negative.

The question is that we have more negative trials than positive trials. The question is, is there a logical explanation, which at least I haven't come to -- it hasn't come to me. And I wanted to hear if the sponsor could shed some light on that.

DR. BOWDEN: Thank you for your question. Just for clarification, this is with regards to the 2119 study being negative?

DR. BUZDAR: That study which was presented by also the ECOG, George Sledge in ASCO. It was a straight Phase II study in which the patients were just given capecitabine with Avastin to see -- there was a hypothesis that this is the time to progression and it should add that much. And when the data is looked at in totum, that it looks almost identical, no improvement was observed.

DR. BOWDEN: So with regards to the

excalibur study you're referring to, that's a single arm Phase II study, and so that doesn't have a control arm and, therefore, making a comparison can't be done.

With regards to 2119 and 2100, please recall from this morning's presentation that there are a couple of major differences between the trials. Capecitabine is the chemotherapy in 2119 versus weekly paclitaxel. On 2119, 85 percent of the patients had received prior anthracyclines and taxanes in the metastatic setting. And the 15 percent how had not, had relapsed quickly after receiving those two drugs in the adjuvant setting. Whereas none of the patients on 2100 had received chemotherapy in the metastatic setting.

And I think the other important aspect is to think about the indication statement that is specific to the E2100 patient population. And I'd like to ask Dr. Miller to come and comment because there was

important consideration when they were designing the E2100 with regards to the rationale and some of the aspects in terms of the drug selection and the patient population as they were putting that study together several years ago.

DR. MILLER: So I think actually the E2100 study may tell us something powerful about biology and results of ongoing trials will see if my current hypothesis is correct. You're absolutely right, Aman. When I first saw the results of these two studies my first intuition was that the largest difference was the difference in the patient populations. And I still that difference in the amount of previous therapy is an important difference. But there was also a biologic rationale and pre-clinically demonstrated striking synergy between prolonged exposure to the taxanes as you would get in a weekly schedule with bevacizumab that has not been shown with

capecitabine. So I also think that difference in chemotherapy may turn out to be critically important in the results that we've seen.

Now, there is an ongoing trial known as the Ribbon 1 trial, also in the first-line setting, that does include a control arm. So we will be able to see the benefits of adding Avastin in that setting. And that looks at a variety of different chemotherapy options, so I think that will give us a better sense as to whether the chemotherapy partner that Avastin is matched with in first-line breast cancer patients has a major or a minor impact on the outcome that we see. I think looking at these two trials suggests to us that it certainly probably has some impact, but it's hard to know what the magnitude of that impact might be without the results from other studies.

DR. BOWDEN: If we could all --

DR. HUSSAIN: Ms. Mason? I'm

sorry.

DR. BOWDEN: I'll make one comment with regards to the previous comment. There were two components of it. One was missing data. And I just want to point out that we did eight sensitivity analyses of the progression-free survival endpoint in an effort to study the robustness of the PFS endpoint, looking at missing data. And in all eight sensitivity analyses the treatment benefit of the Avastin/paclitaxel combination was maintained.

Now, I'd also like to ask Dr. Winer to speak to your specific question about the trade-off, the benefit-risk trade-off, and what that means looking at this data and how that can translate to a physician-patient interaction.

DR. WINER: So I don't think that there's any real attempt to minimize this acute toxicity or the severe toxicity. And, in fact, I think that I certainly, and I hope

all of my colleagues, take very seriously these rare, but life-threatening events. They're a big deal. And I think particularly when we consider moving agents like bevacizumab to the adjuvant setting, and there are now studies going on, one of the major issues will be what the long-term impact is of hypertension, whether that's hypertension for a year or two or three or forever.

In patients with metastatic disease I actually would tend to agree with Dr. Miller that having Grade 3 hypertension, which requires taking an anti-hypertensive medication, in the overall picture is probably not nearly as worrisome as many of the other toxicities that people face with treatments that we have. And as one who has actually administered a fair amount of bevacizumab in combination with paclitaxel and in combination with other agents as part of trials, adding bevacizumab to a

chemotherapy agent adds far less in terms of the day-to-day toxicity than adding a second chemotherapy agent. So while I do think that these serious toxicities have to be taken very, very seriously, honestly, I think that what one has to come back to is what's the symptom burden for a patient on a day-to-day basis?

And if I could make one other comment. I just want to address the comment that Dr. Pazdur made earlier. And I don't necessarily disagree, but I don't know that we should be discounting progression-free survival any more in the first-line setting than in the second- and third-line setting.

I actually think it's very important there as well. And I think maintaining patients in a disease state that is stable and avoiding progression is something that our patients want and, in fact, does avoid symptoms in that setting as well, although I admit that we don't have the

optimal data to answer the questions that you posed.

DR. HUSSAIN: I actually have a question because I've been thinking about all the terminologies that have been used about meaningful, clinically meaningful. And there's no question a five-month delay in progression is meaningful. The question is what does it mean?

And so when I look at a patient and associate a meaningful endpoint with clinical benefit -- so if a patient is not living better, which you have showed us that they are not, and they are not living longer, and if a lesion that goes from 4 centimeters to 2 centimeters and stays at 2 and then goes back up to 4 without any association of symptoms or anything else, and that is 2 months extra, how does that translate into clinical benefit?

And I would argue that the burden of symptoms, these patients are terminal.

And so our job is to make their life better, not say it's okay to have a stroke, it's not going to kill you, or it's manageable; or to say hypertension Grade 3, you're going to have pills, you pile up pills when you're taking all other things. And I'd argue that your quality of life questionnaire, if anything, showed that these patients' quality of life went down, not up. And so -- well, you showed that it decreased, not by comparison to Taxol.

SPEAKER: (off mike)

DR. HUSSAIN: No, no, but compared to their baseline did they quality of life go up or go down? It went down. So you really didn't show they're living better and you didn't show that they're living longer.

And so when you put all of that together, and the fact that in your study the five months' difference in survival eclipses any difference in -- I'm sorry, in progression-free survival eclipses anything

you showed before in terms of the other trials. Yet that did not make it into survival in an era where there is all kinds of second- and third-line treatments, which I don't buy as the reason why, you know, people -- you didn't see a survival difference. The only explanation I'm left with is that those who went on treatment and delayed their progression, somehow their disease did something to them or the treatment did something to them that killed them sooner.

So can you please try to somehow explain that to me?

DR. WINER: There are many questions embedded in that commented question. I'll do my best and you can keep me on track if I stray.

So first, in terms of why there was no difference in terms of overall survival, it's true, there wasn't. There was a small numeric difference.

