

NCI 2007 PRE-OP THERAPY IN BREAST CANCER
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DR. ERIC WINER: We have tried last night, and again this morning, to put together a reasonable summary. And much of this is based on all that has been said here. We've done a little bit of editorializing. And none of this is final, and we would appreciate any feedback afterwards. And we're just going to take it a few slides at a time, and I'll let Julie start.

DR. JULIE GRALOW: And we do apologize that these aren't the most beautiful slides either of us have ever made, given that it got a little late. And, as Eric says, they are a work in progress. So, give your input.

First of all, you know, we were really pleased as we were listening to the panel discussion, that a lot of the things that we pulled out of the conference were questions and addressed. And we weren't that far off on most of them.

So, first of all, we would state that we should speak the same language. And this gets at the issue of, we have called preoperative therapy a whole bunch of different things during this meeting and outside of this meeting. We've called it "neoadjuvant" therapy, "preoperative" therapy, "preoperative systemic" therapy, and then abbreviated it PST, POT, whatever. I think, Dan, you like the "neoadjuvant systemic" therapy or NACT or NAST. Anyway...

DR. DANIEL HAYES: Can I address this a minute?

DR. JULIE GRALOW: Yes.

DR. DANIEL HAYES: Gordon Schwartz had a think-tank that many of us were part of that went through the same routine. And it was sort of by consensus that we chose NAST, NACT, and NAHT, for hormone therapy. And in the publication, that's what we

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suggested be used. So, personally, I think unless people have strong feelings to the contrary, I would vote that we continue to follow that think-tank's publication. It was published in *Cancer* about two years ago or three years ago.

DR. JULIE GRALOW: So, given that we entitled this conference, "PREOPERATIVE Therapy in Invasive Breast Cancer", (Laughter) we can have some further discussion about that topic.

Goals for breast cancer therapy – this was brought up in the first couple of talks in the overview. The goals, pretty much listed in order of importance probably, are no deaths from breast cancer, no recurrences of the cancer, no evidence of having had breast cancer or breast cancer treatment over the long-term, and, then, no acute toxicity of the therapy.

So, what we know, as brought up in our overview, in locally advanced and inflammatory breast cancer, preoperative chemotherapy is the standard of care.

In earlier-stage breast cancer, preoperative chemotherapy is neither better nor worse from the standpoint of overall survival, compared to postoperative chemotherapy. And we look forward to an update of the NSABP-B-18 trial to further address this.

Which operable patients are candidates for preoperative therapy? Well, anyone who will require the therapy in question with certainty. I think that was Dr. Gianni maybe, or Dr. Wood. And if the therapy is in question -- if you do not have enough evidence that you would give chemotherapy, for example -- then surgery first is optimal. And on an appropriate clinical trial, any patient with operable breast cancer could be considered a candidate for preoperative therapy.

DR. ERIC WINER: So, what are the advantages of preoperative therapy? First, of course, there's the increased ability to perform breast-conserving therapy. Although, in fairness,

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if one looks at the randomized trials, the number of patients who are able to undergo breast-conserving therapy who weren't prior to entering that trial is perhaps a somewhat smaller number than we might all appreciate at times. It has been raised as a possibility that there may be improved cosmesis as well, even in patients who previously could have undergone breast conservation. I think that's something we need more information about.

There is the ability to observe an in vivo response, although, in truth, the clinical implications of that are at this time uncertain, with perhaps the exception of the fact that tumors that are overtly resistant to systemic therapy -- and by that I think we mean progression during systemic therapy -- in those patients, that therapy can be abandoned.

And, of course, in clinical trials, there is the opportunity to assess surrogate endpoints, which is a major advantage from a translational research perspective.

What are disadvantages of preop therapy? Well, some would argue that there's a loss of complete pathologic staging.

Perhaps more importantly -- and this isn't necessarily a disadvantage -- but a real consideration is that, when one is using preoperative systemic therapy, it becomes absolutely critical that there be a multi-disciplinary team and a multi-disciplinary approach. And we can all report on results from MD Anderson and Dana-Farber and other major cancer institutes. And the truth is, we're all used to practicing that way. And pulling that off in other settings can at times be more difficult, and it really is critical.

And I think that the point has been raised that it's important for the surgeon and the radiation oncologist and the medical oncologist to be involved upfront. And the team is larger than that. It includes the breast imager and the pathologist as well.

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Appropriate standards for local therapy are less well established in the preop therapy setting than in the standard sequence. And we're going to come back to that issue.

