distributions. The reason for that is that most survival curves contain quite a bit of censoring. There are a lot of patients alive at the end of the study so that these curves do not go back down to zero. It turns out the average, the mean as we know it, is equivalent, is identical to the area under these survival curves, and as long as these survival curves reach the time axis it is very easy to calculate the means and, therefore, very easy to interpret them.

So, I have shown you the mean survivals on here. They are a little bit further apart, 8.7 versus 6.2, just to put that in real terms that actually turns out to be a 5-week difference in the mean survival calculated this way.

Another way to get an estimate is to say, well, let's believe that this hazard ratio is true. I have told you before that proportional hazards are assumed, and they are actually verified here. If you see these curves, they separate early. They stay separated all the way through. All of the statistical tests that we run to demonstrate that

the hazard ratio is constant are satisfied so we can actually apply this hazard ratio now to either of these medians or the means, if we want to.

If we apply this hazard ratio to the medians to the Tarceva group and then infer what the placebo group would have been under those circumstances, or vice versa, you get median differences that are either 5 weeks or 5.7 weeks. So, I think you should probably not be fooled by this pinching together of these 2 particular survival curves, and you should probably think that this benefit is in the neighborhood of 5-6 weeks. I will let the clinicians discuss whether that is a clinically significant difference or not.

DR. CAGNONI: I will invite Dr. Moore first and then Dr. Rothenberg, please.

DR. MOORE: I will just make a couple of comments. I think that is the question that most clinicians are wrestling with when you get a result like this. I mean, I think if you work in the field of pancreatic cancer, first of all, most of the time you expect trials to be negative because

that is the usual result. Having said that, you know, most improvements in oncology are, as one of the advocates mentioned, incremental. If you look at most positive oncology trials the hazard ratios tend to range from about 0.65 to 0.85, which is like a 20 to a 50 percent improvement in survival. This one was 0.8, which is a 25 percent improvement.

So, I guess the question is when you have a horrible disease like pancreatic cancer where the median survival is only 6 months the absolute improvement of a hazard ratio of 25 percent is only 1-2 months. So, it is a question of do we penalize people who have these very aggressive diseases by saying we are going to require a higher standard in terms of survival hazards than we apply to other diseases?

As regards the question of, well, does this mean we now have to use triple therapy and beyond, I think that is probably a good thing. I think we are not going to solve this disease by gemcitabine plus drug X. We are going to solve

this disease by targeting a whole bunch of different pathways that are over-expressed in pancreatic cancer. I am personally hopeful that if we target, let's say, the VEGF pathway and the EGFR pathway and other pathways that we know are over-expressed, we will have a better chance of controlling the disease.

DR. ROTHENBERG: As you know, progress in cancer is not linear. Does this represent progress? I believe it does. But I don't think it necessarily means that we need to proceed in just one line of pursuit. In fact, right now in 2 large U.S. cooperative oncology groups they are actually looking at different complementary approaches. One is using cetuximab and EGFR-targeted monoclonal antibody, combining that with gemcitabine versus gemcitabine alone. CLGB is looking at bevacizumab and gemcitabine versus gemcitabine alone. I think those trials will provide us with very useful information, and it may be that the progress that is made is going to be following many different directions and then we will be able to be in a very

nice situation of having to fill in gaps to see how we can actually use these multiple drugs in an optimal fashion.

Again, I hope that this leads to a situation not unlike that which occurred with colorectal cancer where we had 2 cytotoxic agents that were each being combined with 5-FU and showing significant advantages. Now we have 2 biologics, bevacizumab and cetuximab, and we have these 5 or 6 drugs that are available now, and how can we actually capitalize on the use of those for the ultimate benefit of our patients? So, I think that this is an important first step in developing better therapies for pancreatic cancer patients.

DR. MARTINO: Dr. Hussain?

DR. HUSSAIN: This is perhaps for a brief clarification from the FDA. Given what Dr. Pazdur said, that the magnitude is a hard thing to decide on--days, weeks, months and so on--I am going to neutralize that or remove it to the side for my assessment, and given that this is positive on its own merit--they set up to look at an increase in

survival and they showed it--why are we looking at it? What is it that is bothering you about the outcome of the study that is in your mind suspicious and that brings it to ODAC?

DR. PAZDUR: We wanted a public discussion of it, pure and simple. I do have a question though that I would like to bring up, and that is the issue of the use of the drug Tarceva with chemotherapy. I think this is a question that, if you knew the lung cancer data, would be a glaring elephant in the room, so to speak. When the first-line lung cancer trials were done which combined this drug, Tarceva with several chemotherapy regimens I believe there were 2 first-line trials. Both of those trials were negative in the first-line setting for a survival effect. A very similar drug, and I won't go into the details of it but Iressa also did 2 trials in first-line trials. Again, those were negative. So, we had 4 first-line trials I believe in lung cancer that were completely negative when these EGFR receptor small molecules were combined with

chemotherapy.

This caused many in the field to say maybe these drugs shouldn't be used with chemotherapy. Granted it is a different disease. We do have a trial now that is combining this drug, albeit with a different chemotherapy, gemcitabine plus Tarceva. Do you think that this is the best route to use this drug as far as schedule? Should this drug perhaps be given in sequential use? You know, is that something that you plan on investigating? Again, I am cognizant of the fact that patients with pancreatic carcinoma have short survivals and, hence, second-line therapies don't have the same meaningfulness because many of these will have very rapid progressions. But are we using this drug appropriately?

I am bothered I guess by the fact from the lung cancer data I never got a satisfactory explanation of why those first-line trials were negative. Is it a negative effect that we are seeing with chemotherapy? What is going on? Why does it work in this situation but not in any other

situation as far as the lung cancer--I shouldn't say any other but in the lung cancer situation?

DR. ECKHARDT: Yes, I think that is a great question. You know, I think there is increasing evidence to show that mechanistically there are issues with regard to combinations of chemotherapy and EGFR-directed agents and in particular the small molecules. I think what is interesting about this data is the fact that there is at some level positivity.

Actually, my next question would be to conduct some of those studies because I think clearly there is evidence that you can go with the chemopotentiation strategy that may be different than just drawing both drugs together. Increasing groups are showing that, you know, chemotherapy really stimulates pro-survival responses and, depending on how you time the EGFR-targeted agent, you can either antagonize that or synergistically lead to apoptosis.

