T-DM1 adds to the armamentarium for targeting advanced HER2-positive breast cancer

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The Food and Drug Administration recently approved trastuzumab emtansine (T-DM1) as a single agent for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer who have previously received trastuzumab and a taxane.[1] T-DM1 is a sophisticated antibody–drug conjugate consisting of the cytotoxic agent emtansine (DM1), which targets tubulin and suppressed microtubule dynamics, and the monoclonal antibody, trastuzumab. The agent, which is conjugated by a stable linker, is transmitted to malignant tissues while sparing normal tissues.[2]

The approval was based on findings in the EMILIA trial, an instrumental phase 3 trial that is expected to change the management and outcomes of women with HER2-positive breast cancer.[3] A total of 991 patients with HER2-positive advanced breast cancer who had previously received trastuzumab and a taxane were randomly assigned to T-DM1 (3.6 mg/kg IV) every 21 days or a combination of oral capecitabine (1,000 mg/m^2 every 12 hours on days 1-14 every 3 weeks) plus oral lapatinib (1,250 mg/day) until progressive disease or unmanageable toxicity. Women in the T-DM1 arm enjoyed superior median progression-free survival (PFS) compared with those in the capecitabine-plus-lapatinib arm (9.6 vs. 6.4 months, respectively, hazard ratio [HR], 0.65; $P < .001$) and a higher objective response rate (43.6% vs. 30.8%, respectively; $P < .001$). However, the most striking result was a substantial improvement in median overall survival of 30.9 months among women who were treated with T-DM1, compared with 25.1 months in those treated with the capecitabine–lapatinib combination, with a reduction of 32% in risk of death (HR, 0.68; $P < .001$). Perhaps as important was the finding that the patients who were treated with T-DM1 had better tolerability of the agent than did those who received the capecitabine–lapatinib combination (grade 3 or 4 adverse events in 41% and 57%, respectively). The most common grade 3 or 4 events with T-DM1 were thrombocytopenia (12.9% of patients) and elevated levels of the liver transaminases (2.9% for alanine aminotransferase; 4.3% for aspartate aminotransferase). The survival benefits observed in EMILIA, despite prior treatment with trastuzumab and taxane, were unprecedented. We join the oncology community and our patients in the excitement and hope that T-DM1 and other designer agents will help achieve durable responses with limited side effects in women with HER2-positive metastatic disease.

The challenge ahead is to better define the role of T-DM1 in the metastatic and adjuvant settings. The ongoing phase 3 MARIANNE trial will evaluate the efficacy and safety of the dual HER2 blockade using T-DM1-plus-pertuzumab or T-DM1-plus-placebo as first-line therapy in HER2-postive metastatic breast cancer compared with trastuzumab plus a taxane.[4] The TH3RESA study, another phase 3 trial, will provide data on the efficacy and safety of T-DM1 in heavily pretreated patients with HER2-positive disease.[5]

T-DM1 is also under extensive investigation in the adjuvant and neoadjuvant settings. In the ongoing ADAPT international study, pathological complete response (pCR) rates in patients with HER2-positive and hormone receptor-positive breast cancer who have been treated with preoperative T-DM1 with or without standard endocrine therapy and those who have been treated with trastuzumab with endocrine therapy.[6] Another trial that is currently underway aims to assess the clinical safety and feasibility of T-DM1 after completion of anthracycline-based chemotherapy, as an adjuvant or neoadjuvant therapy for patients with early stage HER2-positive breast cancer.[7]

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Other studies will help define the patient populations that are most likely to benefit from the agent and address rational combinations. An update of the CLEOPATRA trial, which compared treatment with trastuzumab and docetaxel with or without pertuzumab, revealed that mutations in *PI3K* were associated with poor prognosis in both treatment arms, although PFS continued to be superior in the pertuzumab arm. A benefit in the median overall survival was observed in the pertuzumab-treated group compared with the control group regardless of *PI3K* status (wild-type or mutated), however, the benefit was more substantial in the patients with wild-type *PI3K* compared with those harboring a mutation (21.8 vs 13.8 months, respectively).[8] Moreover, novel agents targeting HER2 are under investigation in women with metastatic HER2-positive disease, including afatinib, an oral irreversible dual inhibitor of HER1 and HER2, and neratinib, an oral drug with activity against HER1, HER2, and HER4.

Finally, women with metastatic HER2-positive breast cancer are at a higher risk for brain metastases.[9] Although they can live for several years with advanced disease and brain metastases, the treatment options for brain metastases are more limited. Local approaches as well as systemic small-molecule agents such as lapatinib that can cross the blood–brain barrier should be considered in women with brain metastases. Ongoing studies aim to better assess susceptibility to early brain dissemination and to investigate new agents.

In summary, the results from EMILIA have demonstrated a substantial improvement in survival outcomes and tolerability with T-DM1 in patients who have been previously exposed to other lines of treatment in the HER2-positive metastatic setting compared with capecitabine–lapatinib in the second-line setting. The FDA's approval of T-DM1 extends the range of available therapeutic options for this tumor subtype. We await further studies that evaluate the role of T-DM1 in the first-line and neoadjuvant and adjuvant settings. We also expect additional knowledge regarding rational T-DM1-combinations, novel agents, and predictive biomarkers of response.