And there is at least some suggestion in some of the trials that there is a possible increase in local recurrence.

And, in terms of evaluation prior to preop systemic therapy, pathologic assessment is of course critical, which requires a core. I think we would all agree that an FNA is not acceptable -- that core needs to be able to provide enough tissue so that there can be an ability to look at grade, ER, PR, HER2. And, ideally, these cores... there should be several cores obtained, and preferably under image guidance.

And in terms of other assessments... imaging we discussed at some length yesterday. Mammography, ultrasound is appropriate. MRI may add information, but at least to some extent remains controversial as a standard procedure in all patients. And I think that's particularly true when we're talking about patients who otherwise have operable breast cancer, where in fact the standard of care in the U.S. at the moment is not to perform an MRI in all patients who have operable breast cancer.

A clip placement is critical in virtually all cases, perhaps with some very, very rare exceptions. There are some issues related to clip placement -- the timing, exactly how that clip is to be done, whether it should be in the center of the tumor versus bracketing the tumor.

And staging for distant disease, of course, should be done as it would in any patient who would otherwise be treated in the standard fashion. In patients with locally advanced breast cancer, of course, full systemic staging is necessary. Patients with operable breast cancer -- there are no firm rules and it should be based on the risk of distant disease.

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DR. JULIE GRALOW: So, evaluation of the axilla might've been one of our hottest topics, judging from the question and answer session. So we had a discussion about ultrasound of the axilla with an FNA of suspicious nodes. And, in the hands of experienced operators, this has high specificity and reasonable sensitivity.

We would argue that if the node is positive, there is additional information obtained that could determine whether the patient was even a chemotherapy candidate -- also tell us about prognosis and staging. And there would be low risk and no disadvantage. If you only do an FNA of the lymph node, you leave it behind. So, those of you who feel that the down-staging information is important still have that information available.

So, when to perform a sentinel lymph node biopsy? Well, if you've already, with ultrasound and FNA, documented a positive node, you don't need to do the sentinel node biopsy. Certainly, a sentinel node biopsy wouldn't be indicated in locally advanced breast cancer with palpable adenopathy, or in an inflammatory setting.

And, as we heard at this conference, there's substantial controversy regarding the timing of the sentinel node biopsy. Advantages of doing it after all systemic therapy are that you can achieve a single surgical procedure -- although, I would argue that if that sentinel node is positive and you don't find it out through a frozen in the OR, you end up with the second procedure in a subset. And that might not be a very big subset if your patients are low risk, but it could be high if they are higher risk for node involvement.

The post-treatment sentinel node takes advantage of down-staging and the ability to perform a lesser procedure. You don't need to go on to the full dissection in as many patients if you've completely cleared all the nodes. And then, nodal status after preop therapy may be more prognostic than nodal status pre-

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Now, the advantage of a pre-therapy sentinel node biopsy is that it allows for decision-making about radiation fields and systemic therapy use based on the initial stage. And post-therapy sentinel node is not as well validated, and there are questions -- although we saw some updated data on the false-negative rate and the identification rate, and if it is truly the same as if you did it before any systemic therapy at all.

Now we move on to the area of what kinds of systemic chemotherapy we should give. We had a question in the panel about taxanes. Our consensus, from reviewing the studies, is that the optimal chemotherapy regimen would be -- given in the preoperative setting -- would be one that is optimal in the postoperative setting. There's no inherent reason to believe that a regimen that works and is optimal postoperatively will not work and be optimal preoperatively. So, we believe an acceptable adjuvant regimen is an acceptable preoperative regimen.

DR. ERIC WINER: So, achieving a pathologic complete response is, of course, prognostic and does predict for a better outcome. But, of course, not all patients with a pathologic complete response remain free of recurrence. Identifying what's going on in those tumors and in those patients where in fact there is a pathCR but there is still a recurrence is an important priority.

PathCR is substantially more common, across multiple studies, in patients with ER-negative than in patients with ER-positive disease. I think, as we've heard, not all patients who do not achieve a pathCR do poorly. And that, of course, is particularly true in the setting of ER-positive breast cancer, where hormonal therapy is so critical.

PathCR as a single surrogate, or correlate, is not an adequate surrogate, or correlate, and we need to have better markers. It's our impression that pathCR after chemotherapy is probably most predictive at this point in time in the ER-negative, HER2-negative setting,

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where, in fact, achieving a pathCR is in fact probably quite predictive for benefit in the long-term in those patients who do not or... likely to be at high risk for further disease.