You know, I think really what is happening here is that at least we are seeing with concurrent

usage that there is some small incremental benefit. But I would hope that that would be one of the ideas to pursue next as to whether, indeed, the patient shouldn't necessarily get concurrent therapy. In fact, that could help with toxicity as well. But I completely agree. I don't think that any of us ever felt that that prohibited investigation, but it taught us to go sort of from the clinic back to the bench to start assessing what the mechanistic principles are that underlie that. In fact, there is very nice synergy between things like oxaliplatin and gefitinib that was not anticipated. So, you know, I think that is an important question and I would hope that anybody that sort of has this first approval potentially of a drug in combination with the small molecule would actually conduct those kinds of studies.

DR. PAZDUR: Here again, we saw a pretty persuasive effect in the original Tarceva approval when it was used as monotherapy. When the drug was combined with chemotherapy one did not see any effect. Generally one would expect with

traditional chemotherapy to see better effects with earlier stage disease so it does raise some mechanistic questions that I don't think should be lost.

DR. ECKHARDT: Right, and I think if you look at what is coming out from laboratories now, there are clear-cut mechanistic differences between sequential and then concurrent--you know, two different sequences versus concurrent.

DR. CAGNONI: If I may comment on that? Dr. Pazdur is correct. There have been trials in non-small cell lung cancer which were conducted in first-line in combination with chemotherapy. Both included a platinum compound which is absent from this study. And, the studies did not show an advantage from adding Tarceva to chemotherapy. However, there was no worsening of the results. There was no antagonism. The results from subgroup analyses in those studies were intriguing. There was a very large treatment effect, for example, in the lung cancer trials and never-smokers which suggests that in the right group of patients, at

least in first-line lung cancer, the combination might still be feasible.

Dr. Eckhardt is correct. There are numerous studies ongoing, preclinical, that have suggested that perhaps there are other ways to combine Tarceva with chemotherapy. At OSI, in collaboration with our partners, we are exploring other ways to administer Tarceva relative to chemotherapy to non-small cell lung cancer patients, whether sequential and intercalated. Those studies are actively ongoing and we will be prepared to consider similar proposals in pancreatic cancer patients.

DR. MARTINO: I would like to ask a question to Dr. Clark. Gary, when you presented the data on quality of life, my summary of what I heard from you was that the group that received Tarceva didn't do any better or any worse. Generally speaking, quality of life was not altered with some exceptions, the exceptions being that there was more diarrhea and a little bit more rash. So, if I could summarize all of that, I would say,

gee, maybe I get to live a little bit longer but from a clinical perspective, other than counting whatever those days are--and I am still uncertain what those days are, the very fact that I have to use the word "days" still bothers the hell out of me if what I am going to do during those days is, let's see, I get to have rash and diarrhea. That bothers me a bit, that the quality of life was in no way made better by something that prolongs my survival. And, I have to ask myself as a human being, if I have pancreatic cancer I am uncomfortable and that is a very nasty disease. Yet, no one has suggested here that I will live those few days with a better quality of life. I am just going to get to have diarrhea and a rash. Gee, what a gift you have given me! Help me to understand this.

DR. CLARK: I think it is very important to remember that the quality of life was a secondary endpoint. I prefaced my remarks when I showed you the results to say that these were exploratory analyses and probably no definitive

conclusions could be drawn.

These instruments are not terribly sensitive to picking up perhaps the types of differences that we would like to see. I think, again, those curves--let me just go ahead and put that slide up to show you again the global quality of life.

[Slide]

I mean, there is a little bit of a suggestion that things are a little bit better in those early parts of the curve. The results are not statistically significant. We just felt that it was really important not to make any claims of improvement and the fact that we didn't do any detriment. It certainly doesn't look like there is any harm by adding Tarceva to gemcitabine. I think that is about the only conclusion that we can draw from the study as it was designed.

DR. CAGNONI: If I can ask Dr. Rothenberg to comment on this issue?

DR. ROTHENBERG: Just two points of clarification, one is just to point out that the

incidence of grade 3 or 4 diarrhea in this trial with Tarceva was less than 6 percent. Compared to other drugs I have worked with before and presented to ODAC, that is quite a bit less.

In addition when you look at the incidence of severe toxicities, that is toxicities that occur at any point along the treatment time and if grade 3 diarrhea occurred, then dose adjustments were taken. So, when you talk about that additional life gained by the drug maybe being tainted in some way by this toxicity, that actually may not be the case. The toxicity may have occurred early, been addressed adequately and the patient may have actually enjoyed a good quality of life as the global quality of life indicates.

DR. PAZDUR: I did want to clarify one thing. I didn't want my previous comments to shut off any discussion from the committee regarding consideration of the clinical relevance of this. In fact, we do have questions regarding that and I think that that is something we want to hear about from the committee. This is an issue that needs

discussion. If it is something that the committee wants to discuss, I think it is an appropriate discussion and my previous comments did not mean to curtail that discussion whatsoever vis-a-vis Dr. Hussain's question.

DR. MARTINO: Well, we are glad to hear that because, in all fairness, as a clinician I have a very hard time trying to make judgment of this in the sense that if all you brought me here to do is just to say a p value is a p value, you don't need me here for that. Okay? I could have told you that over the phone or in an e-mail. Okay?

So, I actually do think that the real issues here have to do with is it 2.5 minutes; is it 12 days; is it 5 weeks? Though we are pretending that those numbers are the same, they are not the same. Unfortunately, they are in a very narrow range but they aren't exactly the same, and unless that and quality of life are the issues, then it is very unclear to me why I am sitting here. You know, I could be having a cappuccino

somewhere!

DR. PAZDUR: We do ask those questions here and I do want to preface that.

DR. MARTINO: Who is next? Yes, Dr. Bukowski?

DR. BUKOWSKI: To OSI, do you see the same benefit in the subgroups of patients with locally advanced or metastatic disease, and if you subdivided them by performance status in terms of effect on survival?

DR. CAGNONI: We have conducted those exploratory analyses and I will ask Dr. Clark to comment on those results.

DR. BUKOWSKI: I was asking about subset analyses looking at locally advanced or metastatic patients to see if, indeed, the benefit, whatever it may be, persists.

DR. CLARK: Yes. In the agency's presentation they showed you Forrest plots of various subsets. We have no quarrels with those Forrest plots.

[Slide]

The only thing that I will show you is that, once again, if you go to the most complete data set with all of the follow-up, we have done some multivariate analyses and the reason we have done this is if we start looking at subsets there are some imbalances that can take place just by random chance alone. So, to try to balance out some of these, these are the differences.

With a multivariate adjustment the hazard ratios are 0.80 and 0.80. So, we see no difference by stage of disease. We continue to see a little better result in performance status too, but once again I will remind you that there are only 86 patients supporting that particular hazard ratio and, as you can see, there is probably not a lot of difference by performance status in the results. None of these results has a statistical interaction that is significant that would indicate that we should believe that there is a difference in the response in the hazard ratios between the subsets.

