

Improving Outcomes in HER2+ Early Breast Cancer

Although neoadjuvant trastuzumab and pertuzumab in combination with chemotherapy have improved outcomes for patients with HER2- positive early breast cancer, particularly those with a pathologic complete response at surgery, not all patients enjoy a complete pathologic response. These patients need 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, which is why integrating these new data and medications into adjuvant treatment paradigms for patients with HER2-positive early breast cancer is of high priority.

HER2-Positive Neoadjuvant Therapy

Any discussion of HER2-positive breast cancer must address the goals of neoadjuvant therapy as well as the current 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% 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 treatment to complete one total year of HER2-directed therapy.

However, a substantial number of patients without a pathologic complete response following neoadjuvant therapy with these active combination regimens with 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 new therapies that would reduce their increased risk for recurrence and death. In that regard, a more effective alternative adjuvant therapy has emerged for this subset of high-risk patients based on the persistence of invasive breast cancer following neoadjuvant combination therapy. Recent results from the KATHERINE trial¹ have demonstrated adjuvant administration of the HER2-directed immunoconjugate TDM1, which had been approved by the FDA in February of 2013 for second line therapy of HER2-positive metastatic breast cancer, substantially improves outcomes of patients treated with neoadjuvant combination therapy for HER2-positive early breast cancer and who are found with residual disease at surgery.

KATHERINE Trial

The results from the KATHERINE trial have been practice changing. For one, TDM1 is a unique immunoconjugate that links 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 subsequently released and induces cytotoxicity by inhibition of microtubule polymerization. In the design of KATHERINE study, a major concern was defining an eligibility criteria that would allow broad accrual of this relatively smaller subset of HER2-positive breast cancer patients. Patients could enter KATHERINE 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 *must have* consisted of at least six cycles of chemotherapy containing a minimum of nine weeks of a taxane and a minimum of 9 weeks trastuzumab. This allowed sequential anthracycline/taxane regimens as well as the non-anthracycline carboplatin and docetaxel regimen with trastuzumab as the only HER2 directed therapy or trastuzumab with a second HER2 directed agent such as pertuzumab. KATHERINE did not allow patients to receive half of a sequential regimen, then have surgery with plans to give more chemotherapy. The intent was to enroll patients who had received all the chemotherapy that was planned before surgery so that when a patient was identified with residual disease there was certainty that they had relatively resistant disease. Patients who presented with very small tumors, T1ab/N0, were excluded, but otherwise it was all comers irrespective of their stage of disease at presentation. They had to have residual invasive tumor in their breast or axillary lymph nodes central confirmation of HER2 positive status was required. The patients were randomized to receive standard trastuzumab or TDM1 for 14 cycles. Since there was broad eligibility criteria for patients in terms of presentation, four stratification factors were used, three being: patients by whether they presented with inoperable disease or operable disease; hormone receptor negative or positive status; and preoperative therapy of trastuzumab as the sole HER2-targeted therapy or combinations of trastuzumab with a second agent. This was particularly important in the US because around that time, neoadjuvant pertuzumab had also been approved, and it had quickly become the standard of care to offer both trastuzumab and pertuzumab. Lastly, patients were stratified by whether or not they had positive or negative lymph nodes at surgery. The overall characteristics of the patients who entered KATHERINE are broad and can be best reviewed within the trial publication.¹

When patients were evaluated for invasive disease-free survival (IDFS), a striking reduction in the number of IDFS events was noted; 22.2% of patients receiving trastuzumab had an IDFS event, which was reduced to 12% with TDM1. This corresponded to a hazard ratio of 0.50, a much greater effect than the 0.75 that had been originally designed into the study. With such a large benefit in IDFS across patient populations and such a heterogeneous patient population entering the trial, it was important to look at how TDM1 performed in various subsets, with equally striking and consistent results. The distribution of IDFS first events was assessed and included distant recurrences, local regional recurrences, contralateral breast cancer, and death without prior events; a substantial reduction in the largest category, which was distant recurrences from 15.9% to 10.5%, was noted. Local regional recurrences also substantially diminished from 4.6% to 1.1%; contralateral breast cancers with just three years of follow-up were infrequent in both arms but were lower with TDM1. There were no differences in deaths without prior events; both of which were very low (0.3 and 0.4%), consistent with the favorable

safety profile of TDM1. The three-year cumulative distant recurrence free survival rate was improved from 83% to 90% with TDM1, again a 7% 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. While there is not yet meaningful survival data from KATHERINE, there were very few events at the time of the initial analysis: 7.5% of patients receiving trastuzumab had died compared to 5.7% of patients receiving TDM1. Overall survival data still needs to mature.

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% to 88.3%. The benefit of TDM1 was consistent across all key subgroups, including hormone receptor status, extent of residual invasive disease, and single or dual HER- 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 patients receiving TDM1 with trastuzumab were compared. 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.

Reference

1. von Minckwitz G, Huang C-S, Mano MS, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med.* 2019;380:617-628.