DR. SANDRA SWAIN: Okay, thank you. Sandra Swain, Washington Cancer Institute. I was very interested in Gunter's presentation showing that you had a longer - or a higher - pCR rate in those patients who had ER-positive tumors. And one hypothesis would be that you have more ovarian ablation or suppression in that group. In the NSABP-B-30 trial, when we looked at the AC followed by T, there was about 80 percent of the patients that had amenorrhea, and we'll be looking at it prospectively.

And I think we haven't really talked about that much today, is how that fits into all this for the pre-menopausal patients. For your study, do you have any of that data?

DR. GUNTER VON MINCKWITZ: First -- for understanding the results -- there were, of course, a higher pCR rate in the ER-negative tumors; but the difference was not as prominent as in the receptor positives. We so far do not have data on the amenorrhea rate of these patients.

DR. SANDRA SWAIN: Because I think that… My point is, instead of giving more chemotherapy, maybe we're not giving the right treatment, which everybody's been talking about today, since the pathCR rate is so low in that group of patients.

DR. CLIFFORD HUDIS: So, actually, my question is related to that. At St. Gallen last week, on the issue of taxanes and ER status, I was sort of amazed by the fact that, in contrast to the North American data on ER positive versus negative and ER status predicting benefit, the (unint.) Group with sequential weekly paclitaxel showed absolutely no ER interaction, nor, for that matter, does in a significant way, the BCIRG. And I wonder whether, as one work product from today, we couldn't insist upon some standardized ER testing so that we could start to figure this out.

Because I predict that across our trials we're going to again get disparate results and that's going to undermine what Gabe was talking about this morning, for example -- selecting patients by ER status and what everybody's talking about -- taking out the

luminal A's and B's. If we can't test and test reliably, we can't even get started on that task. I mean, maybe you have comments on that, but that's my view.

DR. GEORGE SLEDGE: Fraser, can you tell us about the reliability of estrogen receptors across centers?

DR. FRASER SYMMANS: In a word? (Laughs) No, your point's well taken, Dr. Hudis. There's no question about it. It's a burning issue that I think the pathology and oncology communities are both interested to solve. I don't know if it answers the question and I don't know whether the discussion from the two previous questioners is really necessarily about the same thing. One is whether or not a different agent would be more effective in ER positive. Another is whether or not an additional two cycles of chemotherapy might be more effective. It might just take longer to get there for that particular phenotype.

DR. GUNTER VON MINCKWITZ: And I'm also not sure, if the pCR rate is an interim response marker -- so the more beneficial long-term outcome of the receptor-positive tumors is not in this marker -- so to compare the outcome of the adjuvant trials is not… you cannot compare this with the pCR results.

MALE SPEAKER: (Unint.), Chapel Hill. Mine's a comment that's reflective of what Cliff brought up earlier. I'm a little worried about the message that leaves here of how we're treating people off clinical trials -- and this is specifically to the imagers. We've heard two talks about MRI in these patients. We have yet to hear about the false-positive rate; we have yet to hear economic analysis of how it changed the care for those patients.

And, as a surgical oncologist who deals with all the quote "abnormalities" on MRI, there's a lot of negative biopsies. I think we need to have a more balanced discussion of the role of imaging in these patients.

DR. NOLA HYLTON: Yes, your point's well taken and certainly in the pre-surgical staging there's a high false-positive rate for MRI. We don't have good ways to address that yet. We also don't have very facile or easy-to-use MR-directed biopsy techniques, either. It's really a difficult procedure to perform, and hopefully we will get better at that sometime in the near future; but it is a concern.

How we use it in the context of response to treatment, again, I think is more that we cannot necessarily trust post-treatment MRI to guide… to make a decision about breast conservation or to necessarily guide the surgical treatment at that point, because at that point there's a clear false-negative risk. But, in terms of looking at the ability to predict response or to capture response more accurately -- again, those are still in the investigational scope -- I think it deserves to be looked at more carefully.

DR. GEORGE SLEDGE: So, let me ask you, then, to give us a definitive statement. Outside of an investigational trial, is there any use for MRI's post-chemotherapy? Yes? No?

DR. NOLA HYLTON: Certainly. I think what we don't have is the very objective data that supports the idea that MRI is beneficial or where its limitations and advantages are for pre-surgical staging. But I think it's clear from using MRI to a large degree that there is some subjective interpretation -- there's certainly conservative uses of it that are not always adopted. For example, if you see occult multi-centric disease, you cannot, on the basis of MR, you don't want to make your surgical decisions. Now you have to follow it up and you have to perform a biopsy to verify it. So, I think we still need guidance on how to apply the information; but there's certainly information there that I think is not provided by any other imaging modality and not by clinical exam.

