

NCI 2007 PRE-OP THERAPY IN BREAST CANCER
20 SESSION 3 TALK 3 - WOLFF

DR. EDITH PEREZ: Thank you, Fraser. To follow up on this session after hearing about the considerations for breast imaging, then pathologic assessment, we invite Antonio Wolff, Associate Professor of Oncology at Johns Hopkins. And Antonio will discuss appropriate endpoints in clinical trials, a [as] marker[s] for long-term clinical outcome. Antonio.

DR. ANTONIO WOLFF: Thank you very much. I'm grateful for being here today for these discussions. We are now halfway through our meeting. And a lot of data have already been presented, and will be presented also in the next few hours and tomorrow morning. And at this point, the organizers asked both Dr. Symmans and I to provide you with some general concepts in terms of what should we use to assess a lot of the data that are being generated on the use of preoperative systemic therapy. And hence the title of my presentation on "Appropriate Endpoints in Clinical Trials and Markers for Long-Term Clinical Outcome".

It also provides me with an opportunity to discuss a lot of concepts and not necessarily show a lot of data, as is being done by others. But at the same time, it creates the potential challenge which is the alternative title of my presentation, "How to Upset Statisticians and Methodologists in Less Than Twenty Minutes".

So the goals of PST [preoperative systemic therapy] in operable breast cancer would be to improve the odds of breast conservation, and we can do that to a degree; to allow the early assessment of treatment effect. The questions become, then, what does it mean in the long run? What are the optimal markers for various phenotypes? And what is the true outcome of interest? And to allow therapy adjustments to improve outcome. And we're not there yet with the questions of when to do it, how to do it, and change to what.

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In essence, we're asking ourselves, what is the clinical utility of preoperative systemic therapy? PST may allow trials that target various breast cancer subtypes and that rely on robust -- and I was hoping I was going to be the first individual to use the word "robust", but Dr. Wolmark beat me to it -- that rely on robust surrogate markers for the outcome of interest. And the idea that we want to become nimbler, smaller, faster, and develop more informative trials and use resources more efficiently. And that's, ultimately, what brought us here today.

But, the more I hear this morning and this afternoon, I think it's becoming clear as well that a great mission we can have in our meeting today is to provide the public at large -- physicians at large -- with a good framework of how to truly incorporate these in clinical practice. As Cliff Hudis mentioned earlier today, we run the risk of doing more harm than good if we don't provide good recommendations.

What is a surrogate outcome? It would be an outcome that would be in the causal pathway of the true outcome. It would replace a distal endpoint, such as survival, by a proxy endpoint. And you can choose whichever you want. And we would use a surrogate marker which would be essentially a measure of the surrogate outcome. And you can begin to imagine the complexity of these issues.

So, if we want reliable, robust measures, we need basic assumptions, such as a method or assay that is used to measure a surrogate marker that has been standardized. And that includes pre-analytical variables from the moment that a sample is collected from a patient to the moment that the assay is going to be performed. We want a method or assay that is reproducible whenever, wherever used. This has been addressed, to some extent, by assays done at a central site -- if you call it the "black box approach", such as gene expression profiles.

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But also, the issue becomes very critical for local assessment. And Fraser just gave an elegant discussion of the complexities of pathology assessment. But even more basic stuff -- ER, PR, and HER2 -- and earlier this morning, Baljit mentioned the effort that CAP and ASCO have had on the assessment of HER2. And I'm pleased to share with you that actually we are in planning stages for a similar effort for ER and PR.

The defining characteristic of a surrogate marker would be that a marker must predict clinical outcome, in addition to predicting the effect of treatment on clinical outcome. You must also, from an operational definition, establish an association between marker and the clinical outcome and also establish an association between the marker, the treatment, and the clinical outcome in which the marker mediates the relationship between the clinical outcome and the treatment.

So it's fair to say that not necessarily every marker will serve as a useful surrogate marker. And where we have potentially relationships that are indirect between treatment and clinical outcome in treatment and the marker, but not necessarily a relationship between the marker and response. And this would be a very simple and I would say a silly example to use.

So if we have various markers obtained during or after treatment to use as surrogate markers for preoperative systemic therapy, these would include response, molecular markers, imaging, ultrasound, path, MRI -- markers that would mediate and allow us to assess the response to various treatments of choice; and, ultimately, we would assess our outcome. I would say, as a medical oncologist, what I'm interested in the most is survival. But I can tell you that local control becomes of interest as well, for many reasons.

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Molecular and imaging markers are being discussed by other speakers. So therefore, I'm focusing on pathologic assessment, as discussed by Fraser, as well as survival. Is pCR a surrogate for survival? I think it is fair to say that it can be and in many cases it is. And here are the Kaplan-Meier survival curves from [NSABP]B-27, showing improvement in disease-free survival and overall survival for patients who achieve a pCR versus not.

We know from the publication of B-27 that doubling of pCR with addition of docetaxel did not result in improved survival. There are various rationales to explain why that was very acceptable. But we must understand, though, the improved survival is not limited to a pCR subset, in that path response is a continuous variable and not an all-or-none binomial event.

The role of pathology response as a surrogate for survival can actually be refined by the use of standardized pathology measures after PST, such as the Residual Cancer Burden, introduced to us by Fraser moments ago, as well as the use of AJCC TNM staging after PST, as published by Lisa Carey and colleagues.