In terms of endocrine therapy, as we've heard, pathCR's are virtually never seen. Clinical responses are not uncommon, and, across several studies, breast conservation rates seem to increase with preoperative hormonal therapy. Ki67 decline with preoperative therapy -- preoperative endocrine therapy -- may be a predictor of long-term outcome. But I think we've heard that it's probably not ready for primetime use in the clinic. And the optimal duration of preoperative endocrine therapy is uncertain. Longer is probably better than shorter, but how long remains to be defined.

Outside of a trial, preoperative endocrine therapy seems to be a reasonable approach for a post-menopausal woman who is not thought to be a candidate, either because of her tumor biology or because of co-morbidity, for chemotherapy.

In terms of HER2-targeted therapy, I think Dan Hayes gave a simple answer on the panel, and I think we would endorse that -- which is that treatment with trastuzumab preoperatively appears to be appropriate. It increases pathCR rates in studies. And the data that we've seen in the preoperative studies is entirely consistent with what has been generated in both the adjuvant and the metastatic trials.

As we heard from Lisa Carey, angiogenesis is a potential target; it's under investigation. There have been small trials to date; there are many planned. There's been some caution raised about wound healing. And I think we've heard that pathCR may not be augmented even if it turns out that there's a better long-term outcome. And this may not just be an issue with anti-angiogenesis agents, but may be an issue with many of the newer biologic therapies.

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DR. JULIE GRALOW: And we ended that session with Judy Garber's discussion of the basal-like disease, which is predominantly the triple-negative, but not entirely ER, PR, and HER2 negative. We found that pathCR rates are relatively high in this group of patients after chemotherapy. But in this group, that actually tends to have quite a high pathCR rate, if you do not achieve a pathologic complete response, it predicts a particularly poor outcome. Small trials are completed in this setting and novel ideas are under investigation, such as the platinum agents and the EGFR inhibitors.

We talked about evaluating response to preoperative therapy. Once we've picked the regimen and we've gotten going, what do we do to monitor response? And we had a discussion of breast imaging to monitor response and heard that there is a moderate correlation between imaging and pathologic residual disease at the time of surgery. And MRI for the assessment of response is under investigation. It may be a promising "surrogate of a surrogate", or "correlate of a correlate".

Again, pathologic assessment to evaluate response to preop therapy -- we absolutely heard during this meeting that we need a uniform definition of "pathologic complete response". We heard that residual DCIS in the breast, just a noninvasive disease, has the same prognosis as a pathCR without any DCIS. We've also heard and seen data that suggest that any nodal disease, even less than 1 millimeter, after preoperative therapy is of concern.

Accurate assessment of the tumor bed and appropriate processing of the tissue are essential. This point has been made a couple of times, just made on the panel. But even if you are intending on a mastectomy, we've heard our pathologists tell us, in order to truly tell you that there is a pathCR, they need to do a very detailed analysis of the tumor bed. So, we need to mark that and tell them in some way where the tumor was, so they can look with finer cuts and more detail there.

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The pathologist needs to know that preop therapy was administered. And this doesn't always happen, and then you get these reports saying, "funny fibrosis, a few tumor cells", and all this -- we need to be a team here.

And then, as Dr. Byrd pointed out in speaking the same language -- in the AJCC Version 6, the little "y" before a T or an N stage indicates the stage AFTER preoperative therapy. And this is kind of new lingo.

So, the definitions of "pathologic complete response" that have been proposed at this meeting are:

--> "That there are no malignant cells at all left behind [in] the breast or the node."

--> Number two -- which, since it's yellow and underlined, gives you our bias and our vote -- "Invasive tumor is undetectable in the breast and the lymph nodes, but DCIS is allowed", given that we have data showing that doesn't... those outcomes seem the same in terms of disease-free and overall survival, as if there is no DCIS.

--> Another definition commonly used is, "No invasive disease left in the breast", but not accounting for the lymph nodes.

--> And then some studies use the definition of, "A total or near-total therapeutic effect in the primary tumor, and evidence of a therapeutic effect on the lymph nodes, with no metastases."

DR. ERIC WINER: So, we heard from Fraser [Symmans] in terms of the need to do finer assessments of what's going on in the breast. And, of course, perhaps at the most gross level, we need to know what's in situ disease and what's invasion.