It is reasonably likely that that

didn't arise by chance alone, but it could have and certainly that difference is smaller than the difference in terms of progression-free survival. And much of that may relate to what is some intrinsic behavior of cancer in women with metastatic disease. And one could argue that particularly in women with ER-positive metastatic breast cancer that our therapies may do very little ultimately to change survival and that it's all about maintaining disease control and symptoms, and that survival is affected by the intrinsic pace of the disease.

In terms of the issue of quality of life, I think this is tougher. I've been involved in many studies over the years that have attempted to measure quality of life. Early in my career I attempted to do that myself in the context of trials and became frustrated. Quality of life is extraordinarily difficult to measure. What was demonstrated in the trial was not that

quality of life improved associated with paclitaxel and bevacizumab, but that, in fact, it declined in less than in women who received paclitaxel alone, and there was a significant difference.

But I think the real issue is does progression-free survival in this setting translate into an improvement in quality of life? And I actually believe it does. And I believe it does because in a substantial number of patients one is delaying symptoms, in a substantial number of patients one is avoiding needing to move to a new therapy with both the physical and psychological trauma. But ultimately, if we had better measures of quality of life that's what we would rely upon and we wouldn't rely upon measures of -- a progression-free survival statistic. But we don't and it's what we're left with here.

DR. PAZDUR: Could I just make a comment regarding this whole issue of quality

of life? Because I think that, you know, we have spent a lot of time at the FDA looking at quality of life tools, et cetera. I would like to underscore we do not have a blinded trial here. We have one trial. We really did not capture other symptomatic measures that were perhaps given to these patients. God knows if they were uneven in both arms. So, you know, this whole area of trying to measure quality of life in an unblinded trial is highly problematic.

We do have a new guidance that is out on patient-reported outcomes. And I think in the future ODAC meetings we will be giving the members some education on our current thinking of quality of life claims to be made. But this type of study that is in this submission doesn't come close to what we would consider for a credible claim for any quality of life, especially with no differences being shown.

DR. WINER: And if I can, that is

why we're having this discussion about progression-free survival because we simply don't have the kind of quality of life data here that we can rely upon.

DR. BOWDEN: I think the other clarification I'd just like to make is that Genentech does not see the quality of life data as being submitted for a labeling claim. But with all the limitations that we acknowledged, the fact that the decrease in quality of life, if we can show CE-29, please, these are the curves for -- in blue for the combination and in yellow for the paclitaxel. And there's less of a decline in the combination relative to paclitaxel.

DR. PAZDUR: With all due respect, I do disagree with you on that point. What we're talking about is substantial evidence to be demonstrated here in making regulatory decisions. And whether they go on the product label, they are going into regulatory considerations for the approval of this drug.

And, therefore, some degree of substantial evidence should be demonstrated on that endpoint.

DR. HUSSAIN: And actually, just for the record, the reason I was raising this goes back to the issue of clinical benefit, not clinically meaningful difference. So I go back and say you've now shown that these patients are living better and certainly they're not living longer. And so that's really where I was hoping that you clarify.

I have a question for Dr. Pazdur. As a clinician who does clinical trials and I feel the pain of the investigators, there's no question, I can't see how your requirement to have a blinded study when someone has to come weekly and get an IV to get IV placebo is reasonable because it really is not.

DR. PAZDUR: No, we totally -- as I mentioned in my introductory comments, you know, the issue with blinding in oncology is very, very difficult. And even in applicants

that come to talk to us about blinded study one of the major questions that we always ask them, is it truly a blinded study? And that's why we have stated, you know, for a subjective endpoint, such as progression-free survival, since these studies cannot be done, this is why we're turning to this radiographic endpoint here.

Quality of life claims, when one wants to make them, are exceedingly difficult in oncology, and here again they would require not only a blinded study. If that can't be done, then it perhaps could be duplicated. There should be a huge magnitude of effect, consistency of endpoints, a prospective plan for evaluation of the quality of life data. It shouldn't just be let's add it on to some trial and then take a look at it and make some vague claim on the results that are generated. It really should be incorporated as an essential primary element in the evaluation of the therapy.

DR. HUSSAIN: Ms. Mason?

MS. MASON: I have one point of clarification and then a question. There was a comment earlier about two-thirds of the patients in the E2100 being ER-positive. Yet on a slide of patient and disease characteristics it says 61.8 percent ER-negative status. And so I was just questioning that because that does have implications as to a subpopulation, and wanted to know if there's a way using the limited collected data to be able to tease out are there subpopulations that really are benefiting? Because I think we're going to see that more and more as we get into different therapies and we're moving into a new era of, I think, treating breast cancer and cancer in general, and it would be helpful. I know there's a lot of missing data here to be able to look at that, but something worthwhile considering.

DR. HUSSAIN: Sponsor?

DR. BOWDEN: I'd like to show slide 15, please. This is with regards to your question about the frequency of patients, women with estrogen receptor-positive tumors. This is ER and/or PR. And you see on the fourth row across, 64 percent in the paclitaxel arm and 63 percent in the combination arm.

DR. HUSSAIN: Ms. Portis? I'm sorry. You're done?

DR. BOWDEN: Yes.

DR. HUSSAIN: Okay. Ms. --

SPEAKER: (off mike)

DR. BOWDEN: Oh, yes, thank you. And if I could see slide 66 from the PFS deck, please. We looked at a number of different subsets, and Dr. Miller showed you just a few of them, to try to understand how consistent the effect was, who might -- and also as hypothesis-generating potentially to explore further other subsets. And if you look at this slide, you can see that we

looked at age, race, region, disease status, locally recurrent and metastatic. If values that are falling to your left are -- favor the combination arm to the right to the control arm. Next slide, please.

They're all in favor of the combination there. Then if you look at disease-free interval less than or equal to 24 months, greater than 24 months, estrogen receptor status, combined, which is a triple-negative population across here, again you can see that in all the subsets the treatment effect is maintained finally. Now looking at number of metastatic sites; measurable disease versus non- measurable, a topic we touched on earlier; the hazard ratio,.37 versus.66. So in all of the subsets examined the treatment effect was maintained.

MS. MASON: I'd question, too, if -- because there's been a significant benefit seen in colorectal cancer and non-small cell

lung cancer with Avastin whether a subset of, like, lobular breast cancer that has a different progression than standard ductal breast cancer, if there might be a subset population there that would be worthwhile exploring.

DR. BOWDEN: Whether subsets -- whether there are comparable subsets within the non-breast cancer indications? To the -- sorry, I missed the question there.

MS. MASON: The progression of -- or metastatic lobular cancer tends to go to more abdominal sites, a different progression than ductal breast cancer. And with the success in those other types of cancers, in colorectal and in the specific lung cancer, perhaps lobular breast cancer would be a valuable group to look at as a subpopulation metastatic disease.