So, how to determine if a marker is useful as a surrogate? And do we need to understand the potential indirect effects, in that the marker may not be in the direct line between treatment and clinical outcome? And this is going to be increasingly affected by the frequency that that marker is observed, as well as the predictive ability or predictive utility of that marker in predicting outcome.

Is pCR a useful surrogate in invasive lobular cancer after chemotherapy? And I think what we have learned from data from M.D. Anderson is that only a small number of patients were expected to achieve pCR after chemotherapy. But, at the same time, this does not seem to affect their much-improved five-year survival compared with patients with invasive ductal carcinoma. So, it would appear that absence of pCR is okay. We

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don't actually know if the patient, the small numbers of patients, that achieve pCR, whether they do better in the long run.

Is pCR a useful surrogate in ER-positive disease after chemotherapy? And, again, additional information from M.D. Anderson showing that patients with ER-positive versus ER-negative disease are less likely to have a pCR, but in fact are more likely to have a better overall survival at five years.

So the question becomes, is the absence of pCR in this population of ER-positive disease truly okay? And is the presence of pCR -- would that help more? And the answer would be "no" to the first question, and "yes" to the second question on the basis of the same dataset, a retrospective assessment showing that, even though you have a substantial improvement in progression-free survival and overall survival with the achievement of pCR in the ER-negative population, in fact, we're also seeing a similar effect in the ER-positive population that achieves pCR versus not.

So, back to the use of surrogate markers after initiation of treatment. Are there lessons from the adjuvant setting? And the answer is, of course there are. I think we know very well we are becoming smarter in understanding that breast cancer is a mosaic, not just one disease. And we are using increasingly predictive markers at baseline, some more characterized and more validated; but essentially various tools are now becoming available, clinically and from a research standpoint, using gene expression, ER, PR, HER2, pharmacogenetics and various nomograms, as shown to us, in which we can assess the... predict the effects of treatment and, hopefully, long-term clinical outcome.

Selection of patient population for various treatment options is key. And, as was addressed in the previous discussion and in the question by Dr. Piccart, the importance of

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truly selecting an optimal patient population and enrich your clinical trials to avoid noise. There are lessons from the past.

The issue, then, becomes, if we have a marker for therapy selection, we are now also interested in having, after initiation of treatment, a surrogate marker, which may be the same or may be a separate marker, that can help us predict clinical outcome. But, again, the same questions will apply -- Do we have a direct relationship? Or do we have an indirect relationship in trying to understand the complexities involved?

The timing of the observation clearly does matter. And, as has been shown already, for patients with ER-positive disease, are we potentially looking too soon for evidence of pathologic response after initiation of endocrine therapy? But the question even becomes, are these two separate mechanisms? In that, the effect on the macro tumor -- in the primary tumor -- is very different than what you would expect in the micrometastasis systemically.

If we look into HER2-positive tumors and the effect of trastuzumab, in fact, you have a significant high rate of pathologic complete response which appears to be early. And the question becomes, will it correlate to survival? And I think it is fair to speculate that it may. And, potentially, in this specific setting, pCR is exactly smack in the line that goes from treatment to survival and could be a very useful early surrogate.

Obviously, what we want here, if we're trying to devise small studies, would be studies where we have a very reliable and robust surrogate outcome. And the question, what if the surrogate outcome truly correlates with the true outcome? -- In this case, the surrogate itself then becomes the endpoint. In this case, we would use pCR instead of survival. But, now, the search begins for a surrogate for the surrogate. In that, we now need a surrogate marker to assess the endpoint that is the surrogate of the final outcome of

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interest, which should be survival. And again, the complexities of the relationships must not be forgotten between surrogate markers, treatment, and the outcome of interest.

So, this is a marker utility trial design in which you would have a marker at baseline, you would start your treatment. You would repeat your marker at midpoint, and then you would have a good result or a bad result and make a treatment decision, and then assess outcome. This assumes, of course, that you have a good, robust marker. This also assumes that you have a good second therapy to use afterwards.

For post-operative decision, Hal Burstein will discuss, after the break, issues of whether you can use a surgical assessment. And on the basis of having a good result or a bad result, however you define it, whether you're going to use the same treatment, a different treatment, or no more treatment.

For preoperative decisions, Gunter [von Minckwitz] will also discuss with us similar concepts -- whether there are potential markers at midpoint, whether they will be imaging markers, whether they will be Ki67, whether they will be clinical assessment, whether you can make decisions about continuing the same treatment, changing treatment, or actually stop treatment.

And I think it is fair to ask whether the prognostic utility of pCR is different if the pCR is achieved after Therapy X, after Therapy 2X, or after Therapy X followed by Therapy Y. Is pCR a pCR regardless of how you reach it? And I would... yes, at this point, it is potentially... it's the same.

So, take-home messages, as it has been discussed a lot: Surrogate markers are significantly affected by the population that you're using, tumor subtypes, by the intervention, by the therapy of interest, by the timing of assessment, which depends on

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the therapy and on the tumor subtype, and on the endpoint, with survival being the gold standard.

And I would stick my head out and say that predictive markers at baseline, at this point, are more critical than intermediate surrogate markers. But more is to be learned for sure.

And the question, is pCR a useful surrogate marker? And I would answer, “Unequivocally yes, but it depends.” And it depends on the population that you’re using, and the population that you’re targeting. And I think these are some of the biggest lessons that we can take from this meeting today.

I’m going to stop here. And I want to thank the organizers -- I think -- for inviting me to be here today. And I thank you for your attention.