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But even among those patients who clearly have invasive disease, we can probably do more than to say, “there’s disease versus no disease.” Miller-Payne is a scale that has been used to assess cellularity. Beyond that, there have been data that have been generated that stage after preoperative therapy using TNM staging is useful. And, finally, there is the system that’s been put together by Fraser at MD Anderson -- the Residual Cancer Burden.

I think all of these have the potential to make pathologic response a bit more robust to give us more information than we presently have with a yes/no measure.

In terms of endpoints in these trials -- of course, when we try to improve the care for women with breast cancer, the ultimate endpoints, apart from quality-of-life endpoints, are disease-free and overall survival.

Surrogates, or correlates, have a tremendous value -- and, particularly, if fewer patients are needed for trials and results are available sooner. And that is what we all want. We don’t want to continue to do trials with 8,000 women, with enormous expense, and with answers that take six and eight years to bring back to the clinic.

PathCR is the best available surrogate that we have in chemotherapy trials. Of course, it’s dependent on two factors: one, the sensitivity of the disease to the therapy in question, but also something that wasn’t brought up quite as much as one might’ve imagined here -- the volume of the initial disease. And, in fact, pathCR is very much affected by the volume of the initial disease.

Clinical response, we heard, is of some value, but clearly less robust.

Are there other surrogates that can be used in preoperative trials? The answer is, we certainly hope so, and these will include both biologic endpoints and imaging endpoints.

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And, to a large extent, this is a situation where one size almost certainly won't fit all, and it will depend very much on the tumor subtype and the treatment.

Can response to initial chemotherapy be used to guide subsequent therapy? And here we've divided this into two categories -- first, early clinical response. So, let's talk about after somewhere in the range of two to four cycles of chemotherapy. In this setting, trials have not consistently shown improvement in outcome with a mid-course switch based on response. We do know that early responders seem to have a better outcome. And the question is, in terms of non-responders, are those patients who ultimately should be switched and who would benefit from other therapies? And the failure to have seen benefit to date, may in fact relate to the fact that our therapies that we're switching patients to are simply inadequate.

In terms of residual disease at surgery -- and here I'm imagining an entire course of chemotherapy has been given, and we've taken the patient through that therapy and surgery is being done. At that point in time, a high burden of disease is a marker of a high risk of recurrence, particularly in the setting of ER-negative disease. Standard therapy, such as hormonal therapy and trastuzumab, when appropriate, should be administered.

No trial, however, has shown that additional chemotherapy after a full course of so-called "modern" chemotherapy improves outcome. But, at least in our view, this is a huge, untapped opportunity for trials. And particularly those patients who not only have residual disease, but do not have other effective therapies available to help reduce that risk, are individuals who potentially can be candidates for clinical trials looking at novel strategies.

DR. JULIE GRALOW: Moving on to the area of locally advanced breast cancer -- it was pointed out that, appropriately, due to the increased risk of distant disease in patients who

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present with locally advanced breast cancer, appropriate staging is critical. If axillary metastatic disease is identified, an axillary lymph node dissection is standard of care here. Mastectomy may not be mandatory in non-inflammatory T4 disease involving the skin. Dr. Byrd went through that in detail. Treatment of regional nodal disease with radiation is of greater consideration in this group, that is at higher risk of both distant and local-regional recurrence.

And, we'll stress again, use optimal and appropriate systemic therapy. This is certainly not a group in which we want to back off on our chemotherapy.

Inflammatory breast cancer -- Dr. Swain reviewed this in detail and defined the presentation and definition of this unique entity within breast cancer as having, frequently, an acute and rapid onset. It generally must involve one-third or more of the breast. A distinct mass is not often evident. Skin changes are present and pathognomonic, including the peau d'orange and erythema, and pathologic identification of dermal lymphatic involvement is not required for this diagnosis, but frequently seen. Distant metastases are present at diagnosis in a substantial minority -- I think Dr. Swain indicated it was between 25 and 33 percent had distant metastases at diagnosis. So, stage for distant disease.

A high proportion of inflammatory breast cancer patients are HER2-positive, however, and we will likely see a change in the course, so in the outcome, of this patient group with the new HER2-targeted therapies.

And the question that we asked Dr. Swain was, is inflammatory breast cancer a unique entity? And I think that her very resounding answer was, "maybe" -- that we do see markers that may pull it out from the rest of breast cancer, including, among other things, an increase in angiogenic and lymphangiogenic markers.