DR. BOWDEN: Yes, thanks for your comment. We're looking at studying Avastin in a number of different breast cancer

populations. And it's something that we'll need to consider in terms of looking at that specific group certainly. Thank you.

DR. HUSSAIN: Dr. Lyman?

DR. LYMAN: Three quick questions for the -- well, one has been already addressed by Dr. Pazdur and that's the blinding issue. I would agree completely that we can't really evaluate the data in a non-blinded study for quality of life. Having said that, as was pointed out, very few labeling indications for oncology therapies or certainly cytotoxic therapies has blinding been mandated and is extremely difficult to do, if not impossible.

The two clarifications that perhaps could be brought forth by the staff, one is among the discordance discussions was a discordance in terms of the dates of progression that was mentioned, but you didn't say how much -- unless I missed it, how much discordance was discordance. If the

dates were a day or two different, I would presume you wouldn't consider that discordant. But how much of a leeway did you give before you would say the dates from the two sources were discordant? That's question one.

And the other goes back to the first-line metastatic approval for gemcitabine and paclitaxel.

I wasn't entirely clear on what the primary outcome for label indication there was. Was it time to tumor progression with reassurance that the survival was at least borderline significant or did survival become the primary determinant there? If you could just clarify what was the major labeling outcome for that approval?

MS. LU: This is Laura Lu. I will answer the first question regarding the discordance in progression date. For that calculation we include any difference in progression date, like including even,

1 although it is rare, one or two days
2 difference. But if there's any, it's
3 included.
4 DR. CORTAZAR: Regarding the other
5 question, gemcitabine, the basis for full
6 approval was a positive time to progression,
7 but that was supported by a strong trend
8 toward improved survival.
9 DR. PAZDUR: We were taking a look
10 at the totality of the data there and we were
11 aware of the survival impact.
12 DR. LYMAN: Are you suggesting it
13 wouldn't have been approved if that hadn't
14 been significant?
15 DR. PAZDUR: I have no idea. We
16 can't go retrospectively back in thinking.
17 DR. LYMAN: Yeah.
18 DR. HUSSAIN: Ms. Portis?
19 MS. PORTIS: Just going back, and
20 not to overly flog the issue of quality of
21 life, I know that it's a very difficult thing
22 to assess. And yet I just want to highlight

my point, though, that we have real data here about toxic effects and they're severe toxic events and there are deaths in this study. And that can't be overlooked even if we can't measure here quality of life, per se, if we don't have a measure that does that. I've made lists of the things that were in there about severe toxic events and I think they're important.

DR. HUSSAIN: Thank you. Dr. D'Agostino?

MR. D'AGOSTINO: I just wanted to maybe make comments, but make sure that the sponsor is thinking the same way that we are. With regard to the subsets, I'm not surprised by the consistency of the subsets. What I was afraid that the question was going to lead to is we were going to start looking for some subsets where survival looked good and I hope the sponsor has no intention of doing that later on.

The other is just to reiterate what

was said about the toxic events. With the cardiovascular profiles getting worse and so forth, you will have a potential real -- and not only the quality of life, but a potential increase in events and you could be exposing a group with their existing problem to tremendous cardiovascular problems. And because of the randomization we can be pretty sure that it's in this combination.

DR. HUSSAIN: Any other burning questions? Dr. Curt? And if anybody has another question, raise your hand. Otherwise, once he is done, we're going to stop the questions session.

DR. CURT: Yeah, 34 percent patient loss to follow-up is certainly higher than you'd like to see, but I'm wondering whether or not that loss to follow-up is balanced across the arms or whether there's an imbalance in loss to follow-up, which could further confound things.

DR. BOWDEN: Thank you for your

question. I'd like to ask Dr. Michael Ostland from Biostatistics, Genentech, to answer your question.

DR. OSTLAND: Good afternoon. I'm Michael Ostland, Genentech Biostatistics. Yeah, could I -- that's the slide. Oh, I'm sorry, number 97 actually. It's a little more focused on your question, specifically about the loss to follow-up.

I'm sorry, 129, 129. I'm a statistician, I can't get my numbers right.

So what this slide will show you is in reference to I think the statistic that was -- yeah, that's the one, thank you very much. So in the FDA presentation you saw a statistic, I believe it was 34 percent was quoted as having PFS censoring. We actually come up with 37, so a slightly different number, but I think it's qualitatively similar.

And what you see here is a breakdown of that 37 percent by various

causes. And what you see here is no scan submitted, so missing data would obviously be a big part of that. But I really want to draw your attention to the non-protocol censoring in the third line down. So a big chunk of that 37 percent that were not followed up to the data cutoff date were actually on account of the fact that in our primary pre-specified analysis of PFS we censor patients at their first instance of non-protocol therapy. Since that non-protocol therapy happened earlier, those patients were not, by definition, followed up to the end of the study. So I think you can subtract those from the rate you might be concerned about.

And I'll also just talk about the last two lines there. So there's a little imbalance numerically between the investigator PD not confirmed by IRF, but that's, you know, 6 percent overall.

Then the data cutoff in the last

line, that's actually expected that those would be imbalanced due to the fact that we have evidence of 50 percent reduction in the risk of death. So you would expect then about a 50 percent difference between those. Thank you.

DR. BOWDEN: And if I could just add -- follow-up on a previous comment. There was a question about the clinical benefit -- risk-benefit profile thinking about cardiovascular toxicity and overall in the first-line population. Dr. Winer, could you comment again on that with regards to first-line versus second- and third-line?

DR. WINER: I just want to come back to this issue of first-line versus second- and third- line. And I want to go back to a point that you made, Dr. Hussain, which is that I agree that we have to be very careful in patients who don't have symptoms from their disease. And there are patients in the first-line setting who have symptoms

and patients who don't. And certainly when I lecture, and when I think many of my colleagues do, we emphasize that if you have a patient who is asymptomatic, you're not going to make that patient feel better with any therapy. That's a matter for education within the oncology community, both patients and doctors. It's sort of a separate issue.

That said, I still don't understand why time to progression would be a meaningful endpoint -- or progression-free survival, excuse me, would be a meaningful endpoint in the second- and third-line setting and not in the first-line setting.

And if I can make one last point. I do believe that within the past two months the FDA actually approved ixabepilone in the second- and third-line setting in addition to capecitabine for an improvement in progression-free survival that was less than two months. And while I realize that we're not necessarily supposed to be comparing

across these agents, in terms of the toxicity, in terms of the day-to-day toxicity of adding ixabepilone to capecitabine versus adding bevacizumab to paclitaxel, I'm actually left speechless. There's no comparison here. It is far, far easier to add bevacizumab to paclitaxel in exchange for a five-month improvement in progression-free survival than to ever considering adding ixabepilone for a six-week improvement in progression-free survival. I'm not disagreeing with the judgment about ixabepilone, but I'm trying to put this in context. Thanks.