DR. MARTINO: Dr. Levine?

DR. LEVINE: I will take on the quantity

of time for a moment. I think one of the issues relates to the fact that none of us can put a statement on a week or a month. You can't do that. The survival in pancreatic cancer is 6 months. If we say to the company we want a year, we want 5 years, that is not fair. That is just not fair.

In fact, if there is an improvement of 1 month over 6, I mean, if it is a 15 percent, 16 percent improvement in survival, then I think that is valid. I also kind of think about what Ms. Schimmel was saying. If it is an extra week or an extra month it is the opportunity to go on another trial; it is the opportunity to buy another little piece of time and that is really what our patients are doing. That is what we are always trying to do, buy another; buy another; buy another. I think that the company has shown that there is a statistically significant--which they were asked to do--advantage as far as survival. It is a small piece of time but given the normal median survival in this disease, it is not negligible.

DR. MARTINO: Dr. Cheson?

DR. CHESON: But it doesn't come without a price and that is the problem I think a lot of us are struggling with. Okay, so it is 10 days. I actually calculated 9.9 days. You are coming out with increased toxicity and no improvement in quality of life. So, you know, that is something we are all struggling with. If it were 10 days and the drug was innocuous, slam-dunk. But there are problems associated with it and what really troubles me is the lack of improvement in quality of life.

DR. MARTINO: Dr. Perry?

DR. PERRY: Could somebody from the company, presumably Dr. Clark, comment on the median duration or response, your slide number 16?

DR. CAGNONI: Certainly. Gary?

DR. PERRY: Where is the drug effect?

DR. CLARK: That is a very good question, where is the drug effect?

[Slide]

The drug effect actually comes from what I kind of think of as a stage migration. Quite

frankly, the absolute survival you see if you have a progressive disease is pretty much the same whether you get that progressive disease by gemcitabine and placebo or you get it by the Tarceva. So, we see survivals that are just about the same, 3.5 months, 3.6 months if you have progressive disease.

If you choose stable disease, it is about the same as well. You have a hazard ratio of 0.82. There is not really a lot of difference between the medians. So, if you have stable disease it really doesn't matter whether you get it from the placebo and gemcitabine or Tarceva and gemcitabine. Similarly, in complete and partial response you have longer durations, longer survivals, but there is not a lot of difference.

What we have done though is we have moved patients, a proportion of patients from the progressive disease up to stable disease, and stable disease and complete response together--let's go back to the previous one where we can see the numbers just a little bit better.

[Slide]

So, we had 41 percent of the patients in progressive disease. We moved that up to 59 percent when we had a clinical benefit, the combination of complete response and partial response. These patients--this line has longer survival than that line. There are more of them now in the Tarceva group than there were in the placebo. So, we have made a shift but by response category they are the same.

DR. CAGNONI: I think Dr. Rothenberg has a comment related to this issue.

DR. ROTHENBERG: If I understand your question correctly, you are concerned that the median duration of response was not different between the control arm and the investigational arm. That is actually a phenomenon that was seen in the original gemcitabine versus the 5-FU trial as well. I just pulled the paper and it is not in the manuscript but I remember it from the data set that was presented at ODAC. The fact is that more patients--well, the fact is that patients who

respond to whatever treatment did respond for equal lengths of time. So, really the overall benefit that we are seeing is not necessarily due to a longer response but more the tumor stabilization as well as the responders. So, it is not a unique phenomenon to this trial.

DR. MARTINO: Mrs. Wells?

MS. WELLS: I would like to respond again to the issue of quality of life. As I said earlier, anecdotally I have not seen too many patients who have solely been on gemcitabine. I have seen some people on gemcitabine who have been very, very ill and for others it has been relatively benign. Typically, it is in combination with something else--one of the platins, irinotican, there is a whole series of things that gem is used in combination with. The quality of life varies from patient to patient on all those combinations. Frankly, on a lot of them the quality of life is not particularly good, but I didn't see anybody in my experience saying I want to get off that; I prefer just to die rather than

to have diarrhea.

I think the population that I have seen has been a relatively young population. My husband was 47. The group in our pancreatic cancer group ranged from 38 to 60. And, I am saying what I am seeing in these stats is that there is an improvement in survival. There appears to be. It is slight but it does give you an opportunity to be around for the next clinical trial, for the next breakthrough and, anecdotally, the information that I have seen on the chat rooms for Johns Hopkins is that the people who have been taking Tarceva and gemcitabine have had issues with rash. Some have had issues with rash; some have had issues with diarrhea. Nobody stated that they felt it was to the point where they wanted to get off the combination. Thank you.

DR. MARTINO: Dr. Hussain?

DR. HUSSAIN: I guess I want to speak for the drug and I want to echo Dr. Levine's comments. I think this is a positive study in a tough disease. The magnitude of days--it is not like one

patient is going to live 7 days extra, there is a trend that is across the board with the drug having a superior curve. I look at this and I say if it was me, would I rather be in the lower curve or the top curve? Certainly, if I would make that decision for myself I would rather be in the top curve.

The issue of risk and benefit, when we pile up drugs I don't know that realistically we should expect that quality of life should get a lot better. I think that would be an important thing if, in fact, you are showing some other--not necessarily a survival endpoint. I think when a combination shows a survival improvement, to me that is the overriding factor. Invariably, yes, patients have a problem with side effects but they choose to go and get a transplant for a possible shaky benefit.

So, I don't think we ought to be the judge on what the patient may choose. I think the approval of the drug would allow an informed conversation with the doctor and the patient, and I

don't think that it is fair for us to make the judgments for the patients that if they get a rash they should not get the drug. All of our drugs are toxic. Some of them kill patients. So, a rash versus dying from, you know, neutropenic sepsis--I would take a rash any day.

I would also point out that a lot of the side effects appear to be manageable. Not to minimize at all the side effects, but there are a lot of drugs out there that do cause significant serious, life-threatening side effects but they are being used daily because of an informed conversation between the patient and the doctor. So, I think that the quality of life at least is no worse. That is an important fact. I don't think we ought to look at it as being a lot better.

DR. MARTINO: Dr. Levine?

DR. LEVINE: Basically I was going to agree. If this drug were available, it is up to the patient to decide with the physician what kinds of risks they want to take. I wasn't completely overwhelmed by the seriousness of these toxicities.

The stroke was an issue to me and I think it would be very helpful if the company could look at that data very, very carefully. Who was appropriately on Coumadin, who wasn't? Who got the strokes? One of the questions that we will want to know as clinicians is whether or not we should be anticoagulating prophylactically. That needs to be known. So, I would ask you to look at that. So, I am not really overwhelmed by these toxicities. We need more information. I hope you can provide that. But it is up to the patient for the decision, and there was a statistical increase in survival.