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Trastuzumab emtansine in advanced HER2-positive breast cancer

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Trastuzumab emtansine is an antibody–drug conjugate composed of trastuzumab (T) linked to a highly potent cytotoxic derivative of maytansine (DM1) by a stable linker (a nonreducible thioether, SMCC).[1] DM1 binds to intracellular tubulin and prevents the assembly of microtubules, resulting in cell death. Trastuzumab targets the conjugate to the human epidermal growth factor receptor 2 (HER2) protein and the stable linker releases the cytotoxic agent only when the compound is internalized through receptor endocytosis. Trastuzumab emtansine (T-DM1) has been in found to be active in trastuzumab- and lapatinib-resistant disease, as well as in trastuzumab-naïve tumors. The conjugate also seems to maintain the antitumor activity of trastuzumab. Primary results of the phase 3 EMILIA trial that compared T-DM1 with capecitabine-plus-lapatinib in advanced HER2-positive breast cancer were reported at the 2012 American Society of Clinical Oncology meeting,[2] with the findings indicating significant improvement in progression free survival (PFS) with the conjugate. It was on the basis of those findings that the Food and Drug Administration recently approved T-DM1 for the treatment of women with HER2-positive, late-stage metastatic breast cancer.

In EMILIA, 991 patients with locally advanced or metastatic HER2-positive breast cancer who had previously received trastuzumab and a taxane were randomized in open-label fashion to T-DM1 (3.6 mg/kg IV every 3 weeks) alone or capecitabine (1,000 mg/m^2 orally twice daily on days 1-14 every 3 weeks) plus lapatinib (1,250 mg orally daily) until progressive disease or unmanageable toxicity.[2] The primary endpoint was PFS on independent review.

Overall, 978 patients received the study treatments. Median durations of follow-up were 12.9 months in the T-DM1 group and 12.4 months in the capecitabine–lapatinib group. Median PFS in the T-DM1 group was 9.6 months, compared with 6.4 months in the capecitabine–lapatinib group, yielding a significant 35% reduction in risk for progression (hazard ratio [HR], 0.650; 95% CI, 0.549-0.771; $P < .0001$).

What's new, what's important

The development of antibody drug conjugates is a major advance in cancer treatment. Ado-trastuzumab emtansine, more commonly known as TDM-1, is the first ADC to be approved by the Food and Drug Administration for HER2/neu-positive patients who have progressed on prior therapy with trastuzumab.

T-DM1 is an exciting development on many fronts. First, the concept and technology of combining a highly toxic drug (emtansine) with a targeted agent (trastuzumab) with a linker molecule will have a tremendous impact on future drug development. Second, and more importantly for many patients who progress on trastuzumab-containing regimens, this could be a highly viable option for improving progression free survival and improve overall survival for this population of patients. It is amazing to see that HER2-positive disease, which used to be considered an aggressive disease, has been redefined as a chronic disease in a short span of 10-12 years with the introduction of trastuzumab and other HER2- targeted agents.

The dose of T-DM1 is 3.6 mg/kg infused (over 90 minutes for the first dose, then over 30 minutes in subsequent treatments) every 3 weeks. Patients need to be carefully monitored for hepatic and cardiac toxicity. Thrombocytopenia is another T-DM1-associated side effect that was commonly seen in clinical trials. There should be appropriate dose reduction in the case of those toxicities. But overall, it is a well tolerated, extremely promising therapeutic option for patients with HER2-positive disease. Future clinical trials with T-DM1 in combination with pertuzumab and other *PI3K* inhibitors might provide us with more therapeutic options for patients with trastuzumab-resistant disease.

— Jame Abraham, MD

An interim overall survival (OS) analysis that was planned to occur at the time of the final PFS analysis had a prespecified efficacy boundary (HR, 0.617; $P = .0003$). At this interim analysis, median OS had not been reached in the T-DM1 group and it was 23.3 months in the

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How we treat metastatic HER2-positive breast cancer

Until the Food and Drug Administration's approvals of pertuzumab in 2012 and trastuzumab emtansine (T-DM1) in early 2013, trastuzumab and lapatinib were the only commercially available targeted agents for the treatment of human epidermal growth factor receptor 2-positive metastatic breast cancer. The anti-HER2 agent is usually combined with a cytotoxic agent, or, in select women, with an aromatase inhibitor. Trastuzumab and lapatinib can also be prescribed in combination. In women who are progressed on HER2-based chemotherapy, clinicians would generally replace the backbone while maintaining an anti-HER2 agent.

The history of metastatic HER2-positive tumors has changed substantially in recent months. In the CLEOPATRA trial, 808 patients with HER2-positive metastatic breast cancer were randomly assigned to first-line trastuzumab and docetaxel with or without pertuzumab.[1] The primary endpoint, progression-free survival, was met with significant improvement in median PFS in the dual anti-HER2 arm (18.5 vs. 12.4 months, respectively; hazard ratio [HR], 0.62; $P < .001$). In addition, the risk of death was reduced by 46% favoring the dual HER2-blockade arm (HR, 0.64; $P = .005$). On the basis of the results from CLEOPATRA, we would recommend trastuzumab, pertuzumab, and docetaxel as first-line treatment for women with metastatic HER2-positive breast cancer.

