five days versus seven days significant given that your findings have "flukiness?" And the answer is no.

DR. MARTINO: Let me take a slightly different tack to this. I do think that there is a difference depending on what your ultimate goal is. There is a thread that runs through the data that

has been presented here. There is a mechanism that has been suggested. It is a plausible mechanism. It makes clinical sense as to why this drug ought to do something in patients with bone metastasis. So, there is a logic to being hopeful. Okay? So, there are times when, depending on what your intent is, there is clinical significance.

So, I do think that there is clinical value--and I don't want to use the word "significance" because most of us think we know what that means. I think there is clinical value in what has been presented today. The issue is do I now want to change my behavior based on it? That is really how I interpret this question.

DR. PAZDUR: And here again, Silvana, clinical value could have a tremendous difference of opinion. Clinical value might mean I think that this agent should be studied further, that there is something here that warrants study, rather than clinical value that warrants approval. Here again, if I had to reword this question or rewrite it, it might be somewhat different.

DR. MARTINO: Dr. D'Agostino?

DR. D'AGOSTINO: Again, I think maybe we need clarification on interpretation because if we are saying can we make interpretations of the clinical importance of these numbers given the studies that we have and the results that we have, I would say no because, as the two of us over here have said, you haven't achieved statistical significance so there is no way of really interpreting the clinical aspects of the study. If you want to talk about is there a story, is there a message that is going on here that would lead to further investigation, I think we should split out this one question into two separate questions because we probably have different opinions on that. But if we are saying are these numbers clinically important in the context of the full study, the study was negative so my answer should definitely be no for the clinical importance.

DR. MARTINO: Dr. Brawley?

DR. BRAWLEY: The value that I take out of this whole presentation is that I do think that the

drug has some activity. I, however, think that the company needs to go and look at the subsets for where that activity was; try to better define the population; and do clinical trials in that population that is very highly likely to benefit. I don't think that one can actually say that seven days is more important than four days in this clinical trial with the rules under which this trial was run.

DR. MARTINO: Dr. Bukowski?

DR. BUKOWSKI: I agree with all those comments and I think that what the data are telling me is that the company needs to figure out how the drug works. There are subsets, clearly, where there is going to be activity. They don't have the exact mechanism quite nailed down yet. They need to refine their groups and they need to refine their patient selection so that they enrich their population to show the differences that they want to show. So, I think clinically meaningful with these data, no; possibly, yes as they refine it.

DR. PAZDUR: Could I offer a suggestion

then, Silvana? Since we have difficulty with some of these questions, maybe we should cut to the chase here and go to question number four and then people could give their opinions in summary?

DR. MARTINO: I would be very happy to do that. Just for everyone's reminder, question number three deals with toxicity of this drug, particularly the cardiac toxicity. I just want people to understand that because in answering question number four it really is a risk/benefit ratio. So, you cannot ignore the toxicity issue at least as you think about this issue. Okay?

The very last question, number four, should this NDA be approved? Recognize that right now there is no guideline to us as to whether we are talking about full or accelerated approval. It is the general concept as a whole that you may speak to.

DR. PAZDUR: And let me address that once again. As I said in my opening comments, you should have confidence that you have an effect on an endpoint here, whether it be full approval or

accelerated approval. Full approval versus accelerated approval, they are both approvals. They allow marketing of the drug. There are nuances that are different, including follow-up studies with accelerated approval, the ability to approve the drug on a surrogate endpoint. It is not a mechanism to approve uncertain results but the effect should be there. The question is on what endpoint and what one considers that endpoint to be.

Here, again, really going to question number four, it is risk/benefit so it really addresses this whole concept of a risk and a benefit which incorporates the toxicities. So, I think we are moving in that direction but for time's sake we could consolidate the discussions because I think that this addresses the meat of the issue in that sense.

DR. MARTINO: Who is ready to deal with the issue? Again, the issue is approval or not approval. Yes?

DR. PERRY: I am going to vote against

approval of this drug. I don't think the company has met their goals and our patient advocate population has I think obscured the endpoint. This is not a curative drug. All the people who get this drug are eventually going to have progression of disease. They are all going to have pain. We throw out the boogie man of poor pain control and maybe you need to have a talk with your physician or physicians about what is adequate pain control because I don't think we ought to be swayed by an emotional appeal that there are thousands of people dying in pain and that this drug will solve that problem or that it will cure them. It will do neither.