DR. MARTINO: Dr. Cheson?

DR. CHESON: Do you have any data on the number of days that these patients in either arm spent in the hospital during the time course, primarily related to drug toxicities or the like?

DR. CAGNONI: We do not have that data, and I will have Dr. Witt comment on that particular issue. I think it is important.

DR. WITT: There was actually an attempt

to capture information about duration of hospitalization during the study but, as you can imagine, patients that are hospitalized and don't have a discharge date, either because they are transferred to hospice care or have incomplete discharge data, make that analysis a little bit questionable. So, it is not something we have looked into at this point.

DR. MARTINO: Dr. Perry?

DR. PERRY: What are the company's plans for this drug if it is approved and if it is not approved?

DR. CAGNONI: In pancreatic cancer or in other tumor types?

DR. PERRY: In pancreatic cancer.

DR. CAGNONI: Currently, there is a large study that has been initiated in Europe which is building on the findings of PA.3, the randomized study, which is being led by our partners from Roche. It combines Tarceva and gemcitabine in one arm and the experimental arm is Tarceva/gemcitabine combination with Avastin as well. That is our most

immediate plan.

In addition to that, there are a number of investigator-sponsored trials that are ongoing with Tarceva in pancreatic cancer, combining Tarceva with chemotherapy and/or radiation therapy at different stages of pancreatic cancer. Depending on the results of those studies, future studies may be considered.

DR. PERRY: I didn't hear you say that there is any study of this combination versus the sequential use of these drugs, did I?

DR. CAGNONI: We have discussed the possibility of those studies and we are still discussing with potential investigators how to design those studies. Patients with pancreatic cancer progress very quickly and building sequential regimens is not a simple way to address this issue. So, we will still entertain potential concepts from investigators but we are not sure how to address that issue yet. We are doing it in lung cancer. We are testing the use of sequential chemotherapy and Tarceva in lung cancer.

DR. MARTINO: Rick?

DR. PAZDUR: We are talking about additional studies and I think the most important area that we have not talked about--we have talked about, as Dr. Perry mentioned, kind of the classical chemotherapy studies, but the big question here is can we identify a subset of patients that is most likely to respond to this therapy? Obviously, this therapy has been touted as a targeted therapy, an EGFR receptor study. There has been work done in lung cancer looking at somatic mutations of EGFR receptors.

I think, you know, we have to have a momentum, and I hope the committee would agree with me in this fashion, to really make this a priority as far as other studies that need to be looked at. You know, we are talking about a small benefit here, regardless of how we want to cut it and we could have innumerable arguments about what is clinical benefit and what is not clinical benefit--is it days, or weeks or what? But, truly, if we could identify the population that is most

likely to respond--you know, we have taken a look at EGFR status in a very gross fashion--the Dako kit that is available looking at immunohistochemistry, but with this class of drugs, these tyrosine kinase inhibitors that allegedly target EGFR receptors, can we have a better understanding on a more molecular basis? That is the cry I think that needs to be issued out here because we have to find out which patients respond better.

I agree with that looking at the drugs sequentially or in combination with other drugs might be important but that is really the major issue I think. And, I would like to hear some discussion from the committee on how to get companies really to do this because I think it is a very important aspect of drug development and needs to be expressed either negatively or positively from the committee on their opinion regarding this.

DR. MARTINO: Yes, Dr. Eckhardt?

DR. ECKHARDT: I think actually that is great idea. At least at our institution one of the

things that we have seen is that some of those collaborations will occur on the large randomized studies, having groups spend a lot of time looking at constellations of markers. Certainly this has been done with Iressa in some of the lung studies and with Tarceva. I really think the idea is that if there is support both from a regulatory standpoint and from the academic investigators, it can be done.

You know, I think what has been interesting with the small molecules is that it may be that you just may need to go beyond the simple immunohistochemistry to get a better sense as to whether or not someone is going to be sensitive. I would assume OSI would continue a lot of these types of interactions that are going on with the lung studies in pancreas.

DR. CAGNONI: Absolutely. We have initiated with our partners, Genentech and Roche, two large studies in lung cancer. Both studies mandate tissue collection. Both studies have a broad panel of molecular correlates incorporated in

them to try to understand better which patients benefit more from Tarceva in different settings, and we are prepared to discuss future studies in pancreatic cancer that incorporate molecular endpoints as well.

DR. BUKOWSKI: Does the Roche study in Europe require tissue collection and analysis?

DR. CAGNONI: It is a study run by Roche. I cannot comment on the specific design of the study, I am afraid.

DR. BUKOWSKI: So, you don't know the answer?

DR. CAGNONI: That is correct.

DR. MARTINO: Dr. Hussain?

DR. HUSSAIN: I just want to say a couple of things, and that is, this is an example where the clinical application or the use of the drugs has gone much faster than preclinical work. The reality of these trials--and I am not going to pretend to be an expert on pancreas cancer, but certainly all of the issues of targets are coming across the board. I would argue that when we have

chemotherapy we think we know how it works, but we still don't know why patients respond and don't respond and in the last 60 years we haven't figured it out.

So, I would say that I don't think that we ought to hold the clinical trials hostage to the mechanism issue. I would also urge companies in general to do more preclinical work because the patient material is valuable and what we think we are looking at is probably not what we should be looking at, and getting more science so that the looking and the patients' material becomes more focused.

DR. CAGNONI: I believe Dr. Moore also has a comment on this.

DR. MOORE: Just to point out that at NCIC we do in general, in Phase 3 studies, collect tissue. In this particular trial we have collected tissue on about 60 percent of the cases. We did a preliminary analysis on the first 200, which was the EGFR analysis which we showed you. The problem with pancreas is that a lot of people have

fine-needle aspirates and we found I think about 30 or 40 percent was insufficient material to do some of these analyses. But subsequent to this we do plan to do other analyses on that material, as much as it will allow us. It is more difficult when you are using combination therapies to sift out the effect of the two drugs when you are looking at these, but we do plan to do more analyses.

FDA Questions to the Committee

DR. MARTINO: Are there any other questions? If not, I am going to turn you to the official questions from the FDA. Dr. Pazdur, do you in fact want each of these voted on as they are written? Okay?

The first question, is the Tarceva survival effect in study PA.3 statistically persuasive? I guess that means statistically significant. Is that what you are trying to ask? Are there questions or comments before we vote? Yes, Dr. D'Agostino?

DR. D'AGOSTINO: A comment. Even with the question in terms of how many events the study was

originally designed for, I think the data is pretty persuasive and the statistical significance of that 0.02 at the end does hold up.

