NCI 2007 PRE-OP THERAPY AND BREAST CANCER
27 SESSION 4_4, Q & A

DR. KATHY ALBAIN: Thank you very much, Dr. Swain, for an outstanding review. I'd like invite the first two speakers up, as well as like to introduce Dr. Tom Buchholz, Professor and Chair of the Department of Radiation Oncology at M.D. Anderson, to join us for radiation-related questions.

And if you could load our two summary slides -- Dr. Sparano and I had two slides, please.

Certainly, we've had an enormous amount of material presented to us today, and in this session -- a group of patients that present with very challenging disease that clearly require intensive, multi-disciplinary evaluation.

Dr. Sparano and I wanted to just put forward to the panel -- if they can see the slides -- what we've covered very quickly in these three talks. We talked a bit about targeted interventions. Do we evaluate targets other than HER2 and angiogenesis and, if yes, which targets? Are these biologically distinct diseases in the locally advanced setting, inflammatory versus not? And, if so, should there be different clinical trial designs? We're already starting to see that with the lapatinib types of trials that Dr. Swain reviewed. Is there an exploitable target in inflammatory breast cancer and/or other non-inflammatory breast/locally advanced?

Is there an optimal combination here that differs from our other preoperative therapy scenarios that we've alluded to today, in terms of sequence or duration? Should cytotoxic therapy be given to all preoperatively or sandwiched? We haven't talked much about that in this population.

And then, in terms of trial designs specifically, what are important questions? Response or target validation -- how to address them? Is there still room for phase 3 trials in this group, or would randomized phase 2 perhaps be better?

And should we focus our resources on cytotoxic agents and schedules still, versus integration of targeted agents?

And then, in terms of the local issues -- there are also many here. Breast conservation versus mastectomy was reviewed and who should have breast conservation in this subset. Who should not have reconstructive surgery. Is there a (Unint.) for breast conservation surgery in locally advanced breast cancer? And what is the role for radiation in preoperative prescriptions?

And, lastly, the management of the axilla, the role of the sentinel node -- pre- versus post-op [therapy?] sentinel node -- and impact of axillary surgery on radiation planning.

So, certainly we're not going to remain for the next hour to consider all these, panel, but we would like you to perhaps pick from among these. And I'd like to go down the row and see where, if you could put your resources into one trial design, perhaps in inflammatory and maybe non-inflammatory, where would you go? Do you think they should be combined into one trial or separate, and which particular types of designs would you prefer?

So we'll start with Dr. Byrd. Give Dr. Buchholz a chance to think.

DR. DAVID BYRD: That's a tall order to even tackle. I guess my plea would be the last question that I asked this room which was, we've had this same conversation now for a

decade with the surgical groups about pre- and post-. We tried to design a trial through ACOSOG. It was not a sexy trial. It didn't have major survival endpoints -- just to try to ferret out, how do you do it, pre- or post-?

And actually the man -- Dr. Abrams -- I think may be still out there. Because he was part of this discussion. Hi, you remember this discussion, don't you? The idea was that the credibility of ACOSOG really needed to show that it could do trials -- phase 3 trials -- and this didn't quite meet that. I would say we can bring it up again, and how you design it -- I don't think we'll have a phase 3 trial with this, but I think sequential, phase 2 trials could probably give us some answers about just being able to speak the same language and all talk about, for example, the staging of the axilla, in a common language. So, I guess that would be my biggest plea for a trial.

DR. KATHY ALBAIN: Okay. Dr. Chia? Where would you put your money for a trial in this group of patients?

DR. STEPHEN CHIA: Let me first -- Clifford [Hudis] has actually corrected me. He was right in that, in the EORTC and NCIC [CTG], it was more of a dose-intensified, not a dose-dose regimen, so you are correct there.

I mean, I think the time has come to look at the biological aspects and, based at least on gene expression profiling, we need to look more at basals, HER2, and that was really shown in the M.D. Anderson trial, where the addition of a biological that was actually synergistic with chemo tremendously augmented the pCR rate.