In the EMILIA trial, T-DM1 was associated with significant improvement in all primary endpoints compared with capecitabine-plus-lapatinib, including median PFS (9.6 vs. 6.4 months, respectively; HR, 0.65; $P < .001$), and overall survival (30.9 vs. 25.1 months; HR, 0.68; $P < .001$).[2] More importantly, T-DM1 was extremely well tolerated. On the basis of the EMILIA results and the recent approval of T-DM1, we recommend T-DM1 as second-line treatment in women with HER2-positive metastatic breast cancer. Lapatinib-based therapy should be considered in the third-line setting in women who progressed despite prior treatment with the trastuzumab, pertuzumab, and taxane combination, and T-DM1.

Of note is that about 30% of women with HER2-positive tumors will develop brain metastasis.[3] Lapatinib is a small molecule and is able to cross the blood–brain barrier. In a phase 2 study in patients who had been previously exposed to trastuzumab and cranial irradiation, about 21% of participants showed at least a 20% reduction in the brain tumor volume.[4] We would therefore consider lapatinib-based therapy in patients with progressing brain metastases. Lapatinib can be administered with a cytotoxic agent such as capecitabine, or in combination with trastuzumab in women with minimal distant metastases.

The approval of pertuzumab and T-DM1 presented new therapy options in the management of women with HER2-positive metastatic breast cancer. However, despite the impressive advances, most women will progress on available therapies and succumb to their disease. We therefore strongly recommend physicians and their patients consider participation in clinical trials throughout the treatment continuum. We anticipate that ongoing and future studies will help further define the role of T-DM1 alone or in combination with other cytotoxic agents such as taxanes or with anti-HER2 agents such as pertuzumab in the first-line treatment of metastatic disease or in the adjuvant or neo-adjuvant setting. Women who have progressed after treatment with pertuzumab-, trastuzumab-, T-DM1-, and lapatinib-based regimens should be considered for clinical trials with newer combinations, novel anti-HER2 agents such as neratinib or afatinib, or in studies in which anti-HER2 agents are combined with *PI3K* inhibitors or other drugs that may reverse resistance.

The recent additions to the treatment armamentarium have helped redefine the natural history of metastatic HER2-positive breast cancer. We are currently in uncharted territory, where women can live with the disease for many years and also expect an excellent quality of life.

— Maria Cristina Figueroa-Magalhães, MD, and Vered Stearns, MD

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capecitabine–lapatinib group, yielding an HR of 0.621 (95% CI, 0.475-0.813; $P = .0005$). This difference did not cross the interim efficacy boundary and thus it cannot yet be concluded that T-DM1 treatment was associated with a significant OS benefit. OS rates were 84.7% (95% CI, 80.8%-88.6%) in the T-DM1 group, compared with 77.0% (95% CI, 72.4%-81.5%) in the capecitabine–lapatinib group at 1 year (7.7% absolute difference), and 65.4% (95% CI, 58.7%-72.2%), compared with 47.5% (95% CI 39.2%-55.9%) at 2 years (17.9% absolute difference).

Objective response was observed in 43.6% of T-DM1 patients and in 30.8% of capecitabine−lapatinib patients. Median durations of response in patients with objective response were 12.6 months (95% CI, 8.4-20.8 months) in T-DM1 patients and 6.5 months (95% CI, 5.5-7.2 months) in capecitabine−lapatinib patients.

T-DM1 was well tolerated with no unexpected safety signals. Adverse events of grade 3 or higher occurred in 40.8% of the T-DM1 group and 57.0% of the capecitabine−lapatinib group. The most common grade 3 or higher events in the T-DM1 group were thrombocytopenia (12.9% vs 0.2% in the capecitabine−lapatinib group), increased aspartate aminotransferase levels (4.3% vs 0.8%), and increased alanine aminotransferase levels (2.9% vs 1.4%). The most common adverse events in the capecitabine−lapatinib group were diarrhea (20.7% vs 1.6% in the T-DM1 group), palmar plantar erythrodysesthesia (16.4% vs 0), and vomiting (4.5% vs 0.8%). Dose reduction was required in 16.3% of T-DM1 patients, and capecitabine and lapatinib dose reductions were required in 53.4% and 27.3%, respectively, of patients in the capecitabine−lapatinib group.

T-DM1 is being evaluated in 2 additional phase 3 trials in breast cancer — the MARIANNE trial, which compares T-DM1 with or without pertuzumab with trastuzumab plus a taxane in the first-line treatment of HER2-positive progressive or recurrent locally advanced or metastatic breast cancer; and the TH3RESA study, which compares T-DM1 with physician's choice of treatment in patients with HER2-positive breast cancer who have received at least 2 prior regimens of HER2-directed therapy.

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