DR. MARTINO: Other comments? If not, I will start the vote and we will start on my left. Please announce your name and your vote.

MS. WELLS: Wells, yes.

DR. HUSSAIN: Hussain, yes.

DR. D'AGOSTINO: D'Agostino, yes.

DR. BUKOWSKI: Bukowski, yes.

DR. CHESON: Cheson, yes.

DR. ECKHARDT: Eckhardt, yes.

DR. PERRY: Perry, yes.

DR. GRILLO-LOPEZ: I don't have a vote but if I had a vote I would vote yes.

[Laughter]

DR. RODRIGUEZ: Rodriguez, yes.

DR. MARTINO: Martino, yes.

DR. MORTIMER: Mortimer, yes.

DR. LEVINE: Levine, yes.

MS. HAYLOCK: Haylock, yes.

DR. REAMAN: Reaman, yes.

DR. MARTINO: The vote is unanimous. The answer is yes. Question number 2, is the size of the Tarceva survival effect in study PA.3 clinically important? I will entertain discussion on that before we vote if anyone has anything more to way. Dr. D'Agostino, you may start.

DR. D'AGOSTINO: You know, so many of the studies that I am involved in, in different arenas beyond cancer, we are dealing with 4-, 5-point scales and we spend all our time trying to talk about clinical significance of change from 3.2 to 3.8 or 3.2 to 3.4. I mean, this is survival. It is very hard to say that survival is trivial. Whether we want to worry about the third question in terms of risk/benefit, but survival is extremely impressive.

DR. MARTINO: Dr. Hussain?

DR. HUSSAIN: [Not at microphone; inaudible].

DR. MARTINO: Seeing no other hands, we will start the vote again on my left, please. The question is, is there clinical importance here.

MS. WELLS: Wells, yes.

DR. HUSSAIN: Hussain, yes.

DR. D'AGOSTINO: D'Agostino, yes.

DR. BUKOWSKI: Bukowski, yes.

DR. CHESON: Cheson, no.

DR. ECKHARDT: Eckhardt, yes.

DR. GRILLO-LOPEZ: I don't have a vote but I would like to comment. My vote would be yes. The reason for that is that I am a medical oncologist taking care of pancreatic cancer patients. Plus, I am, myself, a colon cancer survivor so I can look at this from both sides. And, when I look at the Kaplan-Meier curves it is pretty clear to me that we cannot go purely by a median in this case because the curves do pinch together. But if you look at the separation between curves at all other points and you consider the area between those two curves, I think it is clinically significant. I, as a treating physician, would choose Tarceva plus gemcitabine for my patients, and as a patient I would also like to be in that top curve. So, that is why if I had

a vote I would vote yes.

DR. MARTINO: Ah, but you don't! Thank you.

[Laughter]

DR. GRILLO-LOPEZ: But I can still have a voice.

[Laughter]

DR. PERRY: I think this is statistically significant but not clinically significant so I vote no, Perry.

DR. RODRIGUEZ: Rodriguez, yes.

DR. MARTINO: Martino, probably the toughest decision I have made since I have sat here. I am going to give it a yes but it is a very qualified and heavy-hearted yes.

DR. MORTIMER: Mortimer, yes.

DR. LEVINE: Levine, yes.

MS. HAYLOCK: Haylock, yes.

DR. REAMAN: Reaman, yes.

DR. MARTINO: The vote is 11 to 2 in favor of yes. The third question, is the Tarceva risk/benefit ratio in this study favorable? Again,

I will entertain comments.

[No response]

It looks like you have all done your thinking. We will start again on my left, please.

MS. WELLS: Wells, yes.

DR. HUSSAIN: Hussain, yes.

DR. D'AGOSTINO: D'Agostino, yes.

DR. BUKOWSKI: Bukowski, yes.

DR. CHESON: Cheson, no.

DR. ECKHARDT: Eckhardt, yes.

DR. GRILLO-LOPEZ: Grillo-Lopez, yes but it doesn't count.

DR. PERRY: Yes, Perry.

DR. RODRIGUEZ: Rodriguez, yes.

DR. MARTINO: Martino, no.

DR. MORTIMER: Mortimer, yes.

DR. LEVINE: Levine, yes.

MS. HAYLOCK: Haylock, yes.

DR. REAMAN: Reaman, yes.

DR. MARTINO: The vote is 11 to 2 in favor of yes. The fourth question, the FDA Guidance on when evidence of efficacy from a single trial

without independent confirmation is adequate for marketing approval indicates that the study must be statistically persuasive, such that it would be unethical to repeat the trial. Is a confirmatory trial recommended prior to approval or do we want another study? Who would like to react to that? Dr. Cheson, I am going to choose you.

DR. CHESON: No, I agree it would be unethical to do another study.

DR. MARTINO: Anyone else? Yes?

DR. PERRY: I think we have seen what this drug does in combination and I think it is a well designed, well done study. I think the results are just disappointing. I don't think we need another trial to confirm that. I think what we need is another better drug, another better trial.

DR. MARTINO: Well, I guess I tend to disagree with that. Truly, as I said, this to me is a very difficult decision. I recognize the difficulty of these patients. I recognize the problems. I recognize the discomforts they live through. Yet, I feel like I am approving something

where I am still sitting here, scratching my head as if to whether it is really valuable or whether it is just another thing to offer people without being able to quantify for them what they are going to get out of it.

You know, when someone says your survival is improved that is usually the end of that sentence. Rarely does anyone say but it is, you know, some days. We don't add that sentence and, yes, it is always a patient's decision as to what they want to do, but there are ways in which we bias; there are ways in which we get people to buy things without truly informing them of how much they are buying. That is the fear that I have here, that we are going to be selling a drug and not really explaining to people what it is that they are buying out of this so that they can make a well informed decision. And, as a clinician, I know we don't add those details and that bugs me a lot in this trial. Dr. D'Agostino, you are next.

DR. D'AGOSTINO: I started asking a question earlier which related to this question

before us. I am concerned that while it is statistically significant it is not a huge trial. We have a p value of 0.02 but there were questions about it. There are questions about the safety, and so forth. In many other settings I am facing the dilemma of we can't put studies together because of the response of investigators saying it is unethical. Are there other means, like a historical controlled trial or some other setup that could be possible to try to get at the possibility of putting a study together that would give us some information that takes us beyond the one study we have sitting before us?

DR. PAZDUR: What are you trying to suggest? A historical control looking at this database compared to what?

DR. D'AGOSTINO: A new set of subjects where the new set of subjects are just taking one regimen but they are being compared to some historical database, maybe a contemporary database that is uncontrolled.