Having said that, though, some of the biological targets may not augment chemotherapy, and pCR may not be the appropriate surrogate, or "surrogate surrogate" endpoint there,

and we may need to look at other endpoints if we're looking at changes in vascularity or -- and so, within the basals there's a few genes that's really come out, but again, how the biology of those genes in relation to benefit of chemo I think we'd have to understand well before we try to design trials with endpoints that may not have any clinical… as much clinical relevance.

In regards to randomized phase 2 trials, I mean, I'm not a statistician, but I think they can be useful in terms of throwing out an arm that is unlikely to be beneficial. They shouldn't be used to confirm or be the standard of care, but if we have… now that we have so many agents with so many targets, I think they can be useful to narrow down what the arms should be done in a randomized, phase 3 trial.

DR. KATHY ALBAIN: Dr. Swain?

DR. SANDRA SWAIN: Well, I totally agree with the issue of looking at the biology. I think, in inflammatory breast cancer, it's pretty easy where to put your resources, and I would do some kind of studies like they've -- like [Lisa] Carey's group and other groups are doing -- looking -- and Jenny Chang -- actually trying to identify targets, and it's been done nicely now looking at EGFR and different things in the triple negatives. But this group clearly has a terrible prognosis; so I think that that… I would put lots of money there, potentially looking for different mutations and things like that. As far as any other aspect of it, I think it's interesting, but I think until we figure out how we're going to cure these patients. Right now, so few of them actually make it, that the other issues to me are not as important.

DR. KATHY ALBAIN: Dr. Buchholz, in terms of the role of radiation, classically, it's been last of all the modalities for this group of patients. Not to take from your talk tomorrow morning, but do you want to give us your opinion here?

DR. THOMAS BUCHHOLZ: Sure. I think radiation clearly plays an important role in locally advanced breast cancer, and I think, as a component of multi-disciplinary care, radiation has clearly been shown, in favorable patients -- those with good response to neoadjuvant chemotherapy -- to contribute to the overall curability of the patients.

When you ask what's my most pressing issue in terms of the future and where can we improve, I think it gets back to Dr. Burstein's comment about identifying cohorts of patients in whom all standard therapies achieve some optimum results.

And I think Harold [Burstein] pointed out nicely that patients who have locally advanced disease and fail to respond to anthracycline-taxane chemotherapy, despite mastectomy and despite post-mastectomy radiation, continue to have pressing problems with respect to two endpoints -- the failure distantly and also, as Harold pointed out, the failure in the local-regional. But, despite post-mastectomy radiation, we've shown in our own experience, some patients with Stage III disease who have significant residual burden following mastectomy treatments still have high local-regional recurrence.

I think this poses an opportunity to perhaps look at a novel way of addressing their poor outcome by addressing an enhancement of the local-regional therapy. And one strategy to do this would be to incorporate radiosensitizing agents into the treatment at the time of post-mastectomy radiation. So, working with ACOSOG and RTOG, we actually have designed a phase 3 trial that looks at people with a large residual tumor burden following neoadjuvant chemotherapy, who our own institutional data predicts would be at high risk

for both local-regional recurrence and distant failure, and, hoping to capitalize on a strategy that reduces locoregional recurrence through a radiosensitive approach, and thereby address their overall survival outcome through an enhancement of local-regional treatment.

The way we're proposing to do it would be to combine radiation with capecitabine and bevacizumab as a strategy that's been used in pancreatic cancer as a method for radiosensitizing, and also, obviously, giving an additional systemic treatment at the time.

So, that would be my trial, that I hope would get approved through CTEP; now that's actually been approved through ACOSOG.

DR. DANIEL HAYES: Is that in patients with breast preservation?

DR. THOMAS BUCHHOLZ: No -- no, this is as an enhancement for post-mastectomy radiation for people who have really advanced, locally advanced, disease that's refractory to anthracyclines and taxanes.

DR. DANIEL HAYES: (Dr. Hayes asks a question from his seat.)

DR. KATHY ALBAIN: Dr. Hayes, could you go the microphone, please? Please?

DR. DANIEL HAYES: Do you see that as a strategy to increase breast preservation perhaps in patients that we now say should have a mastectomy?

DR. THOMAS BUCHHOLZ: Well, that's a different strategy. I think for those with…

DR. KATHY ALBAIN: Would you repeat the question, please?