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So, locally advanced breast cancer and inflammatory breast cancer: With optimal systemic therapy, long-term freedom from distant disease is not uncommon, or an unreasonable goal. Systemic therapy has already improved and is likely to improve in the future. So, this all leads up to our conclusion, after listening to all the data, that local-regional therapy and control has greater importance as we do better at controlling the distant disease. And this is an area that we strongly need clinical trials.

DR. ERIC WINER: So, starting this morning, we focused on local-regional issues after preoperative therapy. After preoperative therapy, residual disease, as we heard, is a..... Residual disease after preoperative therapy....

The same residual disease after preoperative therapy, versus before, is associated with a higher risk of disease recurrence. So, 2 cm of cancer after preoperative therapy is more worrisome than 2 cm of cancer in a patient who has not previously been treated.

The MD Anderson data demonstrate that patients who are at higher risk of local-regional recurrence include those with Stage III disease at presentation, 4 or more lymph nodes, and those who are not candidates for endocrine therapy.

And Dr. Buchholz nicely outlined those patients who are potential candidates for radiation in the post-mastectomy setting, emphasizing that it's important to consider both the pre-therapy clinical stage and the post-therapy pathologic stage.

There have been relatively few trials done of radiation post-preop therapy and surgery. I think the sense is that there's no need to repeat trials to demonstrate a benefit there. What we really need are better predictors of who is and who is not at risk for local-regional recurrence after optimal preoperative therapy.

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In terms of some of the surgical issues, as we've heard, preoperative therapy does increase breast conservation rates. It is important not only for the medical oncologist to see that patient upfront, but for the surgeon to see the patient upfront, and, ideally, for the surgeon to see the patient during the course of treatment at least at some point in time.

The timing of surgery in the absence of progression should occur after a pre-determined course of therapy has been completed -- meaning that when you go into the treatment program, it should generally be clear in your mind, as the clinician, when that surgery is to be performed. That said, it is not entirely clear whether that should be after all of the chemotherapy, or if it can be sandwiched during the chemotherapy. And, notwithstanding the NSABP experience and point of view, there are certainly those who believe that it is reasonable -- particularly within the context of a clinical trial -- to administer a course of chemotherapy, perform surgery, and then give additional chemotherapy.

In terms of what to resect -- we've heard repeatedly that shrinkage of the tumor may not be concentric. Adequacy of margins in this setting I think is not fully determined. And this is where it becomes ever more critical for that multi-disciplinary team to be working well together. The pathologist and the surgeon and the radiation oncologist and the medical oncologist and the breast imager have to communicate at this point in time, because it often can be very, very complex. And there are still questions about long-term local recurrence risk in this situation.

And we heard about reconstruction. The plastic surgeon as well needs to be part of this team. And Dr. Miller expressed a view that there needs to be a better understanding of the kind of morbidity and the degree of morbidity that results from breast deformity and unhappiness with cosmetic outcome.

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Julie and I listed 10 unresolved clinical issues. I have no doubt that we left several off the list. In fact, we probably left 10 or 15 off the list. I will tell you that, in going through these, it struck both of us that many of them related to local therapy.

And I will just read through these 10:

One -- and these are not necessarily in order of importance. One -- The role of MRI in initial assessment and in monitoring response.

Two -- The need for axillary evaluation prior to therapy, and the timing of sentinel node biopsy.

Three -- Adequacy of margins following systemic therapy.

Four -- Radiation: who should get it, what fields.

Five -- The definition of pathologic complete response.

Six -- Optimal therapy for patients who develop disease progression during preoperative therapy.

Seven -- Can lack of response, either clinical or radiographic, be used to change therapy?

Eight -- The timing of surgery with regard to systemic therapy.

Nine -- Should we be giving preop therapy to improve rates of breast conservation in patients with ER-positive breast cancer, where we see less dramatic responses? And that question may be particularly appropriate for those patients who have invasive lobular cancer.

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And, finally -- Appropriate therapy for patients with significant residual risk after preoperative therapy.

DR. JULIE GRALOW: So, now we just have a few slides on the research issues that were brought up. The preoperative setting, as we've discussed throughout this conference, provides a unique opportunity to study the impact of systemic therapies on breast biology. This approach -- using these drugs in the preoperative setting -- has the potential to facilitate drug development and lead to more rapid improvements in the care of women with breast cancer.

We have the potential, if done properly, to get answers available in less time, and a greater potential to understand predictive markers to find what therapies will work in what subsets of breast cancer, which is absolutely where we're going. We know it's no longer one size fits all.