DR. PAZDUR: Yes, but I don't need to

lecture you about historical databases, that is for sure.

DR. D'AGOSTINO: Well, it is being done in other arenas.

DR. PAZDUR: I don't even know if we have that--

DR. D'AGOSTINO: That is my question.

DR. PAZDUR: --that would really be a matched control situation.

DR. D'AGOSTINO: That is my question. I don't see a database and I don't see a study full of subjects.

DR. PAZDUR: We could always have some type of Phase 4 commitment here.

DR. SENDEROWICZ: For example, with regard to the study with gemcitabine, 70 percent of patients had PS2 or worse so you couldn't compare this drug where 20 percent had PS2 versus the gemcitabine pivotal trial that had a much worse prognosis.

DR. D'AGOSTINO: Where I am coming from is obviously the same thing as the Chair and other

people are saying, that because of this trial trying to put another randomized, controlled trial together, double-blind is hopeless--using it to the extreme saying it is hopeless--it is unethical. Are there other ways of doing it? My colleague on the side here is going to say that he can put together a randomized trial--

DR. BUKOWSKI: I didn't say I could put it together but I certainly think that when you look at the degree of benefit which is small--we have to face it, this is minimal at best--there is no reason why one couldn't test this combination versus another combination without Tarceva. You could test bevacizumab plus gemcitabine versus this combination. You wouldn't get the exact answer. It is not the exact trial you want but, certainly, you could test this combination again in the setting of a randomized trial, and I think that should be done. I think that is really what we need to do, to test this further because the data we have is limited right now.

DR. D'AGOSTINO: But that is not what the

question is. I mean, you could do a lot of studies that are randomized, but for the approval--

DR. BUKOWSKI: No, no, but we are asking what else can we do to look at this combination--

DR. D'AGOSTINO: Prior to approval.

DR. BUKOWSKI: Can we test it versus gemcitabine alone? It would be difficult in the U.S. to do it. I think that is true. But if you tested it versus another potentially active combination you could test this combination further.

DR. D'AGOSTINO: I don't know--

DR. PAZDUR: That poses a lot of problems, folks. What other combination? Obviously, to demonstrate benefit on a survival endpoint you have to beat it. Okay? Because to try to do a noninferiority to an exploratory combination of gemcitabine plus whatever, probably we don't have any idea of any of the control effect that would need to be maintained in a noninferiority study, and then we are putting really a higher level in front of this drug to be approved basically.

Because, remember, it is safety and efficacy. You don't have to prove that you are better than some non-approved agents.

DR. BUKOWSKI: I am not suggesting that that be a requirement for approval of this drug--

DR. PAZDUR: Okay, just a Phase 4--

DR. BUKOWSKI: It could be a Phase 4 way to look at this drug further. I didn't mean to imply that this drug needed to be held to that particular requirement.

DR. PAZDUR: Because here, again, one of the problems that we have in oncology--I shouldn't say problems, challenges that we have in oncology in terms of other therapeutic areas, is that placebo-controlled trials are done in other therapeutic areas. Here they are not for the most part, especially in another trial that you are contemplating. So, you would be raising the bar here for approval that you would have to be superior to on a clinical endpoint, which would not be appropriate probably.

DR. BUKOWSKI: I agree.

DR. MARTINO: Dr. Rodriguez?

DR. RODRIGUEZ: I just wanted to bring up a point that I heard Ms. Wells mention, and that is that I don't have a personal experience with this because I treat patients with hematologic malignancies. I don't treat patients with pancreatic cancer so I don't know what is happening out there. But Ms. Wells mentioned that many patients are already, the majority are already being treated in combination with something else and those other something else are not approved drugs for pancreatic cancer. And, we are beating ourselves about the toxicity of this particular compound that seems to be manageable, whereas patients might, unfortunately, be treated with drugs that are truly much more toxic than this combination. I think what this combination does is it may set a new standard to which others should be compared for purposes of ethical conduct of treatment so that patients do not suffer unnecessary toxicity for no additional benefit.

I would say that there are additional

studies that are required, perhaps not necessarily to reconfirm the benefit of survival but to confirm the benefit of lesser toxicity or more tolerance of this regimen compared to other combinations that are being done out there without confirmation of survival benefit.

DR. PAZDUR: There could be Phase 4 commitments. But I want to ask Ralph a question. Why do we think we ask in other therapeutic areas to do two trials? Generally, it is not to see if we get better results. It is because there might be some interest that we have or feel a need to verify the results, to replicate the results.

DR. D'AGOSTINO: Exactly. Are we uncertain about these? Is that what you are expressing, the statistical validity of the one trial? Actually, I am going to vote to approve it. I am trying to see what the options are. You know, the cardiovascular arena, for example, where I spend a fair amount of my time, when we talk about one trial we want the p value to be 0.001, something like that and you hear about 0.01 and

here is a 0.02. So, we are setting ourselves for a different level of conviction in terms of what do we actually need.

As far as the two trials go, I mean, other investigators are doing it. I am often in the setting of where one study is produced and it is done by superlative investigators, the next study doesn't come out as well so a couple of trials give you a feel for that. This is a fairly broad trial. It has I think very consistent results. So, my vote would be to actually say let's live with this one trial, and what I want to do is to flesh out so that tomorrow morning we aren't saying, you know, we didn't really have to do a randomized, controlled trial. And, I think you should do some Phase 4.

DR. PAZDUR: Okay, because, you know, I think there is a difference between Phase 4 studies, which we could discuss with the company, versus, you know, another trial needed before approval of the drug. Those are two separate issues here that need to be distinguished from each

other. But I think the question that is being asked here is whether an additional trial is needed before approval of the drug. Remember, drugs generally are developed even after--not even but after approval with multiple other studies; cooperative groups take them on and compare them to different regiments, etc.

DR. MARTINO: Dr. Hussain?

DR. HUSSAIN: Do you want me to reiterate what everybody else said?

DR. MARTINO: No. No, I am just giving you the opportunity if you have something new to say.

DR. HUSSAIN: No, other than that I was going to say ODAC's discomfort with mediocre, or I should say modest results, is not enough justification in my opinion for a repeat trial. I take "repeat" as the same. I think unless the consent forms are going to be misinforming, I can't see how the IRBs or the patients will sign on. The drug is out there so "doability" is not possible I think in that setting. Finally, is this the most

optimal use of patient resources in a deadly disease, you know, dollars and otherwise? We ought to invest it in better treatments. This is, at best, modest and we need better results. So, I think we just go with this and build on it or improve outcome.

DR. MARTINO: Dr. Cheson?

