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Improving Outcomes in HER2+ Early Breast Cancer

Announcer:
Welcome to CME on ReachMD. This activity, Improving Outcomes in HER2+ Early Breast Cancer: Focus on the Adjuvant Setting, is provided in partnership with Prova Education and is supported by an educational grant from Genentech.

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Your presenter is Charles Geyer.

Although Trastuzumab and Pertuzumab have improved outcomes for patients with HER2 positive early breast cancer, some patients do not achieve a pathologic complete response and are in need of better approaches in the adjuvant setting since residual disease is associated with increased risk for disease recurrence and decreased survival. New approaches are showing improvements over the current standard of care and integrating these new data and medications into adjuvant treatment paradigms for patients with HER2 positive early breast cancer is therefore of high priority.

This is CME on Reach MD and I am Dr. Charles Geyer, Professor of Medicine and Associate Director for Clinical Research at Virginia Commonwealth University Massey Cancer Center in Richmond, Virginia.

Today we will begin our discussion by looking at the goals of neoadjuvant therapy and HER2 positive early breast cancer, as well as the standard of care for these patients. Patients presenting with T2 to T4 or node positive, HER2 positive early breast cancer should receive dual HER2 targeted therapy with Trastuzumab and Pertuzumab in combination with chemotherapy as neoadjuvant therapy with the goals of greatly reducing the tumor burden prior to surgery and assessing for pathologic complete response at the time of surgery. With combination neoadjuvant therapy, 45 to 70 percent of patients with HER2 positive early breast cancer will have a pathologic complete response documented at surgery. These patients enjoy a favorable prognosis with a low risk of recurrence and should continue HER2 targeted therapy as adjuvant therapy to complete one total year of HER2 directed therapy. However, the significant number of patients without a pathologic complete response following neoadjuvant therapy with these active combination regimens who have residual invasive disease documented at surgery, have a substantially less favorable prognosis with increased risk for recurrence and death. Previously these patients would also receive Trastuzumab as adjuvant therapy to complete one year of HER2 directed therapy and would initiate endocrine therapy as well if their disease was also hormone receptor positive. However, these patients clearly had an unmet medical need for alternative therapies, which could more effectively reduce their identified increased risk for recurrence and death. We now have identified a more effective alternative adjuvant therapy for this important subset of patients readily identified as high risk by the persistence of invasive breast cancer following neoadjuvant combination therapy. Recent results from the KATHERINE trial have demonstrated adjuvant administration of the HER2 directed immunoconjugate TDM1, which was approved in February of 2013 for second line therapy of HER2 positive metastatic breast cancer, substantially improves outcomes in patients treated with neoadjuvant combination therapy for HER2 positive early breast cancer who are found with residual disease at surgery.

Let's review the design and the results of the practice changing KATHERINE trial. First of all, TDM1 is an immunoconjugate linking two to four molecules of the chemotherapeutic agent in Emtansine to Trastuzumab. The Trastuzumab component binds to HER2

overexpressing cells and is internalized along with the Emtansine, which is then released and induces cytotoxicity by inhibition of microtubule polymerization.

In looking at the KATERHINE study design, a major concern we of course had, was defining a broad eligibility criteria that would allow accrual of this relatively smaller subset of HER2 positive breast cancer. Patients could enter KATERHINE who had presented with clinical stage T1 to T4 disease, N0 to N3 disease at presentation and had received a standard neoadjuvant chemotherapy regimen that had to consist of at least six cycles of chemotherapy containing a minimum of nine weeks of a Taxane and minimum of Trastuzumab. Essentially this was a way we got around trying to describe specific regimens since this was a global breast cancer study, but this really covered the sequential Anthracycline Taxane regimens as well as the non-Anthracycline TCHP. What it did not allow for was patients to receive half of a sequential regimen, then have surgery with plans to give more chemotherapy. The intent of the trial was to enroll patients who had received all the chemotherapy that was planned before surgery so that when we had a patients with residual disease, we could be certain that they had received a Taxane and they had relatively resistant disease. We did exclude patients with very small… who had presented with very small tumors, T1ab to N0 patients were excluded, but otherwise anybody else could get in irrespective of their stage of disease at presentation. They had to have residual invasive tumor in their breast or axillary lymph nodes and we did also require central confirmation. The patients were randomized to receive the standard Trastuzumab or TDM1 for 14 cycles. Since we had some broad eligibility criteria for patients in terms of their presentation, we had to plan our stratification factors carefully and we chose four. We stratified our patients by whether or not they presented with inoperable disease or operable disease, hormone receptor negative or positive status, preoperative therapy could consist of either Trastuzumab as the sole HER2 targeted therapy or combinations of Trastuzumab with a second agent. This was particularly important here in the US because around that time neoadjuvant Pertuzumab had also been approved and that had become standard of care quickly in the United States to offer both Trastuzumab and Pertuzumab and then finally patients were stratified by whether or not they had positive of negative lymph nodes at surgery.