DR. HUSSAIN: I think what you raised is the low bar that we have overall. And if it's up to me, I would tell you that a lot of those approved drugs in the second-line, if I was the president, I would not approve them. Okay? So I think to compare, you know, I don't want to say mediocre, but suboptimal with suboptimal to

make a case, we could discuss that at ASCO maybe. Dr. Mortimer?

DR. MORTIMER: I have a question for the statistician. So in the negative capecitabine/Avastin trial, appreciating that these are totally different patient populations, but the reassessments were performed twice as often as they were on the ECOG -- on this, the ECOG 2100 trial. And the long-time interval between reassessments in 2100 I think has raised some concern that perhaps that does, in part, account for a longer progression-free survival. And if you could just comment about the difference in those two trials and reassessment interval.

DR. HUSSAIN: Thank you. I think -- does the FDA have any comments that they want to make.

DR. KEEGAN: Well, I think one trial we had input on and the other one we didn't. So, you know, it's very difficult for us to justify the E2100 evaluation

period. We didn't have an opportunity to really get good input on it.

DR. MORTIMER: Because I guess, you know, there's no question that these are much -- they're very superior results and how much of that can be accounted for by the frequency of reassessment? And I guess I would raise concern (off mike).

DR. BOWDEN: Pardon me. Could we make a comment with regards to the question as well?

DR. HUSSAIN: Please do.

DR. BOWDEN: Thank you. I'd like to introduce Dr. Ostland from Biostatistics.

DR. OSTLAND: Thank you. Could I get the PFS Kaplan-Meier curves from the main deck, please?

Yeah, I think the issue of the timing of assessments is an important one. And just to hop on some comments a bit earlier, yeah, I think we do need to keep a very high bar for PFS. And part of that is

having a benefit that we can really sink our teeth in and establish with confidence. And yeah, if you could put that up, please.

And I think certainly it's true that when you are assessing less frequently, you run the -- you have less precision to detect a small difference. And indeed a priori in the setting, having a 3-month -- excuse me, a 12-week assessment interval gave us less precision to detect a difference than we had in the 2119 setting with 6 weeks. But the good news is it didn't matter here, clearly. The size -- it might have been a very different conversation had the benefit that we've seen here been on the order of six weeks or two months. But I think as you can see from this curve the assessment interval really manifests in these sort of bumps in the curve as you ride these down. Because that's when patients are coming in for their assessments and you tend to have progression events clustering around there as they get

detected by the investigators.

So I think what we're really talking about, having a more frequent assessment interval, would smooth out some of these bumps and give you a little bit more of a refined estimate there. But I think in this setting we can be really confident that the magnitude of the benefit we're seeing wouldn't be sensitive to that particular difference.

Thank you.

DR. HUSSAIN: Dr. D'Agostino and that's the last question.

MR. D'AGOSTINO: Yeah, and just to comment. I think, you know, the question you asked, it would have worked in the opposite direction. It would have made the study we've seen before us more significant had we had more frequent, so they probably lost some significance by doing the grouping.

DR. HUSSAIN: Thank you. Ms. Hinestrosa, are you here? Excellent. Ms.

Hinestrosa is a representative of the Breast Cancer Coalition, is that correct?

MS. HINESTROSA: I want to thank the chair very much for the opportunity to make a brief comment. And I'm compelled to speak just to try to explain the absence of many people in the breast cancer community at this hearing. We rely on communications that come to us from the Office of Special Health Issues at the FDA. We realize information is available in the public register, but in the advocate community many of us rely on those communications. We didn't receive one this time, unfortunately. And we -- through the grapevine people found out yesterday, so we received e-mails last night are you coming to this?

And the reason I make this comment is because the absence of testimonials can be a statement in itself. And the reason we're not here is because we didn't know in advance and we were not prepared.

The National Breast Cancer Coalition is going to make comments and send them to the FDA on these issues. We care deeply about this issue and we urge the committee to set the highest bar always in breast cancer, for this medication or any other that is considered by this committee. We feel well- represented in the ODAC by members of the consumer advocacy community, but we ask you to really look ultimately what is the value of this or any medication that you're considering in breast cancer.

Thank you.

DR. HUSSAIN: Thank you very much for sharing your thoughts. So now we go to the questions that are posed by the FDA to the committee. And if I may have, please, the first question.

So the way we're going to run this is that we'll have one question at a time. After the question is read there is an opportunity for committee member discussion.

This is your opportunity to explain your thoughts because once the vote is happening, I'm not going to ask why you voted this way or that way. So this is your opportunity to speak up if you have any points you want to raise.

And then I will -- great, we have the questions now. So the first question that has been posed to us, that in the E2100 study PFS is not a surrogate endpoint for overall survival in the first-line breast cancer. The discussion that's been requested from us is whether PFS alone, without a demonstrated survival advantage, should be considered a measure of a direct clinical benefit in the initial treatment of metastatic breast cancer. Dr. Buzdar.

DR. BUZDAR: I think that will be going backward and we need harder endpoints. As I pointed out in these data that differences in measurable disease between the two groups could even explain all these five

months differences by chance alone, even though all the measures and everything is accurate, it could be just that biology of breast cancer is very heterogeneous. And we need endpoints which are harder, fixed, and not observer-dependent.

DR. HUSSAIN: Dr. D'Agostino?

MR. D'AGOSTINO: You know, in terms of these statistics that we start off with that very first line, it's not a surrogate endpoint for overall survival, then what is it, is really, you know, the issue. And what we're hearing from basically both sides around the table and the sponsor is that we don't have any way of saying how it translates into quality of life, how it improves symptoms. Well, I don't want to get into the toxicity, but we don't have anything to put our hand on outside of the fact that it's a measure that has been -- with an appropriate measurement instrument has said that it is an improvement over one group

versus the other. But we don't have anything to pin it on in terms of what it actually means. So I would think that it's very, very serious that in this first-line treatment that we do not buy into this progression-free survival.

DR. HUSSAIN: Any other person who wishes to make a comment? Dr. Lyman?

DR. LYMAN: Maybe it has something to do with what breast cancer doctors eat and drink, but I have a somewhat different perspective on this. And clinically I think there's no question among my colleagues and myself that progression-free survival is clinically meaningful. Having said that, it challenges how much and, again, the safety and toxicity side of it.

We have data in the adjuvant setting, a different setting very clearly, from a compilation of all the randomized control trials in the adjuvant setting conducted over the last 20, 25 years by the

Oxford Group, the Early Breast Cancer Trialist Collaborative Group, that in their most analysis demonstrated that differences in disease-free survival at 5 years seemed to translate into overall survival differences, significant differences, at 15 years. This is a different setting and I recognize that may not entirely extrapolate.