If we approve this drug now, I think what we are actually going to do is slow down the appropriate clinical trials to find the place for this drug because it is going to be used for everybody out there with prostate cancer. So, I think there is an absolute disservice to approving this drug now and I can't see how we can do anything but disapprove it.

DR. MARTINO: Yes, Dr. Levine?

DR. LEVINE: I will also vote to disapprove it at this time. On the other hand, I am impressed that there are data there that need to be evaluated more carefully and it would be a real shame if the company were to throw this away. I think there is data there that needs to come back in patients with bony metastasis, looking very, very carefully at objective, sequential evaluations of pain, perhaps doing the scans a little bit differently. So, I don't think you gave us the data to allow me to approve this but I am sad about it actually.

DR. MARTINO: Dr. Eckhardt?

DR. ECKHARDT: I agree with not voting for approval and I think the qualification I would make again is that, you know, this is an interesting compound that, rather than just general effects on the bone, it appears to have a mechanism base with regard to the pathophysiology of prostate cancer. I think that is important.

I think going forward, the idea is going

to be to really look carefully at patient selection parameters. But I think, even more even importantly, to really think carefully about the types of endpoints that can enhance the quality of these patients' lives. You know, I think that a lot of these will center around pain and performance status.

DR. MARTINO: Dr. Reaman?

DR. REAMAN: I would also vote against approval, but also add to the comments made to the company that I do also feel that there are some exciting data that have not, in fact, been presented and would urge you to explore this further, as well as better define time to progression either clinically and/or radiographically. I would also echo Dr. Perry's comments that I think if [not at microphone; inaudible]...It is certainly an appeal for the advocacy community to take that back to their physicians.

DR. MARTINO: Dr. Cheson?

DR. CHESON: Yes, I would just like to

offer a cautionary word, and that is although it is important to move forward with combination trials, one has to approach those carefully because I haven't heard--and I don't know the prostate field that well--any evidence of in vitro synergy from combinations of this with Taxotere, or whatever, and there are ways to combine drugs that are positive, and there are ways that might give you a falsely negative result. So, just taking the other drugs that are active and mixing this in there--they need to be careful in how you do it and preferably have some rationale for the dose, schedule and combinations that they approach because we would hate to have a big false negative.

DR. MARTINO: I would like to echo that personally. I am actually concerned that as we move into these multi-agent sort of trials that we will deprive patients of what many of them seek and many of us as physicians seek, which is a simple therapy which is easy to give and which is effective. When you take a drug which is effective and is easy to give and you combine it with

therapies that are not so easy to give or easy to tolerate you sort of lose what many of us long for, which is a therapy, especially in patients that are asymptomatic, that may do something in terms of prolonging the point where they become symptomatic. So, I am also concerned that the drug on its own needs further study without confusing it and without always creating therapies that are complex for patients. Dr. Rodriguez?

DR. RODRIGUEZ: I also do not consider this drug at the present time to be ready for approval. I also would like to add that the toxicity of the drug has been, in my opinion, down-played significantly. I am from Texas and the specter of Vioxx looms very large over us. If this drug is going to be combined with other chemotherapy drugs that are heart toxic I can see that patients would, in fact, suffer rather than benefit.

DR. MARTINO: Dr. Mortimer?

DR. MORTIMER: I agree with the group that this drug should not be approved. I have one other

sort of concern as the company moves forward. We talk about combination agents as always being cytotoxic agents but I think in the setting of prostate cancer with a drug which you now seem to demonstrate mechanistically with an osteoblast, now looking at a population that is receiving combined therapy with lytic agents against lytic components of the disease as well, I guess I would just worry if we didn't take that into account.

DR. MARTINO: Dr. Brawley?

DR. BRAWLEY: Briefly, I have hope for this drug and I do hope it continues to be developed. I, however, think that approval at this time based on the current information is premature. I take care of prostate cancer patients and I would like to see prostate cancer patients have options. However, I want them to have legitimate options. I keep pictures in my office of patients who have been harmed by illegitimate options of therapy. Development of this drug I think would be slowed down right now if we were to approve it at this time.

DR. MARTINO: At this point then I am ready to take a vote. Again, the question is are we ready to give any type of approval to this agent today? We will start again to my left, please. Please state your name and your vote.

MR. KAZMIERCZAK: Eugene Kazmierczak, no. The drug does appear to, in certain cases, delay progression of the disease but in the current context of the study I can't see how I could vote for approval of the drug so I am a no.

DR. BRAWLEY: Brawley, no.

DR. D'AGOSTINO: D'Agostino, no.

DR. BUKOWSKI: Bukowski, no.