DR. CHESON: Well, that is sort of what I was going to say but I was going to put a different spin on it. To expand on what I said before, I think it is unethical because I think this is the wrong regimen and the results are modest, at best. I know this is going to get approved based on the conversations, but we are going to be putting a regimen out on the streets as something that is recommended that I have no confidence in is the optimal combination of these two drugs. We have seen it with some of the other targeted therapies that were combined with chemotherapy that have been negative, and I think that we could probably do a whole lot better with this combination if it were done differently. I think we are doing a

disservice putting out a drug combination that is getting us ten days when, if it were thoughtfully constructed better, might give us several months of benefit. So, that is why I think it is unethical to do another trial because I think this is the wrong regimen.

DR. MARTINO: How would you structure another trial? I mean is your concern with this drug or is your concern with the design of this trial?

DR. CHESON: I don't know. I think we need to look at it differently. I think we need to bring in our scientists to tell us how to do it rather than making the Iressa mistake again, which is what we are doing here except here there is a little bit of a difference. I think we need to talk to our scientists, like Dr. Eckhardt sitting next to me, and learn which patients may benefit; learn which schedule may be optimal; learn how something up-regulates something else and how the chemotherapy may sensitize the cells to the subsequent administration of this drug.

I think we are putting out an inferior regimen on the streets, and that is what is going to be in the package insert. That is what we are going to be recommending to our patients. And, I think actually if you wanted to do a second trial and you had patients looking in the informed consent that said in the first study we can get you ten days, I am not sure there would be a lot of takers.

DR. MARTINO: So at least one other person understands my feeling on this. Dr. Eckhardt?

DR. ECKHARDT: I mean, I think we are all agreeing it is a marginal drug for a bad disease and the last thing in the world we want to see is another marginal study. You know, I think the way I look at pancreatic cancer patients, it is really looking in the face of such a bad disease that we are willing to look favorably upon very marginal data.

But I would just really reinforce the idea that what needs to be done next is either a trial that has a better design or, you know, certainly

better drugs. We need to be really focusing on that. It may mean that we don't just build upon this data. This drug may or may not be part of the next active regimen. This is really just the next step and the bigger step may or may not include this drug. It may include this drug in other regimens, and that should really be where we go with this whole field, particularly with this cancer.

DR. MARTINO: Dr. Levine?

DR. LEVINE: I also agree that I don't believe we need another trial. This was well done. It accomplished the purpose. In fact, the rules of the FDA state that you don't have to have a second trial given these circumstance; it is an approved drug and one clean study was done.

On the other hand, I would be very much in favor of Phase 4 testing after approval, and one of the things that might be interesting to me would be a randomized trial between this regimen and the exact drugs but given sequentially, or however the laboratory data will help. That would be very

interesting, to try to figure out how it might be used more optimally.

DR. MARTINO: Dr. Grillo-Lopez?

DR. GRILLO-LOPEZ: We rarely approve drugs for cancer based on having found the optimal regimen within which they should be used, the optimal combination. In fact, more often than not that optimal combination is discovered after many more years of clinical research, sometimes as much as 10 or 15 years after approval.

What I hear a number of people around the table saying and expressing is their desire and their concern that there should be additional studies post approval. What happens usually is that once a drug is approved the pharmaceutical company will almost immediately set up a Phase 4 program for additional studies to be done. They will accept proposals from investigators for investigator-initiated studies. Thirdly, they will go to the cooperative groups and try to get studies started within the cooperative groups, or they will be approached by the cooperative groups. So, there

are at least three ways where the need that is being expressed here for additional studies will be addressed.

DR. MARTINO: I guess I am still bothered by the very concept that one study, when the differences between the two arms are so meager is, in fact, adequate for all future decision-making, and that is what I am hearing here. If that is the policy that we have adopted, I would like us to rethink about it.

DR. REAMAN: I question whether we are the right group to be sitting here and deciding what is meager and what is marginal benefit. I sort of sympathize with your position about selling patients ten days, but if someone sold me ten days--and this is definitely not a disease that I have a great deal of familiarity with--but we heard in this morning's presentation about people with advanced hormone refractory prostate cancer who refuse chemotherapy because of perceived toxicities. I don't think we are the right group to be sitting here, deciding what is really the

correct risk/benefit ratio. We did see a study that was designed well, presented well, with a statistically significant difference in survival. With it is ten days or ten weeks, it is significant. I think on that alone, it should be approved and I don't think we should sit here and ask for another study to be done. I think that is definitely unethical.

DR. MARTINO: But this, to me, implies that there is no chance in the universe that one study could ever have a different result if repeated, and you know that is not the case. But that is what I am hearing here. Yes, I will grant you it is a lovely study that did a decent job; they are decent people. There is no arguing their intent here. We appreciate their intent. I am arguing the basic human principle of is one study what everything is based on. I mean, is that it? Is that what science is all about? I am not a statistician but I don't think that is what science is all about.

I disagree with you that we are not the

right people to make these judgments. Well, if we are not, with all due respect, who in the hell is? You know, we take care of these people. They are part of our families, not only our patient family but our own personal families. If you ever watched someone dying of pancreatic cancer, giving them an additional few days isn't always a gift. Sometimes it is; sometimes they would do anything for that next breath. But some of them are awfully happy to go. That is why there is a whole hospice program. That is why you and I know how to do certain things to make them unconscious so they don't feel their pain. So, I am sorry, I do think we are the right people to make these judgments. I don't know that there is anyone who is all that better qualified. You know, the duty falls on us but I think we have what it takes to make those decisions. You know, we can't just kind of give everything away as though, you know, somehow there is someone else who is better qualified. I mean, I think we all understand these issues very clearly.

DR. ECKHARDT: But I think that really

gets into an issue even with that question of sort of the ethics and utilization of patient resources. Again, you are facing that patient population where you have shown, in a deadly disease, a marginal benefit and you are going to, once again, randomizing these patients again to gemcitabine plus placebo versus gemcitabine plus Tarceva. I have concerns that at the end of the day you could end up with the marginal benefit once again and we haven't really taken the field forward. So, I think it is some of the same questions. I understand your concerns but in some respects that is subjecting patients to even more disappointment, or, you know, the fact that they don't have access to perhaps gemcitabine/Tarceva/Avastin study. I mean, we need to move on. I think we all agree it is marginal.

DR. MARTINO: But maybe what we should be doing is either confirming that it does have marginal benefit or finding that it doesn't have any, in which case you might be sparing people this experience. But I will not belabor the point. I

think I have made at least my views clear to most of you. Yes, Dr. Cheson?

DR. CHESON: Two more points, one, I would like to disagree with my good friend Antonio. Yes, we have approved regimens like the one you are very familiar with that are probably not the optimal ones, but not with this minimal benefit. So, I think that is one thing that is troubling.