But I do think raising the bar for first- line metastatic breast cancer to an unequivocal overall survival difference, given the difficulty in many cases of documenting, monitoring, and standardizing subsequent therapies that these patients have -- many of my patients after their first-line approach go through five, six, seven additional regimens. And that just adds enormous noise and can cloud the survival differences of a first-line regimen.

And when we see differences in progression-free survival that reach a certain level, and, frankly, I think this may

have done that, one has to wonder if the survival differences aren't being clouded by the fact that there were probably multiple treatments done separately subsequently. And, in fact, we don't know because that data wasn't collected.

And this on top of the fact, I think the point was made, that the differences between managing first-line metastatic disease and subsequent second- and third-line therapies really in the last few years has become very, very cloudy as well. And that has to do with the fact that the vast majority of patients that come to me for first- line metastatic treatment have had an anthracycline, they've had an alkaloiding agent, they've had a taxane. If they're HER2-positive, they've had Herceptin and often other agents. So they come in already fairly extensively treated before -- admittedly in the adjuvant setting, before I see them for first-line metastatic disease.

And I'm not sure that population overall is any different than a patient who comes back, a recurrence after their first line of metastatic failure.

So obviously, again, there may be -- I mean, I wouldn't go out and suggest that we start setting different rules for different malignancies.

Obviously we need something that can extrapolate across diseases. But from the breast cancer management perspective, I find progression-free survival to be a fairly compelling endpoint.

DR. HUSSAIN: Dr. Eckhardt?

DR. ECKHARDT: Yes. You know, I think that PFS over response rate and the ability to look at durability of that disease status is one that is a real advantage. And I think really what we're struggling with is the measurement. And I think here the concern is clearly in patients that have bone-only diseases that, you know, it becomes

more and more difficult to really set the time of progression.

But I also am struggling a lot with the survival endpoint and front line because, you know, I think that what we've seen here is a fairly robust response rate and PFS. And, you know, the question -- I think we could say, well, that's why randomized studies. But if you look at again the control arm essentially going from 11.7 months for a single agent taxane to 24.8 months in 10 years, it's hard to make the case that that's patient selection. I really think some of that can be due to salvage therapies and the variability of application.

And for instance, if you just ask, well, would the physician take a patient here that had had a taxane, would they give them cape -- docetaxel? Would they go ahead and add gemcitabine to capecitabine to a patient that has failed? A taxane -- I think there's a million different ways that post-protocol

therapy could be applied. And I think that it is very difficult to say that just because it was a randomized study that that should be equivalent between the two arms.

So I'm really struggling with -- I do think it's a clinical benefit parameter. The measurement bothers me and I think, again, the overall survival just in terms of what's happened in the past 10 years even to the control arm really to me signifies that there is something there with regards to variability of second- and third-line therapy, which really has implications I think going forward in front-line metastatic breast cancer.

DR. HUSSAIN: Dr. D'Agostino?

MR. D'AGOSTINO: I guess I'm reading this question only in terms of first-line breast cancer.

And I think we -- you know, I think we have to be careful that we say it's clinically meaningful and then describe a

completely different set of parameters to interpret that.

You know, I'm a statistician and not an oncologist, but I've lived through all of these discussions where we pull up a surrogate and we know, you know, reducing arrhythmias is great. And then we get drugs, you reduce arrhythmias, and you kill people. I mean, there are lots and lots of examples where surrogates and intuition doesn't work and where clinically meaningful in one set of outcomes doesn't really translate. And my response earlier was solely for this first-line breast cancer, and I thought that's what we were being asked.

DR. HUSSAIN: Dr. Mortimer?

DR. MORTIMER: I'm going to reiterate what Dr. Lyman said. I think progression-free survival is an important endpoint. And I think as we talk about first-line therapy today, again, to reiterate what Dr. Lyman said, most of these women have

been heavily pretreated. And so, in fact, very few truly are first-line therapy, making it harder I think to expect overall survival advantage.

I happen to be of the school that outside of trastuzumab I don't believe that any chemotherapy alters overall survival. And I think this just reflects that we don't know who the subsets are who truly benefit from each of these different therapies. And I think it would behoove us to find out who the subsets are who potentially might be in this group. But from a patient perspective, progression-free survival I think is a very meaningful endpoint for second- and third-line therapy.

The other thing I'd like to say, again, reiterating what Dr. Winer said, is ixabepilone was approved with a 70 -- and I appreciate this is second- and third-line therapy, but with a 70 percent incidence of neurotoxicity and a 65 percent incidence of

Grade 3 myelosuppression. And I think that we're being inconsistent here.

DR. HUSSAIN: Dr. Buzdar?

DR. BUZDAR: Yeah, one point I disagree, that the thing is that if you look at the survival, the issue which was being raised is all because there is heterogeneity in the therapies. These patients who were on this protocol, the majority of these patients were treated in the U.S. So we can't talk out of both sides of the mouth, saying that, oh, maybe patients got a different type of therapy upon progression. These patients are uniformly being treated in the U.S., and most of the practice is very similar. Because these are the patients who are treated by selected investigators and their practice pattern should be very, very similar. That should not be the only reason that why we didn't see the survival advantage. I think we have to look for other reasons that why there is progression-free survival and there

is no advantage in survival.

DR. HUSSAIN: So I am also struggling with it and I wonder if there is like a middle of the road thing in terms of approval. So this is just a thought I'm going to throw at you, the FDA.

You know, I respect my colleagues' opinions about progression-free survival. And there's no question if I'm in the clinic, my psychology is much improved when my patient is not progressing, not to mention their psychology is, and there's no way to capture that as a clinical benefit.

I also come from a field whereby there has been at least one or two examples where early positive indications did not translate. And I don't want to bring drugs' names here, otherwise I'll be written up again. But did not translate actually into a survival advantage. If anything, despite early therapy in populations with drugs that should not have harmed them, indeed resulted

in worse survival. And therefore, if you ignore the survival and you've just gone by response or progression-free survival, you would have actually put harmful drugs in the market. And then, of course, in medicine there is numerous examples.

And I'm wondering if there is a way of coupling an approval process with at least equivalent survival, understanding that equivalence is hard to prove. But maybe a non-inferiority or something whereby, yes, the progression is delayed and, by the way, you have to have survival data and that you have to show that there is really no significant chance of a harm. Because I do think that I look at the drug and I can't disregard the toxicity, with all due respect to all the experts here. I would say that a little nausea is not like a Grade 3 hypertension or a stroke or a perforated gut or a bleeding. And I think that a patient who's in the ICU, no one's going to check

their quality of life. And so we really have to be very careful, you know, in terms of the statements we make.