DR. THOMAS BUCHHOLZ: Dr. Hayes was wondering about the use of radiosensitizers to offer breast conservative treatment, or extend the realm of breast conservative treatment. I think we've come a long way at offering breast conservative treatment for locally advanced disease, but, I think, at least in our own institutional experience, I think this has been borne out in a number of European centers and also other Cooperative Groups: that patients who don't respond well to neoadujvant chemotherapy treatment probably aren't going to do well with breast conservation approach.

And I think, for people with advanced disease, you have to be very selective in whom you offer breast conservation therapy to. Now, the issue of whether you could make them do well by the addition of chemo-radiation strategies -- I think, when you have an option of doing mastectomy for people with somewhat refractory disease, that's still my bias, because I think we'll still be able to achieve a better probability of local-regional control. So, that strategy I'm not aware of anybody pursuing at this time, Dan.

DR. KATHY ALBAIN: Are their questions from the audience? Don't be shy. …the microphones.

FEMALE SPEAKER: Just to follow up on Dr. Esserman's question, Dr. Piccart's, and in reference to the discussion about the lack of efficacy of the dose-dense (dose-intensified?) in the locally advanced, Dr. Chia. Again, I wonder, you know, if we can subset these locally advanced -- because all of these tumors are so heterogeneous -- and if you have a tumor that's been growing a long time and comes in with a slow growth fraction, most likely we don't expect a response from dose-dense, whereas a tumor that grows very rapidly, though it's not an inflammatory -- has a high Ki67, we might expect

dose-dense to be more effective. So, it seems to me that one strategy -- again, the whole notion of the biologic subsets -- is that we really have to subtype these tumors so that we can use the therapies to pick off the ones, you know, the bird's nests on the ground as opposed to the ones high in the tree.

DR. LARRY NORTON: You know, if you call a kangaroo a horse, it doesn't make it a horse. I mean, "dose-dense" is a specific biological definition, okay? Just because you give therapy at higher doses, or you give them, you know -- it doesn't define "dose-dense". And I think that, you know, that trial was not a trial of dose density. And, as is defined, and as Cliff and I and many other people have written about, as the Germans have done in the AGO trial -- I mean, let's just use our terms right. I mean, I just think that, frankly, a lot of our problems today is that, you know, we're all using words differently to mean different things, sometimes even in the same sentence, you know, and I think that's one of the problems that's haunting us through a lot of this conversation today. It's not just even standardization of tests -- we don't have standardization of terms. And "dose-dense" is just one example.

FS: Dr. Shak.

DR. STEVE SHAK: Just first a historical footnote. In evaluating the pivotal phase 3 trial for Herceptin in metastatic breast cancer in 1997 -- again, the primary endpoints were time to progression and also secondary endpoints of survival -- but, we did also look at response rate, and it was notable there were relatively few complete clinical responses in the study; but, anecdotally, it was very easy to see that they occurred most often in patients with inflammatory breast cancer. And, again, that was notable in a small number of cases.

So, again, it may well be since that was a signal for certainly, you know, an effective combination, it could be that inflammatory breast cancer, in terms of neoadjuvant treatment, might indeed be a good setting for evaluating novel therapies in combination with chemotherapy.

And then the question is that -- given that we think the pathogenesis relates to cells being stuck in lymphatics -- how much focus has there been on those adhesion molecules that could be expressed on the surface of the cancer cells, or the effect of cancer cells on the lymphatic endothelium that could cause up-regulation of molecules, or that could lead to the symptoms that we observe?

DR. SANDRA SWAIN: No one has really looked at that in detail, clinically. I think I showed you the extent of the data in gene analysis and RT-PCR. So, they had found some (phonetic: potoplanin?) and different things like that have been increased, which is associated with lymphangiogenesis. So I mean, it's very scattered, sporadic data. But there are two xenograft models that would suggest that E-Cadherin… that show E-Cadherin's increased and do discuss some of the issues that you're talking about, but not really clinically in patients.