DR. CHESON: Cheson, no.

DR. ECKHARDT: Eckhardt, no.

DR. PERRY: Perry, no.

DR. RODRIGUEZ: Rodriguez, no.

DR. MARTINO: Martino, no.

DR. MORTIMER: Mortimer, no.

DR. LEVINE: Levine, no.

MS. HAYLOCK: Haylock, no.

DR. REAMAN: Reaman, no.

DR. MARTINO: The vote is unanimous, all no. At this point I thank all of your for joining us this morning, specially the company for presenting their data and, again, realize that we have hopes for your drug and we hope to see you again. Thank you.

[Luncheon recess.]

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

Introductions

DR. MARTINO: Good afternoon, ladies and gentlemen. This afternoon the committee will discuss NDA 21-743, Tarceva, OSI Pharmaceuticals, proposed indication for the first-line treatment in combination with gemcitabine for patients with locally advanced, unresectable or metastatic pancreatic carcinoma.

The first thing I would like to do, I would like the committee members to introduce themselves, starting on my left, please.

MS. WELLS: I am Jennifer Wells. I am a patient representative, from Santa Barbara, California. I am the widow of Philip Katz who died of pancreatic cancer 16 months ago after a 17-month battle with it.

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

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

DR. BUKOWSKI: Ronald Bukowski, medical

oncologist, Cleveland Clinic, Cleveland, Ohio.

DR. CHESON: Bruce Cheson, hematologic oncologist, Georgetown University Hospital.

DR. ECKHARDT: Gail Eckhardt, medical oncologist, University of Colorado.

DR. GRILLO-LOPEZ: Antonio Grillo-Lopez, medical oncology. I am the industry representative on the committee. However, I will not receive any support whatsoever from industry for my attendance at this meeting.

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

DR. RODRIGUEZ: I am Maria Rodriguez, hematologist/oncologist, M.D. Anderson Cancer Center in Houston, Texas.

DR. MARTINO: Silvana Martino, from the Los Angeles Clinic Santa Monica, California, medical oncology.

MS. CLIFFORD: Johanna Clifford, FDA, executive secretary for the meeting.

DR. MORTIMER: Joanne Mortimer, University

of California San Diego, Moores Cancer Center, medical oncologist.

DR. LEVINE: Alexandra Levine, hematologic oncologist, University of Southern California.

MS. HAYLOCK: Pamela Haylock, oncology nurse, University of Texas Medical Branch in Galveston.

DR. REAMAN: Gregory Reaman, pediatric oncologist, Children's Hospital, Washington D.C., and the George Washington University.

DR. LE: Charles LE, statistical reviewer, FDA.

DR. SRIDHARA: Rajeshwari Sridhara, statistical team leader, FDA.

DR. SENDEROWICZ: Adrian Senderowicz, medical officer, FDA.

DR. JUSTICE: Robert Justice, acting director, Division of Drug Oncology Products, FDA.

DR. PAZDUR: Richard Pazdur, Office director.

DR. MARTINO: Thank you. Dr. Pazdur, do you wish to make any comments to the committee

before we start?

DR. PAZDUR: Just a similar comment to the one I made previously when you had asked me whether we are considering this for full approval versus accelerated approval. Since the claimed benefit is on overall survival this would be considered for full approval, not for accelerated approval.

DR. MARTINO: Thank you. The next item of business, Ms. Clifford will address conflict of interest for the committee.

Conflict of Interest Statement

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

In accordance with 18 U.S.C. Section 208, full waivers have been granted to the following participants:

Gail Eckhardt for unrelated advisory board activities for the sponsor of Tarceva, for which she receives less than $10,001 a year and for unrelated consulting for the distributor of Tarceva, for which she receives less than $10,0001 per year.

Pamela Haylock for owning stock in the distributor of Tarceva, valued from $5,001 to $25,000.

Ronald Bukowski for unrelated speakers' bureau activities for the distributor of Tarceva, for which he receives less than $10,001 per year.

Jennifer Wells for owning shares and a sector mutual fund that invests in the healthcare industry, valued from $25,001 to $50,000.

Bruce Cheson for unrelated data safety and monitoring board activities for the distributor of Tarceva, for which he receives less than $10,001 per year.

Michael Perry for owning stock in the distributor of Tarceva, valued from $25,001 to $50,000.

A copy of the wavier statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building. We would also like to note that Dr. Antonio Grillo-Lopez is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Grillo-Lopez is employed by Neoplastic and Autoimmune Disease Research.

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 products they may wish to comment