But is it possible to couple it with some other measure that says you have to prove one and two? And then, well, okay, you don't have to prove survival superiority, but at least that there's no harm.

DR. PAZDUR: You have to show safety and efficacy to get the drug approved. And in many situations, for example adjuvant breast cancer, we would approve a drug on a disease -- or disease-free survival endpoint with the sponsor basically looking at or submitting subsequent data to make sure that there's no harm to overall survival. So yes, we don't -- we want to make sure that no new therapy is producing a decrement in survival because that's going backwards here. We have accepted, as I said before, you know, and we've made it quite clear that PFS is -- we have approved drugs not only in breast

cancer, but in other disease settings, usually in the refractory disease setting.

Here again I think you're grappling with a concept here. You're trying to say -- enunciate what is this clinical benefit, and perhaps you know in your heart that it may be, but you're having a difficulty in kind of enunciating it or really clarifying what it is. And I get this feeling from hearing several people here.

DR. HUSSAIN: The other concern I have, if you do not look at survival, is you cannot capture bad events that might happen after patients have been removed from study, which I go back and say something bad happened that led -- I really truthfully have not yet heard any credible evidence that says post-protocol therapy impacts outcome. In fact, if that's the case, then there should be never a positive trial in breast cancer, and that's not true. If there's a disease that has numerous active agents in it, it is

breast cancer. And yet you were able to show a survival advantage in colorectal cancer. And other -- gemcitabine and Taxol had the trend in an era where there are other agents. And so I'm not so sure that I buy that argument.

But I really would encourage the sponsors in the future is to make sure that as much data is collected as possible to make sure that that hypertension in someone who's borderline heart failure did not, three months after study registration, lead to their death. And anytime you have a cancer patient who dies with metastatic cancer, you know what the likelihood is going to be that this is going to be recorded secondary to cancer. And so there may be subtle harmful effects that are not being picked up and may explain why your survival is not different.

DR. SCHENKEIN: David Schenkein, Genentech. Just to address that. We agree with you and that's why we're very committed,

as I mentioned earlier, not only to continue to study Avastin in breast cancer with many ongoing studies, but also in the other diseases in which we've already received approval, both in colorectal cancer and lung cancer.

We continue to follow these patients. We follow them both in clinical trials and in disease- specific registries, where we follow these patients long after they've completed their protocol therapy, so we can look for those late signals that may occur. So we have made that commitment and will continue to do that not only in diseases that we've already achieved approval, but also in breast cancer.

DR. HUSSAIN: Ms. Portis?

MS. PORTIS: Yes. I agree that we absolutely have to raise the bar in terms of safety and that that's very important. Otherwise, there have been mistakes made in the past and they have caused people their

lives. And I know that everyone wants to offer women with metastatic breast cancer hope, but I don't think we should offer false hope.

And I hear that there's been inconsistencies perhaps that things have been approved in the past, but I don't think that's a reason to go forward and make a similar mistake if, in fact, that's a mistake. So I just think it's important that we hold that in our mind.

DR. HUSSAIN: Thank you. Dr. Eckhardt?

DR. ECKHARDT: Well, I mean, I would just go back to a comment where I think I would be willing to say that PFS is an adequate endpoint for clinical -- or does include clinical benefit. I think really what I'm struggling with and many of us are struggling with is the measurement in these kinds of studies. And, you know, I think that's going to be something that will have

to be decided going forward as to whether -- you know, I think in this trial, because it was something that initially started out as a non-pivotal trial, certainly there were a lot of variabilities in there, including the 30 percent lack of follow-up. So I think -- I'd hate to see us throw out the whole endpoint just based on the fact that this was a fairly difficult to apply endpoint in this kind of setting.

DR. HUSSAIN: Dr. Lyman?

DR. LYMAN: Yeah, I just want to make sure that we have this in context. Women with metastatic breast cancer are being treated with Avastin every day in combination with chemotherapy, second-, third-line, or later therapy. So the real issue is whether we have an indicator, like progression-free survival, that says it's safe to do that and efficacious to do that first line.

As I've already stated, I think that most breast cancer oncologists and I

would dare say most breast cancer patients probably would accept progression-free survival as a reasonable endpoint.

And Rick made the point in the adjuvant setting, I mean, certainly Arimidex and some of the hormonal therapies, were approved not based on survival difference, which ultimately needed to be looked at and should be required to be submitted, but were approved based on disease-free survival, again the early stage kind of surrogate for progression-free survival in the metastatic setting.

So, you know, I really think we've got a legitimate efficacy point here and we're all wrestling with was it measured correctly and was the toxicity or the risk-benefit justifiable. And I think that gets us into the second question.

DR. HUSSAIN: But Dr. Lyman, are you arguing that -- because the question as it's posed by the FDA is, if you forget about

what was presented, this is more of a philosophical question, are we now saying that for anyone who is to do a trial with a new agent that they can get away without a survival also data collected? That we now are not going to require survival? We're going to say if you show progression-free survival improvement, therefore, this is a home run and we're done. Because I'd like that clarified. It is my understanding that a lot of us still consider survival as the gold standard.

DR. LYMAN: No question survival is the gold standard. I would argue I think reasonably that first-line metastatic breast cancer may be one of the most challenging settings to show that because of the fairly -- not compared to other diseases, GU and so forth, a relatively lengthy disease course after the development of metastatic disease and the multiple regimens that they get placed on. So whether it should be

extrapolated to all settings and so forth, I'm not -- I have some discomfort as well. But in this setting I think it's very clearly a clinically significant and important endpoint.

And I think where I would encourage we go with it -- and I liked, in fact, your suggestion that maybe we need to couple it with some documentation that there's no worsening of survival as well as no tremendous increase in toxicity. But I think it still doesn't negate the fact that this is an important clinical endpoint.

DR. PAZDUR: Let me guarantee you that we would demand that the sponsors provide survival data as a follow-up. That would -- that is not even a question here. If we are going to be approving these drugs and progression-free survival it isn't progression-free survival and then let's forget about it.

The way we're wording this question

is, you know, the situation if you have progression-free survival -- and perhaps their survival is in this case where we don't see the advantage here. That's what we're really talking about, not a disadvantage, okay. If we saw an inferior survival we wouldn't even be here.

DR. HUSSAIN: Well, but my concern is this. If you're going to somehow begin to say progression-free survival now is the primary endpoint for everything, then studies will never be powered for survival. Sample sizes go down, follow- up time goes down. And as you know --

DR. PAZDUR: Let me assure you in our discussions with sponsors on this, okay, when we are negotiating a progression-free survival, whether it be -- and here, again, these conversations are usually in the more refractory disease settings, we ask them to power the trial to ensure that we could take a look at overall survival and obviously

you're going to need larger numbers of patients to show a survival advantage. The reason behind that is obviously if we never ask the survival question, we'll never see the answer. And as you pointed out, and we have repeatedly mentioned this to sponsors and also at ODAC, if we go on a slippery slope of having smaller and smaller trials, then we're really doomed to failure here.