For those just tuning in, you are listening to CME on Reach MD. I'm Dr. Charles Geyer, Professor of Medicine and Associate Director for Clinical Research at Virginia Commonwealth University Massey Cancer Center in Richmond, Virginia and we are currently reviewing potential new approaches to adjuvant therapy in patients with HER2 positive early breast cancer found to have residual disease following neoadjuvant therapy.

The characteristics of the patients who entered KATHERINE included approximately 20 percent of the patients, less than 40, a little under 10 percent were above the age of 65 with the remaining being 40 to 64. Three-quarters of the patients received Anthracycline as part of their neoadjuvant regimen. One-quarter of our patient population had presented with inoperable, unresectable breast cancer, which is a new group to be included in a global indication trial. Not surprisingly, a little over 70 percent of our patients were hormone receptor positive. Just under 20 percent of the patient received more than Trastuzumab as their HER2 directed therapy; the large majority of those received Pertuzumab as a second agent and about 45 percent of patients were node positive at the times of surgery. About 40 percent – 40-45 percent of patients had relatively small amounts of residual disease in the breast, measuring 1 cm or less. About the same percentage had negative lymph nodes. When you combined those two, small primary residual tumor and negative lymph nodes, 20… a little over 20 percent of our patient population had both of those, what lower risk characteristics, so we did have good representation of that lower risk group in KATHERINE. When we evaluated KATHERINE for IDFS, we saw a striking reduction in the number of patients who had developed an IDFS event by the time of the analysis, 22.2 percent of patients receiving Trastuzumab had had an IDFS event which was reduced to 12 percent with TDM1. This corresponded to a hazard ratio of 0.50, obviously a much greater effect than the 0.75 that we had originally designed the study to detect. With such a large benefit in IDFS across our patients population, and such a heterogeneous patient population entering our trial, it was important to look at how the TDM1 performed in our various subsets and equally striking to our overall hazard ratio of 0.5, was the fact that that hazard ratio was remarkably well-maintained and consistent throughout all of our stratification variables. We also of course wanted to look to see how the distribution of IDFS events looked across the different categories. IDFS events include distant recurrences of first event, local regional recurrences of first event, contralateral breast cancer and death without prior events, and we saw substantial reduction in the largest category, which was distant recurrences from 15.9 percent to 10.5 percent. Local regional recurrences also substantially diminished, 4.6 percent to 1.1 percent, contralateral breast cancers with just three years of follow up were infrequent in both arms, but were lower with TDM1 and happily we did not see any differences in deaths without prior events, both very low percentage 83 percent to 90 percent consistent with a favorable safety profile of TDM1. The three year cumulative distant recurrence free survival rate was improved from 83 percent to 90 percent with TDM1, again a 7 percent improvement for this very important end point, which focuses on the most serious of the IDFS events in the one that leads to patient death distant recurrence, so clearly a very clinically meaningful impact there as well.

We don't yet have meaningful survival data from KATHERINE. At the time of the initial analysis we had very few events that 7.5 percent of patients receiving Trastuzumab have died compared to 5.7 percent of patients with TDM1, so overall patient populations were doing

well. We did analyze the data because we knew this would be of interest to regulators, but we clearly are going to need more follow up on survival.

So in summary, the efficacy results show that adjuvant TDM1 demonstrated both a statistically significant and clinically meaningful improvement in IDFS compared with Trastuzumab with an improvement in three year IDFS rate from 77 percent to 88.3 percent. The benefit of TDM1 was consistent across all key subgroups, including hormone receptor status, extent of residual invasive disease, and single or dual HER2 targeted neoadjuvant therapy administered with chemotherapy. The safety data were consistent with increases in the known, but manageable toxicities of TDM1, such as neuropathy, thrombocytopenia, and hepatotoxicity when you compared the patients receiving TDM1 with Trastuzumab. As I mentioned, additional follow up will be necessary to evaluate the effect of TDM1 on overall survival, but the magnitude and breadth of the benefit of TDM1 demonstrated in the KATHERINE data has provided a foundation for a new standard of care for routine use of neoadjuvant therapy and HER2 positive early breast cancer in all patients with the exception perhaps of low risk patients presenting with T1 N0 disease who were shown to do very well with initial surgery and adjuvant Paclitaxel and Trastuzumab alone in the APT study. Neoadjuvant therapy is the only way we have to identify this very important subset of patients who can derive substantial benefit from receiving TDM1 as adjuvant treatment, so the effectiveness of TDM1 as an adjuvant therapy has really transformed the way, I think the way we will be treating HER2 positive breast cancer moving forward, making neoadjuvant therapy the standard of care for all but that small very low risk group at presentation.

With that, I would like to thank you for your participation.

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