DR. DAVID MANKOFF: Hi. Dave Mankoff, from Seattle. I had a question for Dr. Swain, and this was referred to in Dr. Carey's talk earlier. You both mentioned that you saw changes in both your molecular markers and imaging studies on the bevacizumab trial, but then said that it didn't correlate with response. Do you have any preliminary data on whether that correlates with other outcomes -- disease-free survival, distant relapse?

DR. SANDRA SWAIN: No. The question was whether the, I guess the change in the activated VEGF receptor 2 or the MRI changes correlated with disease-free survival. We

didn't really look at it -- the study was so small, with only 21 patients, so I think the problem is that it's limited data, so you really do need to look in a bigger dataset.

DR. DAVID MANKOFF: It might be interesting to look at that. I think sometimes those type of markers, even in relatively small studies, as we've heard, may not correlate with our traditional pathologic measures of response, but in some of the studies that are coming out, including some of our data, they're actually pretty powerfully correlating with some of these other outcomes. It might be interesting to see if that shows up, even in a small dataset.

DEBORAH COLLYAR: Hi -- Deborah Collyar, patient advocate. And you have to excuse me. I'm going to ask a couple of questions just for clarification, and then I have an idea and I wanted to ask the panel what they think.

So, did I hear you correctly, panel-wise, that we haven't done many studies on radiation in locally advanced cancer? Breast cancer?

DR. BUCHHOLZ?: I think radiation's been around in the management of breast cancer for over five decades, so there've been a number of studies and, not surprisingly, as all cancer treatments evolve, the importance of radiation evolves with it. I think we've learned through time that radiation plays an important role in the management of breast cancer. It's clear now, from the data that Dr. Harris alluded to earlier, that, by using radiation, decreasing the rates of local-regional recurrence, we're having an overall impact on survival of breast cancer patients.

I think Dr. Whelan here in the audience did a meta-analysis where he looked strictly in those patients who also received chemotherapy, and I think a lot of us suspect that, as the

systemic treatments get better, the risk of a distant metastasis goes down, and the improvement achievable in local-regional control is likely to have an even greater impact on overall survival.

It is true, I think, that there has been a lack of randomized trials for people who came in with inoperable breast cancer, received preoperative chemotherapy, really the focus of this conference, and then were randomized to receive radiation or not receive radiation. Frankly, I don't think that study will ever be performed, because I think the role of radiation's been clearly established.

DEBORAH COLLYAR: Okay. There are some of us with locally advanced breast cancer that do survive -- it is an abysmal rate, unfortunately -- or a very small rate -- but it brings up lots of different questions. So, I apologize if this doesn't make a lot of sense, but one thing is, we've talked about biological markers in regards to chemotherapy. I'm wondering about biological markers that we're studying in relation to radiation therapy as well. Women are treated with more than one kind of modality, so we've got chemotherapy, we've got radiation, we've got surgery.

Is there a way for us to start putting some of the newer trial designs, like the phase 2, randomized phase 2's, rather than the phase 3's, together with analyzing biological changes or pathological CR in not only the chemotherapy drugs that we're using but radiation and what the long-term impact of that could be? And with that I'm thinking, you know, we get so myopic within one disease within breast cancer -- are there things that we could be learning from lymphoma and leukemia, for instance, with the way that they've gone to profiling their different cancers and how they're studying the different subtypes that both lessons, good and bad, that we need to be incorporating into our

discussion -- perhaps… maybe that's more tomorrow's discussion -- but I'm sorry, these are just things that are floating through my head.

DR. KATHY ALBIAN: Yes, and they're all outstanding thoughts. Would any in the panel like to comment?

DR. BUCHHOLZ?: Well, just with respect to the question concerning determining the molecular determinants of radiation resistance -- this is a, I think, something that most radiation oncologists continue to be interested in. Local-regional recurrence after radiation in breast cancer is a difficult endpoint, because it's a component also of surgical treatments, it's a component of the imaging modalities; but nonetheless, I think, over time, we're going to be learning things.

In our group, we've even shown that estrogen signaling is an important determinant of radiation resistance, both in the lab and in clinical samples. Just recently, from Taiwan, there's been a nice microarray platform identifying the first genetic signature for breast cancers that recur despite radiation. And I think Dr. Pusztai's work at M.D. Anderson, while focusing currently on the endpoint of distant metastasis, with the accumulation of more and more samples and with longer-term follow-up, where we start to see some local-regional recurrences, we'll be able to use the same dataset that's already been accumulated with this new endpoint.