So we would require not only a look at survival, but we've also recommended basically powering for overall survival and perhaps looking at the endpoint of PFS as the approval endpoint. But if you do demonstrate obviously a survival advantage, that would be quite a marketing advantage for the drug.

The disadvantage of that, for the members here in the audience, is that when you do overpower a trial for progression-free -- for -- because you're powering it for survival, you may get a statistically significant finding for PFS and it could be

relatively marginal. And then we really have to have very careful discussions about what is the clinical meaningfulness of a very small impact on progression-free survival that may be highly statistically significant.

DR. HUSSAIN: Isn't that why you have ODAC?

DR. PAZDUR: Oh, yes.

DR. HUSSAIN: Dr. Link?

DR. LINK: I was just going to ask if there was a signal anywhere in this trial that the survival was worse? It was better, just not statistically better. So in other words, you're sort of -- you know, I don't see that we're worried so much now that there's an inferior outcome in terms of survival that we even see here.

The second question I had is how are you going to control for what happens to a patient after relapse? So I can think of scenarios, which happens in pediatrics all the time, how you can shorten a patient's

survival once they fail their primary therapy by doing some sort of, you know, bone marrow transplant kind of thing. And if that happens after that, you will definitely shorten survival. And so you could actually be totally misled. You could have a program which is actually very useful and clinically meaningful in terms of event-free survival or progression-free survival, whatever you want to measure, but then you can blow the survival advantage by what you do post-relapse.

DR. PAZDUR: One would hope in a randomized study those disasters would be allocated randomly between the two arms.

DR. LINK: Well, you may have more patients in the --

DR. PAZDUR: It could be.

DR. LINK: -- inferior event-free survival arm that get that there if you --

DR. PAZDUR: Could be, but one -- that's the process of randomization.

DR. HUSSAIN: Dr. D'Agostino?

MR. D'AGOSTINO: I just would like to know what the clinical benefit is in this setting outside of the fact that it's progression-free survival. I haven't heard anybody say any clinical benefit outside of the measurement of progression-free survival. Shouldn't we sort of give a little list on why we think progression-free survival in this context has some clinical benefit outside of, let's say, the measurement itself?

DR. HUSSAIN: Because they pay me --

MR. D'AGOSTINO: It doesn't lead to survival in this study.

DR. HUSSAIN: Yeah. No, I know. Because they pay --

MR. D'AGOSTINO: It doesn't lead to quality of life.

DR. HUSSAIN: They pay me as the chair, so I'm going to take a stab at this,

but I'm going to welcome others. I think part of the problem is that we have no way of measuring some subtle issues that are of benefit. So those of us who sit in the clinic in front of patients, I will guarantee you there is not a tool out there that captures the nightmares, the sleepless nights, the worry about scans by the time they come. And so if one wants to be removed about it and just put party line in terms of things you can measure, I agree with you that there is really no clinical benefit. And that's why I was trying to put the pressures on Dr. Winer to tell me where there is the clinical benefit in the traditional context, and there isn't. There's no disagreement there.

But isn't it -- for those of us who are clinicians, when you sit with patients, assuming therapy is safe, and I have a question with safety because I'm not so sure it's that safe, but if you put that aside,

patients are a nervous wreck when their disease is progressing. And that you have no tool to measure. So it is one of those intuition things, which you just said it cannot be by intuition. Unfortunately, that's a question we face every day when we're at the clinic.

I don't know if anybody else wants to take a stab at that. Dr. Lyman and then Ms. Mason after Dr. Lyman.

DR. LYMAN: Yeah. I mean, my -- I don't think you're going to find the data there in breast cancer that's going to convince everybody. A couple of recent elegant studies in the metastatic colorectal setting done by, in fact, statisticians have demonstrated across multiple trials in the metastatic colorectal setting as very strong, highly significant correlation between progression-free survival and ultimate overall survival. This is a setting where there's many fewer options for subsequent

downstream therapies, so conceivably it could be that you're going to have less blurring and muddying of the early treatment's survival impact in that setting. But there's just not much out there that I'm aware of.

MR. D'AGOSTINO: So is it on the hope that it makes sense? Sort of the model that you would have says that we think ultimately survival will improve? We don't have it now. Is that where we're getting the clinical benefit from?

DR. MORTIMER: Well, response rate, you know, people who hurt have less pain. People who are short of breath have less shortness of breath.

MR. D'AGOSTINO: Well, response rate is one thing that turned out to be significant. Is that something?

DR. MORTIMER: And that's consistently been a signal.

MR. D'AGOSTINO: I'm just looking for is there some list?

DR. HUSSAIN: Any other comments from the committee members? Ms. Mason, I'm sorry, yes.

MS. MASON: Just wanted to share that since I represent the consumer, but I'm also a survivor, and so I'm seeing this from a lot of different angles. And clearly, as you stated, you know, when you're a clinician or a patient looking at these issues, it's a very, very difficult place to be. There are not a lot of options for patients, especially the HER2-negative population, in terms of what to do with metastatic disease. And it's so hard when we're looking at whether you're talking about first-line metastatic treatment or later because of the pre-treatment for initial breast cancer. Yet, I am also concerned about the toxicities and whether we lowered our standards more and more. There's been some comments to that effect.

So I think for myself I have a very difficult time choosing which side, since I

have to choose a side, where I want to fall on this. Because either way, you know, you're making some very difficult decisions based on people and their outcomes.

DR. HUSSAIN: Thank you. Any other comments? Dr. Pazdur, do you have all the discussion you want on this?

DR. PAZDUR: I think so. We can move on to the voting question.

DR. HUSSAIN: Excellent. So this question is not a voting question. We're going to go now to the voting question, which they'll have up in a moment. Okay. So Question 2, Summary Results, estimated 5.5-month improvement in median progression-free survival claimed by Genentech. No improvement in overall survival. Increased toxicity/toxic death. No effect on progression-free survival or overall survival in the second- and third-line metastatic breast cancer. Are the data provided sufficient to establish a

favorable risk- benefit analysis for the use of bevacizumab plus paclitaxel for first-line treatment of patients with metastatic breast cancer?

So we're going to also take time to discuss this question, and this is a voting question. Once we're done I'll tell you what the rules are about voting. So who wants to take a stab at this one? Dr. Buzdar?

DR. BUZDAR: Yeah. I think the thing which we have to -- when we vote, we have to look at the data in totality, that what -- first thing, the study which turns out to be positive was not designed for FDA approval. The study, FDA's reviewers have pointed out a number of shortcomings.