DR. ERIC WINER: So, I just want to underscore a point that Fraser actually briefly touched on just two minutes ago in the questions and answers which is that, in these trials -- so there is both B-27 and in the German trial -- that have shown proportionately greater benefits of more taxane in patients with ER positive tumors. The other variable is time; and it

may just be allowing more time to elapse with or without chemotherapy, and I'm just wondering if anybody has any comments about that.

DR. GUNTER VON MINCKWITZ: This is exactly why we have designed the GeparQuattro study, where we can address the addition of capecitabine and also the addition of time. We hope that we can get some data out of that, but we are aware that time is… And we also have reviewed the literature. There's quite consistent results that all other(?) treatment came to a higher pCR rate; so there might be something on this.

DR. HOLMES: (unint.) Holmes, Texas Oncology, Houston. In regards to the question about measurement of ER and PR, I know Dr. Pusztai will be presenting, I guess, tomorrow, but we've collaborated with him in a trial of locally advanced breast cancers where just using RNAlater. So -- this is a community oncology setting -- the surgeon takes the biopsy, puts it in RNAlater at room temperature, and it's shipped to Dr. Pusztai's lab. And he just published in *Lancet* the genomic analysis of ER/PR… well, ER and HER2. And that new way of looking at ER may abrogate all the inconsistencies that we've had with the IHC and the other methodologies. Did you want to say anything more, Fraser, or do you think Dr. Pusztai will be talking about that tomorrow?

DR. FRASER SYMMANS: I'm not sure if Lajos is talking about it tomorrow; but I think that in the same way as the RT-PCR-based assays, I think, very strongly will also demonstrate that there is similar results in much larger numbers of patients -- that genomic measurements may end up being more robust than immunohistochemical, semi-quantitative assessments; but it sort of remains to be fully proven in terms of survival.

DR. LAURA ESSERMAN: Laura Esserman, UCSF. I want to bring up a point that I think was hinted at by those slides that Nola [Hylton] showed earlier that, as the tumors got bigger, the physical exam actually did better than some of the ultrasound and mammography, and that's probably because a lot of these Stage II-III cancers actually are mammographically occult. It also shows in Fraser's data from the early data to the later data -- when

probably the earlier data had larger tumors or more of the Stage II-III tumors, and the later ones had patients that behaved a little bit better because they're more…… including smaller tumors.

I think it is really quite possible that the Stage II-III cancers are really a different disease than the mammographically occult cancers and may not simply be larger Stage I cancers. And so I think there's -- and I guess that's sort of what Martine was trying to talk about is: do we run a risk of including these… of assuming that the 2 cm tumors are really the same as these 3 and 4 cm, 5 cm, tumors? And that really maybe we ought to be focusing on these tumors that are 5 cm and greater. Anyone want to comment on that?

DR. FRASER SYMMANS: Well, I think, just in terms of survival analysis with the RCB, when we factored in stage and patient age and grade and hormonal therapy, as well as pCR versus residual disease, and in both cohorts, RCB was independently and strongly prognostic. But I think the other part of the question is about imaging of these patients with more advanced stage disease -- is that correct?

DR. LAURA ESSERMAN: No, I'm actually concerned. I think the separation of your curves was really quite a bit better when the tumors were larger; and I think it's important not to just assume that the 2 cm tumors are just smaller versions of these larger tumors -- that these may be different disease… more mammographically occult disease. I don't know -- just a thought.

MALE SPEAKER: (Unint.). I just want to go back to what Dr. Wolmark said earlier, in that when a surgeon took out the tumor, everyone felt better and we kind of fooled ourselves into feeling that everything is fine. And I'm wondering if, as medical oncologists, we are kind of in the same game now with accomplishing the complete pathological response and then it's all said and done. And at NCCN, we actually tried to address the issue of, is there a role for chemotherapy after a plateau phase in a metastatic setting once it accomplishes the rare CR?

And I am not optimistic that in this country we are ever going to have a randomized study of consolidative therapy in patients in CR, which is really the equivalent here. But is there any European attempt to look at duration of post-surgical adjuvant therapy of four-month or eight-month? Because we don't really have good non-cross-resistant agents. So, maybe it's an issue of duration, if we can do it, rather than choosing different drugs, until we have something better.