And finally, NSABP, Terry [Mamounas] had a nice study looking at the Oncotype[DX] and its prediction. Not just on distant endpoints, but also on local-regional endpoints. So, I think some of the same tools that are already being done looking at the outcome for systemic failures can now be also looked at for local-regional failures, because I agree with your interest.

DEBORAH COLLYAR: And there are many people that are working on the new classification for breast cancer, as you know about -- looking at the basal, luminal, and all that. I think that was a beginning and many more… Lajos [Pusztai]'s group is looking at it… There was a *Science* and *Nature* paper in the last year looking at all the mutations in breast cancer… So, people are looking at it, but we are definitely not in the same place where the group is that's with the classification of lymphoma.

DR. KATHY ALBAIN: Dr. Winer, you may have the last question.

DR. ERIC WINER: I'll let Laura ask, and then I'll…

DR. KATHY ALBAIN: Oh, I didn't know there was a mike there. Laura.

DR. LAURA ESSERMAN: Sorry. Yes, I'm up here [in the balcony], sorry. I just wanted to point out that it's really important for us to try and correlate -- try and bring together the imaging and the molecular features, because I think there's a lot to be learned from that. And I wanted to ask Sandy, in particular, in their study -- we've noticed in inflammatory cancer that, in fact you don't, on MR imaging, you don't see a mass, and you see this sort of diffuse infiltrate going in. There again, which sort of begs the question, if you can't clear that, there may not be -- and it's all through the skin lymphatics -- surgical treatment may not have a role until you get that under control. But have you seen that, and did you indeed have trouble getting adequate tissue for your biopsies from, at least preoperatively? Did you see sort of very diffuse as opposed to solid masses?

DR. SANDRA SWAIN: Well, we did see that, definitely, on some of the MRI's. They were not definite masses, but we still could, with the contrast-enhanced MRI -- the dynamic MRI -

- we still could see changes and decreased permeability and flow. So, we did see that in almost every patient.

And as far as the biopsies -- not all the biopsies were wonderful. Some of them just had a few cells, and I think that's one of the problems with doing the microarray in some of the other studies that are in the literature and what we've been trying to do, so it is very limiting, because of the small numbers of cells.

DR. LAURA ESSERMAN: Did you do MR-directed biopsies trying to go to the areas of greatest enhancement?

DR. SANDRA SWAIN: Usually, our mammographer was able to do it by ultrasound, was able to find it, so she didn't do MR-directed most of the time.

DR. ERIC WINER: So, I just want to put in a plug for studies that focus on local-regional questions, since I do believe that we're doing better than we have done in the past, and I think we're likely to do even better from a systemic therapy standpoint. And even though locally advanced breast cancer isn't so very common in Washington, in New York, and Boston, in other parts of the U.S. it still is, and in other parts of the world, it's very, very common.

And I wonder, as we think about this, whether we shouldn't think about a strategy where we in fact allow women to have different treatments based on biologic subtypes, since we do have to respect biology and not just pay attention to anatomy, and then ask cross-cutting local-regional questions, or questions about local-regional therapy that go across all of those subtypes. I don't know if Tom [Buchholz] or others have any final thoughts about that.

DR. THOMAS BUCHHOLZ: Well, thank you for your endorsement. Both David and I appreciate that, and I agree with you that I think the issue of local-regional management of breast cancer is an equally important component to the curative management of breast cancer and, unfortunately, we haven't perhaps in the United States done as well as we could have at addressing some of these trials.

Lori Pierce started a beautiful trial looking at this important issue, that today we're still struggling with, of whether to use post-mastectomy radiation in Stage II breast cancer. That remains very relevant. That wasn't completely embraced by the United States' community, which is a great disservice; and I think perhaps now is the time to re-address local-regional issues in clinical trials. I couldn't agree with you more.

DR. KATHY ALBAIN: Well, thank you all very much, panel. And thank you all for staying.