**NCI 2007 PRE-OP THERAPY AND BREAST CANCER**
**21 SESSION 3, TALK 4, VON MINCKWITZ**

DR. GEORGE SLEDGE: It's a pleasure to welcome you back to this session on "Evaluating Response to Breast Cancer Preoperative Therapy". It's now my pleasure to introduce to you Dr. Gunter Von Minckwitz. Gunter is Associate Professor of Gynecology at the University of Frankfurt and is chair of the German Breast Group. He'll be speaking to us today on when to consider mid-course changes of therapy based on early response. Gunter.

DR. GUNTER VON MINCKWITZ: Thank you George. And thank you very much to Eric and Julie and Jo Anne for giving me the opportunity to talk about this interesting topic and this -- I also want to thank Anthony [Antonio] for introducing this second surrogate as another surrogate for pCR and maybe for other endpoints.

And this is how I want to structure my presentation here -- and I want to cover the topics on early response as a predictor for pathologic response, as a predictor for long-term outcome, as a decision aid to switch therapy at mid-course, and also to identify patients who might or might not benefit from a switch.

So if we have a look at, in the literature, it starts maybe early, but this is one of the first trials I've found where people from the Royal Marsden looked at response after two cycles of neoadjuvant chemotherapy and how far this predicts the pathologic complete response on here -- pathologic complete response in a variety of different chemotherapies. And they found that, beyond size and age, the response after the second cycle was highly significant, and it was, in the end, the best predictor in their multivariate analysis.

So in our German trials -- the GeparDo or GeparDuo and GeparTrio study -- we put a focus on this early response evaluation. At the time that the trials were designed, there

were no good predictors that could be detected at diagnosis of the disease. And whereas the interim assessment was quite easily possible, especially in Germany where the gynecologists are doing surgery and give the chemotherapies, the interaction that is necessary for providing neoadjuvant chemotherapy to the patients has an optimal infrastructure in my country. And so this response assessment after a couple of cycles was well taken up by the investigators.

In this overview here, it's a clinical response assessment by physical examination, and we had two trials where dose-dense Adriamycin-docetaxel scheduled for four cycles was used, and the early response was assessed after two cycles.

Then there is the GeparDuo sequential arm that was similar to the [NSABP-]B-27 arm, where response was assessed after four cycles of AC. And in the GeparTrio study, we used the TAC regimen, and the early response was assesses after two cycles of TAC.

And, altogether, if you see this, around two-thirds of the patients have an early response, and one-third does not. And this has a strong correlation with the… with regard to the pathologic complete remission rate. It is around four times higher in those patients who have responded compared to those who have not responded.

If you do a multi-variate analysis -- and we did this here, for example, in the GeparTrio study -- there are other factors that can predict pathCR, like young age or high grade, ductal -- histologic – type, or receptor negativity. But if you stick on, on those patients who have a very good early response or have already complete clinical remission after two cycles, these are the patients who had the highest odds ratio to get a pCR at the end.

And if these factors again were analyzed in those patients who had a response after two cycles, still this early response was independent significant predictor for pCR in the group of responding patients comparable to the other markers.

Just to give you a chart on this, and to compare it to the receptor negativity that was addressed multiple times already today [shows graph].

You see that the quantitative extent of the response after two cycles is significantly correlated with the pathologic complete remission. And those patients -- it's only a small group -- it's about 5 percent of all patients who had a complete remission. They had a pCR rate of 40 percent, and that was only reached by patients who had a triple-negative tumor in this subset of patients.

But also those patients who had a partial remission had a considerable pCR rate, whereas in those where there was no change or -- and then there were a few patients with progressive disease -- early on during the first six weeks of treatment, the rate of pCR is very low in this cohort.

In our last trial, the GeparQuattro study, that has just finished recruitment in December last year with 1,500 patients, patients were again stratified according to early response. In this trial, it was EC four times -- EC schedule that was given to all patients, and then patients were randomized to docetaxel either alone, or simultaneously given with capecitabine, or in the sequential docetaxel-capecitabine regimen. All patients in this trial received trastuzumab if they were HER2-positive, and we have now a cohort of almost 500 patients in this trial that received all through the whole chemotherapy Herceptin, and we hope that we can present the data of this trial at the end of this year or maybe beginning or end of next year.

We are also sub-analyze this trial according to the early response, and maybe there we find some differences in how these arms have different efficacy according to this early response.

Let me come to the next topic, with regard to the long-term outcome. There is some data available from the B-27 trial. When you look in the manuscript, in the publication in the *JCO*, you can count that those patients who had a clinical complete remission after four cycles of AC, the event rate was about 25 percent; whereas those patients who had only no change after AC, they had -- half of the patients had an event during their follow-up that was reported in this trial. So, early response has also an impact on long-term outcome in these patients.

In one of our trials, the GeparDuo study, we also analyzed this, in maybe a little bit different way. And as you can see here, that those patients who had an early response after four cycles of AC, and they of course had a response also at surgery -- they had the best prognosis. Whereas, those patients who had not responded to the first four cycles of AC, it was irrespectively to their response to the docetaxel part of treatment what their outcome was. So what could be gained at the beginning or what could not be gained at the beginning, was not possible to regain after the addition of docetaxel.

And so, we believe that this early response might aid as a decision aid to switch therapy, and there are some trials already in the literature that tried to explore this. And probably the oldest trial doing that was a French phase 2 study where an old type of chemotherapy was given for three cycles, and the response was assessed by clinical examination. And what they found is that those patients who have responded, they had a better five-year overall survival compared to those who have not responded.