Although the excitement about preoperative therapy stems from the ability to conduct translational research and develop new systemic treatments, many of the unresolved clinical issues that we've just listed relate to local-regional disease. If we're to pursue an aggressive agenda in the preoperative arena, we need to address these unresolved local-regional questions if we're going to provide optimal care to women with breast cancer, both on trial and off trial.

We reviewed research considerations, including tissue collection on clinical trials. And we will stress again and again the need for uniform procedures in collecting tissue of whatever kind, and the value, if it can be done in a clinical trial, of also acquiring frozen tissue or tissue in RNAlater or whatever -- fixative that allows us to do these big microarrays and look for patterns and genes and proteins that can be prognostic and predictive.

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Within imaging and research, imaging -- MRI, PET, etc. -- is promising both in terms of prognosis and as predicting responses. Imaging may help guide local and systemic therapy. And we strongly urge for a standardization of tools, just as we're doing for the collection of tissue. We need to be doing MRI. We need to be doing PET. We need to be doing all of these imaging techniques, so that they can be compared across centers. And we do not have that going on right now.

Biomarkers of interest -- we heard talks about genomic profiling and microarray, some of which are more ready for primetime than others. Markers of proliferation and apoptosis may have a role not ready for primetime. Many others.

We'll stress again the need for standardization of the way in which we do markers, including HER2, which we've just seen in ASCO and CAP combined guideline for doing HER2 testing. We urge everyone to read that and follow it.

And we now have a resolution that for estrogen receptor, we will have the same sort of guideline in the near future, because as long as we've been staining for estrogen receptor and evaluating estrogen receptor, we are still doing it in a variety of ways, and we know that we are not necessarily doing it reliably and with the best techniques right now.

Novel trial design was discussed. These window-of-opportunity studies which -- Marylou, you're right -- those are really designed for research purposes, where you give a few weeks of an interesting agent not intended for primary therapeutic intent, but where we're looking to see if we can get some hints about the biology that will better let us use the drug in the future.

And then Don Berry outlined some adaptive designs that could help us get through trials, move on to phase 3 sooner with less patients. And so we're hoping that we can use

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preoperative therapy in a more nimble way and have a better clinical trials process. And then, of course, we have other issues, besides just the adaptive designs, of statistical considerations.

DR. ERIC WINER: All right, so I guess I'll do the last couple of... few slides. I think there are four left.

So, advocacy: this is an area, as in all areas of breast cancer research, where there is a balance that needs to be struck between care and research. In considering these studies, we have to think about participant burden. It's easy to think about adding on imaging study after imaging study, but we are asking people to participate in these studies who often have busy lives as well. We have to be realistic about what can be accomplished within clinical trials at major centers versus community hospitals.

And, again, as is always the case, women with breast cancer are our full partners here. As Cokie Roberts said, they're not patient; and, as I would add, we're not patient, either.

In terms of conclusions -- in our view, there should be a continued emphasis on the preoperative setting for clinical trials. There is tremendous promise here.

That said, there are not surrogate endpoints, at this point in time, that can be used in the preoperative setting that are sufficient to change clinical practice. So, a preoperative trial, in and of itself, cannot lead to a widespread change in standard practice.

Outside of a clinical trial, preoperative therapy is standard of care for women with locally advanced breast cancer or those who are not deemed to be candidates for breast-conserving therapy and who want it.

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Caution is still needed when considering preoperative therapy in other settings. And -- perhaps the single greatest caution -- is that, if you're going to do it, there needs to be that multi-disciplinary team in place.

And the preoperative setting is not a license to, as I would put it, practice "creative oncology". Evidence-based treatment guidelines need to be established. We were talking about this and felt that a local therapy panel should be convened to discuss unresolved local therapy questions, with a goal of developing feasible clinical trials. We need to move beyond underpowered, single-institution phase 2 trials.

We will need larger datasets, particularly for many of the correlative studies that were suggested this morning. Lajos Pusztai talked about the risk of false discovery with microarrays, and this is true with other investigation as well when we have very, very small sample sizes.

And trials of systemic therapy, generally speaking, should be done with respect for the known biologic subtypes that already exist.

And, finally, funding issues -- a major priority for all of us researchers, women with breast cancer, everyone. We need partnerships between academia and the government and foundations and pharma. And this research is expensive, but we have to figure out how to fund it. Thank you all very much.

DR. JO ANNE ZUJEWSKI: I just wanted to really say again to Julie and Eric... Their particularly impressive slide set to summarize some really tough issues, and so I wanted to give them a particular hand, for organizing this.