The other is, you know, we saw that there was no difference--and I am getting back to what you said because that really struck a note with me--there was no improvement in quality of life but do we know what the baseline quality of life of these patients was? If it was okay and you didn't improve it, that is fine. But if it was poor to begin with and the patients were taking narcotics and opiates because they were in pain, or whatever it was, and that is what you are not improving on but that is what you are prolonging, then what is the point? So, do we have that information? It became a question because I don't have the answer and if they tell me that these were patients who

were all very, very sick and you didn't make them better, it is different than if they were just fine and didn't do better or worse.

DR. MARTINO: But realize this is a study. Therefore, you have selected the best in the first place. You know that about studies.

DR. CHESON: You are right; you are right.

DR. MARTINO: So, recognize that even when you get an answer, you have to interpret it in the fullness of this experience.

DR. CHESON: You are right.

DR. CAGNONI: I am afraid we do not have a slide with that detailed information to share with you. Twenty percent of the patients in the study had performance status 2. The rest of the patients had performance status 0-1. That is what I can tell you right now. The information is in the report however and has been submitted to the FDA.

DR. MARTINO: Rick, did you want to say something?

DR. PAZDUR: In response to Bruce, basically if you take a look at the number of drugs

that have labeled information on quality of life, there are woefully few and I think that points to some of the methodological problems, how many patients were symptomatic, etc. So, you know, that we don't have good quality of life data here that shows an improvement is not a big surprise to me because I haven't seen that really in any of the clinical trials.

Before we move on to the vote--

DR. CHESON: But that also holds for stable disease. If the patient has a big tumor mass and it hasn't changed we say, oh, that patient had stable disease. But is that a clinically positive endpoint? I think not. And, we are lumping together stable disease with PRs so it is the same conundrum. If we don't know what it was when we started and it hasn't changed, we don't know that that is good for the patient.

DR. PAZDUR: Yes, I guess the point I am trying to make is that there are many methodological problems with quality of life to hold that up as something that somebody has to meet

before we really view a therapy as beneficial.

But before we move on I would like the record to show that I do agree with Dr. Grillo-Lopez. Okay? And I think that we have to view that drug development is a dynamic process, that the drug approval process is one step in the development of a drug. We have approved drugs on response rates. We have approved drugs on time to progression. This is a rather difficult endpoint to meet in a very difficult disease here, and I doubt that the whole development of this drug will come to a cessation here with the approval of the drug. I think cooperative groups will look at this in different combinations in a sequential fashion perhaps, or comparing the two different combinations, and all we need to do is to have a superior combination and this whole discussion might be a moot point. So, let the record show Dr. Pazdur agrees with Dr. Grillo-Lopez.

[Laughter]

DR. MARTINO: Dr. Mortimer?

DR. GRILLO-LOPEZ: I would like to extend

my hand in a peace offering.

[Laughter]

DR. MORTIMER: I just wanted to address this sort of ethical dilemma. As somebody who is a breast cancer person who spends the majority of their clinical time in giving adjuvant therapy to women who are possibly cured without it, in whom I am giving long-term toxicities, life-long toxicities, perhaps even shortening their lives, I can't be critical of this. This is an absolutely positive study. They met their primary endpoint and I don't see the quality of life issue as a dilemma here.

DR. MARTINO: Dr. Bukowski?

DR. BUKOWSKI: I just agree with Dr. Mortimer. I think quality of life is something that doesn't help us in most studies that we do. Although it is certainly additive and it does support it, for the most part we never get any useful information from it, probably because the methods are not yet developed that allow us to do that. So, I tend to ignore quality of life data.

DR. MARTINO: Dr. Perry?

DR. PERRY: No comment.

DR. MARTINO: You forgot what you wanted to say?

DR. PERRY: No, I am just trying to shorten the meeting and get done before midnight.

DR. MARTINO: All right. With that advice and I will take it as such, we will put the question to a vote. The question is basically is a confirmatory trial recommended prior to approval? We will start the voting on my left again. Please state your name.

MS. WELLS: Wells, no.

DR. HUSSAIN: Hussain, no.

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

DR. BUKOWSKI: Bukowski, no.

DR. CHESON: Cheson, no.

DR. ECKHARDT: Eckhardt, no.

DR. GRILLO-LOPEZ: A non-voting no.

DR. PERRY: Perry, no.

DR. RODRIGUEZ: Rodriguez, no.

DR. MARTINO: Yes.

DR. MORTIMER: Mortimer, no.

DR. LEVINE: Levine, no.

MS. HAYLOCK: Haylock, no.

DR. REAMAN: Reaman, no.

DR. MARTINO: The no's have it by a wide majority. Rick, are you now ready for us to deal with the final question? The final question is are we ready to give this agent full approval for this indication? It is not accelerated approval. The request is for full approval.

DR. PERRY: Madam Chairman, could I suggest that this is not our purview? I mean, as you have stated it, we are not approving it; we are making a recommendation to the FDA.

DR. MARTINO: You always make a recommendation. Always. Nevertheless, that is our job.

DR. PERRY: We are not approving this, we are making a recommendation.

DR. PAZDUR: You are making a recommendation to the Division for consideration.

DR. PERRY: I just want to be correct.

DR. MARTINO: No, I think you are trying not to take on the full responsibility. That is actually what I am hearing here but I understand.

DR. PAZDUR: We will totally take on that responsibility.

DR. MARTINO: Discussion? Seeing no hands, I guess we will take a vote, again starting on my left.

MS. WELLS: Wells, yes.

DR. HUSSAIN: Hussain, yes.

DR. D'AGOSTINO: D'Agostino, yes.

DR. BUKOWSKI: Bukowski, yes.

DR. CHESON: Cheson, no.

DR. ECKHARDT: Eckhardt, yes.

DR. GRILLO-LOPEZ: Grillo-Lopez, non-voting yes.

DR. PERRY: Perry, no.

DR. RODRIGUEZ: Rodriguez, yes.

DR. MARTINO: Martino, no.

DR. MORTIMER: Mortimer, yes.

DR. LEVINE: Levine, yes.

MS. HAYLOCK: Haylock, yes.

DR. REAMAN: Reaman, yes.

DR. MARTINO: The vote is 10 to 3 in favor of yes. Are there any other issues, Dr. Pazdur, that you wish the group to discuss?

DR. PAZDUR: Thank you for a very stimulating afternoon.

DR. MARTINO: You are welcome. Thank you, all. This is the end of this committee's deliberations. Thank you.

[Whereupon, at 4:10 p.m., the proceedings were adjourned.]

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