But you can see is that the differences in treatments that were given afterwards -- they were not too much different, especially in this cohort. They switched only one or two drugs whereas others were continued, but only in this group they used some other compounds that are, of course, not very common today for the treatment of breast cancer. But what they found was that those patients who have responded at the beginning, they had a favorable prognosis. Those who have not responded to the first and to the second treatment, they had the worst outcome.

And I'm not sure if the curve of those patients who have not responded at the beginning, and then responded to the second treatment -- if this is due to the small number of patients or maybe to the old-fashioned chemotherapy that was applicated, that this curve is in the same range as those patients who have responded. So these data do not correspond to the data we saw, and they do also not correspond very much to the data of the Aberdeen trial that was already addressed this morning.

Here, again, an evaluation was performed after four cycles of CVAP, and there was a randomization taken for those patients who have responded to either continue or to switch to docetaxel, and you have already seen that there was a difference in pCR rate, and this also corresponded then to a difference in progression-free survival.

What is to my opinion one of the important result in this trial is that, in those patients who had anthracycline pre-treatment and have not responded, the addition of docetaxel did not lead to an improvement further on.

So, this might be a population where it is very difficult to really find a good chemotherapy, and we tried that in a larger trial, in the GeparTrio study, where we used

this in vivo chemotherapy testing to go into -- towards two different directions to explore two different strategies.

So, for the non-responding patients with no change after two cycles of TAC, we add the continued TAC, or we switch to non-cross-resistant chemotherapy with vinorelbine and capecitabine, whereas in those patients where there was a clinical response, we thought these are the chemo-sensitive tumors, and they might benefit from further addition of two further cycles of TAC. So, it was, overall, a comparison of six versus eight cycles of TAC in this trial.

So, we have no long-term follow-up of this trial right now, but we have the pCR rates. And what you can see here, again, is that there was a strong difference in pCR according to the earlier response. But there was only maybe a trend that eight cycles of TAC in this chemo-sensitive group appears to be more active. And there was, more or less, no difference in response with TAC… the NX regimen [switching to vinorelbine-capecitabine] after this initiation treatment [shows graph].

So, can we identify patients who might benefit from a switch? And we tried to analyze the GeparTrio study according to this, and we tried to look at, are factors that can discriminate patients that might have benefit from one or the other arm?

And what comes out is that those patients with receptor-positive disease -- they benefit more from a more intense treatment. They benefited from the larger number of cycles, and they benefit from the more intense taxane-anthracycline-containing regimen. As well, those patients with a partial response -- with maybe partial resistance -- they also had more… higher benefit from a prolongation of chemotherapy.

And this fits very well to other observations that have been made. For example, the MD Anderson experience -- it was just recently published an overview of all their trials where a taxane was added to FAC. And you can see here that there is, of course, an improvement in pCR rate for the ER negatives, from 15 percent to 29 percent, but according to the hazard ratio, the improvement for the ER positives is much larger. It's more that four times the pCR rate that could be reached -- when taxane is added in this population.

And it also fits very well to the analysis that has been done for the B-27 study. It appears that only those patients with a partial remission -- they had a benefit from the addition of docetaxel in the pre-operative setting, whereas those patients who have already gained complete clinical response to AC -- they did not benefit from the docetaxel. And the same … the group of patients with no change as response to AC.

So, there might be a group of patients where a switch, or more intensified treatment, is beneficial, and there might be a group that can be detected according to early response that might be chemo-resistant to further treatment.

And as it was also already addressed in the discussion before the break, this group of non-responding patients -- of chemo-resistant patients -- is a population where you might have to look especially with new compounds, targeted compounds, compounds that might reverse resistance.

And this is what we are trying to do in our next trial, the GeparQuinto study. And this is one part of it, where patients who have not responded to initial treatment of EC with or without bevacizumab -- the non-responding patients -- they are going out of this part of

the trial, and they will be randomized to weekly paclitaxel with or without an mTOR inhibitor, Rad 001.

So, the whole design of the GeparQuinto study is to try to really get distinct populations and to ask various questions in these.

So, the HER2-positive patients -- they will receive chemotherapy with EC followed by docetaxel-capecitabine, and the randomization will be between trastuzumab and lapatinib as a head-to-head comparisons of the two compounds.

Whereas, those patients with HER2-negative setting -- they will be first randomized to EC versus EC plus bevacizumab, then the response is being assessed. If they have responded, the patient continue in this part of the trial, and they change to the taxane-capecitabine chemotherapy and continue bevacizumab, and they are randomized to this arm. Whereas, the non-responding patients are getting into the non-responding setting and get the randomization to [weekly paclitaxel] with or without Rad 001.

So, as a conclusion, I can summarize that early response appears to be an independent predictor of pCR. It's another surrogate of a surrogate, and it's also a good predictor of long-term outcome. And it can be also sub-quantified according to the extent of response that is observed at this early point. The benefit of late response is so far a bit unclear, as there are contradictory results.

And, as a hypothesis, it might be possible to state that patients with an early complete clinical response might not need further treatment intensification. Whereas, those patients in early clinical partial response, due to incomplete chemo resistance, maybe ER-positive patients, might benefit from more intense treatment. Whereas, patients with

early no change, or even progressive disease, that these are patients who are at high medical need for new treatment options. Thank you very much.