DR. GUNTER VON MINCKWITZ: Well, I'm not aware of any post-neoadjuvant chemotherapy trial -- maybe Luca knows something about that. But we wanted to do such a trial before the NaTan study -- we tried to set something like that up -- and it appeared that patients were not very… they were so exhausted from the pre-surgical treatment that they didn't want to take this up. Even the bisphosphonate treatment, this is a very hard trial to go, because patients do not want to continue IV treatment.

DEBORAH COLLYAR: Deborah Collyar. I'm a cancer patient advocate in many areas. And I've been trying to be really good. I'm amazed at the complications that we're finding out -- the more we find out, the less we know and the less we figure out how to explain this well or put our results together. So, I have a couple questions and part of it gets to what we were just talking about.

There's only so much I think we can ask research participants to contemplate, as well as how we're going to explain how to start implementing this in the community. A lot of people work, a lot of people have other lives that… they're caregivers, they're involved. And so a lot of life decisions which we haven't been talking about are going to play into whether or not people will be willing to do not only preoperative therapy but post-operative therapy on top of that.

So, we have to be cognizant of that. That doesn't mean we can't study cool things; but we need to be remembering that if we want to implement this on a standard therapy kind

of approach, we've got to be taking a lot of these things into consideration. And we haven't even talked about cost -- I think somebody was starting to bring that up. But, you know, what can we realistically expect? We're adding imaging, we're adding testing, we're adding two different kinds of therapy regimens; so, again, it's not to say we don't want to research this, but we need to be talking about these things as well as we move forward.

And one of the things that I thought was interesting was your presentation on the decision tree. So, one of my questions is: how are we going to move forward with what we're learning from this conference? How can we keep an up-to-date decision tree that will help summarize the findings of the research so that we can move forward quickly on implementing this as standard therapies when we find things that make sense, for different sub-populations?

DR. ANTONIO WOLFF: I guess I'll start by saying that patients are willing to do a lot. And I think we ask patients to do a lot for us and for themselves and we owe them a huge amount of respect and making sure that we are asking them to do things that are reasonable, that we have the scientific rationale behind it, and sometimes not to add stuff to clinical trials just because we can do it. And we live in a technology-driven society and medical environment, and I think we need to be very cognizant of that. These are times with limited resources. We heard discussions this morning about this. So I think, number one, we need to be asking ourselves the usual question: would I have my sibling, my spouse, my mother, my whoever -- is this something that I would have my patient participate in a reasonable fashion?

At the same time, I think we need to be cognizant of the importance of tissue acquisition. And I think the lessons that we have learned from the NSABP going back to the B-14 studies, and the prospective validation using retrospective, well-annotated clinical data and tissue -- how much have we learned?

So I think we have reached the point that not collecting specimens from patients, to answer immediate questions or answer future questions -- it's an unethical issue. But, at the same time, we have to be very cautious about what we ask patients to do. I don't have a good answer for you.

DR. BURSTEIN?: I would just add briefly that all the points Deb made are absolutely true. On the other hand, there is heterogeneous practice out there, and in the real world patients are getting all sorts of stuff after neoadjuvant chemotherapy in the absence of any data. So, better to generate some data.

And the other related point is that the vast majority of preoperative chemotherapy is not given as part of the clinical trial -- it's given in the community to downstage patients, and there will be different studies presumably at different intake points for different groups of women. And it's not just that we're sort of signing them onto a research agenda for the next seven years or something.

DR. EDITH PEREZ: I think one of the challenges that we have is that we have a standard of care which is the adjuvant therapy, and we want to change it because it takes too many patients to get answers. So the alternative is to do the preoperative therapy, and we're trying to make it standard where it's still not standard. It's not better than the old standard, but it has some potential and we need to do some more trials before every patient with a 1.5 cm tumor gets neoadjuvant therapy as standard of care.

DR. IAN SMITH: Ian Smith, London. Hal, your argument for novel therapy trials in non-pCR patients is very powerful, and it's a very obvious thing to do, and it's encouraging that you've started these cohort studies. I've got really two questions. The first is: people have been talking about this for about 10 years or so, and yet these trials up until now have not started. So, where do you think the barriers have been in the past? Or have they gone? You know, are you encouraged that this is going to happen on a larger scale?

And the other question is: although it's a great idea, the downside is that these patients have already had six or eight courses of treatment, some of which at least have presumably not given any benefits. So, are you thinking of ways of trying to get patients before they've reached the pCR stage who are not responding? Gunter, for example, showed that even after two courses, if there's no change, you don't do very well. So what were the barriers, and how can we get patients into this kind of trial area (earlier?)?