There's no study which is perfect. We are all clinicians and all patients are humans, so there are going to be shortcomings, but there are major shortcomings in this study. So I think we have to keep that in mind, that a single

study which shows one endpoint which is positive, there are other studies which do not support that.

The thing is that are we enhancing the patient's choices? Here we're putting something which is of not established value. It may be of value. But the data -- I think we have to look at it critically that is the data which is available today, does it meet the standard to put the drug on the market and change the label?

DR. HUSSAIN: Anyone else wants to make a comment or discuss this question? Dr. Lyman?

DR. LYMAN: Since I'm getting in trouble I might as well continue. This is actually to me a more difficult question because of the nature of the data and, as was alluded to, probably designed and run initially without anticipation of a label extension. I do think, as I've stated before, that in this context a 5-1/2-month

difference in progression-free survival is clinically meaningful.

Certainly it's statistically significant and seems to hold up through a variety of both FDA and sponsor sensitivity analyses.

It is true that there's not a significant if it's an overall survival, but there certainly is a trend. Statisticians don't like trends, but it at least assures me to a large extent that subsequent studies' design may be a little bit better, whatever, would show any worsening of survival. I think the probabilities, if we ran the numbers, would be extremely low that this is such an extreme false signal.

So the real question in my mind and where I'm really having most difficulties with the toxicity and are we doing any harm or not. And that's why I asked the questions earlier about how well we can adjust the differences in the arms, the toxicities in

the arms, to how much is the addition of Avastin to a drug that is used in the first-line setting and how much is the fact that the patients didn't relapse for an additional 5-1/2 months? They stayed on treatment in the majority of those cases.

And obviously that can -- certainly for the neuropathy, that may completely explain the differences that were observed there.

There are others that are Avastin-specific toxicities, but as has been pointed out, they are not new. They were there when it was approved for second- and third-line metastatic setting. Do we really need to make a distinction in terms of those are unacceptable in the first-line setting and not in the second- or third-line setting? Keeping in mind these are all metastatic patients. With the exception of that 1 to 2 percent that were local regional, it's very unlikely any of these patients will not die

of breast cancer or some other co-morbidity or accident or whatever. It is a fatal disease.

And we have to put in context if we can prolong, almost double -- actually more than double the median survival in these patients or nearly double the median survival. You know, yes, they will go on to die. Those curves will come together as they do downstream. And if you follow patients long enough, the curves come together at the baseline.

So I am certainly not at all as convinced here, but I would -- I'm leaning towards voting yes on this.

DR. HUSSAIN: Dr. D'Agostino?

MR. D'AGOSTINO: Yeah, just to reiterate some of the comments that I was making before, that there is no improvement in overall survival. If the survival went the other way, we wouldn't have the presentation before us. If the survival were

really with a P value of.98 or something, we wouldn't have it. We have it before us because it looks like there might be a signal and all of us have lived through chasing after signals and their flattening out.

So I don't think we really can say that there's a trend there. There might be, but the data isn't -- shouldn't convince us. The toxicity I think is a real problem. So putting this in, you know, sort of as a package of all these different comments that are made, I think that our approval would rest completely on buying into the progression-free survival as an appropriate measure of efficacy. And I don't think we have that ability at the moment given the data that's before us.

DR. HUSSAIN: Okay, Ms. Portis?

MS. PORTIS: Well, I see that the question really is about is the data provided sufficient to establish a favorable risk-benefit ratio? And I really take that

question to heart. And I know I keep probably saying the same thing over and over again. And absolutely, it's a very painful reality that metastatic breast cancer is not curable. And I don't think that means then that we should just say, well, here, try this, if there isn't meaningful data to support it. And in this study as presented there is missing data. There are inconsistencies and I remain very uncomfortable about that. And that along with all the comments that I've made and others have made about the toxicity, I think that that is too high a price to pay.

DR. HUSSAIN: I guess when I looked at the data first before the discussion, I was really impressed by the overall survival. And then we began to see the holes, one hole after the other, one piece of information that is incomplete. And so if things were not perfect, but semi-perfect, I would have been willing to vote yes.

I am leaning to a no vote because I think there are too many uncertainties in the way the data was collected, the discordance as far as imaging, the fact that things were not set up from the beginning for a registration so that you have everything done in a line that makes the case. And so I think that a vote of a yes today on something like that to me lowers the bar.

I think there are other agents out there that are available for this patient population. I fully recognize that it's imperfect, but I don't think we could sanction suboptimal conduct of trials necessarily. And I have the utmost respect for ECOG. I work with SWOG and I know the limitations and the strengths of the cooperative groups. But I think that what we saw today in terms of deficiencies is concerning enough for me that I would -- it takes away from the positive results otherwise.

Anyone else who wishes to discuss the nature of their vote? Because that's your opportunity.

Okay, so before we go to a vote is there anything else, Dr. Pazdur, that you need discussion- wise?

DR. PAZDUR: No.

DR. HUSSAIN: Okay. So as I understand it we're going to vote first those who say yes. And again, the question is are the data provided sufficient to establish a favorable risk-benefit analysis for the use of bevacizumab plus paclitaxel for the first-line treatment of patients with metastatic breast cancer?

What I'm going to ask is those who want to vote yes to raise your hands simultaneously, keep your hands up in the air, and then one-by-one mention your name, and just for the record say that your vote is yes so that they can capture that in there.

So I guess on a count of three

we'll raise our hands. One, two, and three, those who are voting yes, please raise your hands. Okay, can you -- this is -- keep it up, please. And for the record state your name and that your vote is what.

DR. LYMAN: Gary Lyman, I would vote yes on Question 2.

DR. MORTIMER: Joanne Mortimer and I'm voting yes on Question 2.

DR. ECKHARDT: Gail Eckhardt, I'm voting yes on No. 2.

DR. LINK: Michael Link, yes on No. 2.

DR. HUSSAIN: So now those who are voting no to Question 2, raise your hands. And then I'll begin with Dr. Buzdar. Please state your name and --

DR. BUZDAR: Dr. Buzdar, I'm voting no.

MR. D'AGOSTINO: Ralph D'Agostino voting no.

MS. PORTIS: Natalie Portis voting

no.

MS. MASON: Virginia Mason voting no.

DR. HUSSAIN: Hussain, no. And then we'll tally the vote and we'll give you the final vote.

So we have four for yes, five for no. Thank you.

Is there any other thing, Dr. Pazdur, before we adjourn this component of the meeting?

DR. PAZDUR: No, thank you.

DR. HUSSAIN: Okay. Thank you, everyone. The committee will have a closed session, so those who are not members of the committee will have to leave. Thank you.

Yeah, we'll have a 10-minute break for the committee.

(Whereupon, the PROCEEDINGS were adjourned.)

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