DR. HAROLD BURSTEIN: So, I think something working to our advantage now is there is the perception, at least, that there are more choices in the way of novel therapeutics to test. It's not just chemotherapy variations. So we have more agents to bring into bear to this study which may be of value. I think the second point is that these are related sides of the same coin, though it's not clear that a non-responder after two or four cycles is the same as someone who has residual disease -- and they could be worse, they could be better in several respects.

So, I think the work that the German group has been doing really is remarkable and shows that there is the opportunity to start to look at this and these other ideas would be sort of related issues for patients who aren't captured at the moment of their diagnosis, but have finished what would, again, be a more traditional course of therapy, however defined.

MALE SPEAKER: Kenneth Kearn (ph.) from Pfizer Oncology Research & Development. I'd like to get the panel's opinion about a biomarker that goes one step beyond pCR, which is circulating tumor cells or circulating endothelial cells or even marrow cells; and that's something I didn't hear mentioned here. Presumably, that's because there isn't a lot of data, but it's something that comes to us frequently and it might help explain, obviously, why complete pCR women still relapse and those who only have a modest response rate relapse quicker. But where are we at the state of the art in the assays of circulating cells, malignant cells, and endothelial cells and marrow cells? And where does that fit into future research efforts? I'd like to hear a broad opinion.

DR. ANTONIO WOLFF: I can try, and I see Dan Hayes, who may want to say something about it. The whole issue of circulating tumor cells in the pre-op setting is a concern, in terms of the sensitivity of the assay -- at least the current commercially available assay -- for patients with small volume of disease in the pre-op setting. Metastatic disease, you're talking about 5 cells per 7.5 mL of blood. So, the sensitivity of that specific assay, at least as commercially available, for the regular, operable patient with breast cancer is unclear.

I mean, I actually did have in my slides circulating tumor cells. Other assays deserve merit. We have an internal, purely research effort on methylation as a (unint.) of measuring patterns of DNA methylation in serum before and after surgery. And it has been observed that this may correlate to bulk of disease; patients who have no residual, who have had their primary surgery, or who have received pre-op therapy -- and we've seen changes -- and even though there is no residual disease -- that this may identify patients with residual disease. Those are ongoing, purely research questions at this point.

DR. GUNTER VON MINCKWITZ: We have -- in our GeparQuattro study -- we have collected blood from 250 patients by now and have detected circulating tumor cells and this will be presented at ASCO. There are some changes throughout treatment, but what that means is, up until now, we don't know, actually.

DR. GEORGE SLEDGE: We have time for one final question.

DR. STEVE SHAK: Steve Shak from Genomic Health. With regard to the areas of focus -- one of the ones was mentioned earlier, which is the importance of standardization for the analysis of biomarkers, and that that's made a difference and obviously will continue to make a difference.

The other area, in thinking about looking at tumor size as a response marker, relates to the issue of the tumor being heterogeneous -- that there are the recycling cells; some people call them stem cells, or those cells which are capable of dividing. And then there are differentiated cells. In looking at some of the things, either by pathology or by imaging, we maybe can't differentiate between the recycling cells well enough and those that are differentiated.

I guess the question for the group here: that would appear to be an important area for research, and do we have any insights into that from some of the standardized assays that are being developed now?

DR. FRASER SYMMANS: I agree -- the residual cells, although removed by the surgeon and then irradiated, if they're still behind are probably informative of a lot of great deal of biology. And there probably is an opportunity to marry with the micro-metastatic protocols as they become more online in terms of really truly measuring biomarkers. But I think one of our greatest challenges right now is to really get a good handle on what are the molecules of these progenitor type cells, and what are the molecules that are just phenotypic, and what are the ones that are biologically relevant.

DR. ANTONIO WOLFF: And I just want to make one final comment, as I listen to all these questions and a lot of these questions we're essentially stumped because we don't have answers so we can't as, as was said this morning, debate as much as we want in the absence of data… A lot of the commitment initially behind this meeting was to come up with a research agenda, but the more I hear these conversations, I think an incredible responsibility we have is to come up with some guidelines for the physicians out there; because these discussions about what to do after pre-op therapy if there is or if there is not residual disease in the absence of… what to do with these patients and what to do with local recurrences is incredibly important. So I think this is something we cannot forget.

DR. GEORGE SLEDGE: So would these be real guidelines or surrogate guidelines? (Laughter) I will thank all of our panelists for a wonderful discussion.