

# Adjuvant Treatment With Ado-trastuzumab Emtansine in HER2-Positive Early Breast Cancer

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*In the Clinic* provides overviews of novel oncology agents, addressing indications, mechanisms of action, administration recommendations, safety profiles, and other essential information needed for the appropriate clinical use of these drugs.

Earlier this year, ado-trastuzumab emtansine (T-DM1) was approved for the adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane-based and standard trastuzumab-based treatment.<sup>1,2</sup> Patients should be selected for treatment based on a U.S. Food and Drug Administration (FDA)-approved companion diagnostic for T-DM1. The FDA approved both the Ventana Medical Systems, Inc. PATHWAY anti-HER-2/neu (4B5) Rabbit Monoclonal Primary Antibody assay and the INFORM HER2 Dual ISH DNA Probe Cocktail assay as companion diagnostic devices for selecting patients for treatment.

## Supporting Efficacy Data

Approval was based on findings from the phase III open-label KATHERINE trial (ClinicalTrials.gov identifier NCT01772472),<sup>2,3</sup> in which 1,486 patients were randomly assigned to receive T-DM1 at 3.6 mg/kg intravenously (n = 743) or standard trastuzumab at 6 mg/kg intravenously (n = 743) on day 1 of a 21-day cycle for 14 cycles. Patients were required to have had neoadjuvant taxane-based and standard trastuzumab-based therapy with residual invasive tumor in the breast or axillary lymph nodes. Patients received radiotherapy or hormonal therapy concurrently with study treatment per local guidelines.

## OF NOTE

T-DM1 has boxed warnings for hepatotoxicity, including liver failure and death; reductions in left ventricular

The primary endpoint was invasive disease-free survival, defined as the time from randomization to first occurrence of ipsilateral invasive breast tumor recurrence, ipsilateral local or regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, or death

ejection fraction; and embryofetal toxicity.

from any cause. The median age of study patients was 49 years, 73% were white, 72% were hormone receptor-positive, clinical stage at presentation was operable in 75%, and 46% had node-positive disease after preoperative therapy.

After a median follow-up of 40 months, the trial showed a significant improvement in invasive disease-free survival in the T-DM1 vs standard trastuzumab group (hazard ratio [HR] = 0.50,  $P < .0001$ ), with 3-year event-free rates of 88.3% vs 77.0%. The benefit was observed for invasive disease-free survival including second primary non-breast cancer (HR = 0.51, 95% confidence interval [CI] = 0.40–0.66) and disease-free survival (HR = 0.53, 95% CI = 0.41–0.68). Overall survival data were not mature at the time of the current analysis.

### How It Works

**T-DM1** is a HER2-targeted antibody-drug conjugate comprising trastuzumab and the small-molecule cytotoxic microtubule inhibitor emtansine. After binding to the HER2 receptor, T-DM1 undergoes receptor-mediated internalization and lysosomal degradation, resulting in intracellular release of DM1-containing cytotoxic catabolites. The binding of emtansine to tubulin disrupts microtubule networks in the cell, resulting in cell-cycle arrest and apoptotic cell death. In vitro studies have also shown that, like trastuzumab, T-DM1 inhibits HER2-receptor signaling, mediates antibody-dependent cell-mediated cytotoxicity, and inhibits shedding of the HER2 extracellular domain in human breast cancer cells that overexpress HER2.

### How It Is Used

**The recommended dose** of T-DM1 in the current indication in early breast cancer is 3.6 mg/kg via intravenous infusion every 3 weeks (21-day cycle) for a total of 14 cycles unless there is disease recurrence or unmanageable toxicity. The first infusion should be given over 90 minutes; if infusion is tolerated, subsequent infusions may be given over 30 minutes. Infusion should be slowed or interrupted in patients with infusion-related reactions, and the drug should be permanently discontinued in those with life-threatening reactions.

Recommended dose reductions for adverse events are stepwise to 3 mg/kg and 2.4 mg/kg, with treatment being discontinued if further dose reduction is needed. The dose must not be re-escalated after dose reduction. Product labeling provides instructions for dose modification, including treatment interruption and permanent treatment discontinuation, in the setting of early breast cancer for elevated alanine transaminase (ALT), elevated aspartate transaminase (AST), hyperbilirubinemia, nodular regenerative hyperplasia, left ventricular dysfunction, thrombocytopenia, heart failure, peripheral neuropathy, pulmonary toxicity, and radiotherapy-related pneumonitis.

### Safety Profile

**The most common** adverse events of any grade in the T-DM1 group in KATHERINE ( $\geq 25\%$ ) were fatigue, nausea, increased transaminases, musculoskeletal pain, hemorrhage, thrombocytopenia, headache, peripheral neuropathy, and arthralgia. Grade 3 or 4 adverse events occurred in 26% vs 15% of patients, with the most common in the T-DM1 group ( $> 2\%$ ) being thrombocytopenia and hypertension.

Adverse events in the T-DM1 group led to dose reductions in 14% of patients and dose delays in 14%. Adverse events led to permanent treatment discontinuation in 18%, with the most common causes ( $\geq 1\%$ ) being platelet count decreased, blood bilirubin increased, left ventricular ejection fraction decreased, AST increased, ALT increased, and peripheral neuropathy.

### T-DM1 for Early Breast Cancer

- Ado-trastuzumab emtansine (T-DM1) was approved for the adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane-based and standard trastuzumab-based treatment.
- The recommended dose of T-DM1 in this indication is 3.6 mg/kg via intravenous infusion every 3 weeks (21-day cycle) for a total of 14 cycles unless there is disease recurrence or unmanageable toxicity.

T-DM1 has boxed warnings for hepatotoxicity, including liver failure and death; reductions in left-ventricular ejection fraction; and embryofetal toxicity. Patients must have hepatic function monitored prior to initiation and prior to each dose. Patients must have left-ventricular ejection fraction assessed prior to initiation of treatment and monitored thereafter.

T-DM1 also has warnings/precautions for pulmonary toxicity; infusion-related reactions and hypersensitivity reactions; hemorrhage, with fatal cases having occurred in clinical trials among patients with no known identified risk factors; thrombocytopenia; and neurotoxicity. Treatment should be permanently discontinued for interstitial lung disease or pneumonitis and for radiation pneumonitis in the adjuvant setting of grade  $\geq 3$  or grade 2 and for those not responding to standard treatment. Platelet counts should be

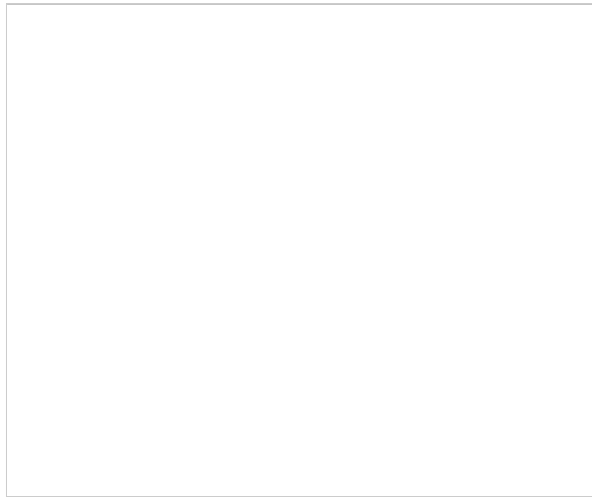
monitored prior to each dose. Patients should be monitored for signs or symptoms of neurotoxicity. Patients should be advised not to breastfeed while receiving T-DM1. ■

### REFERENCES

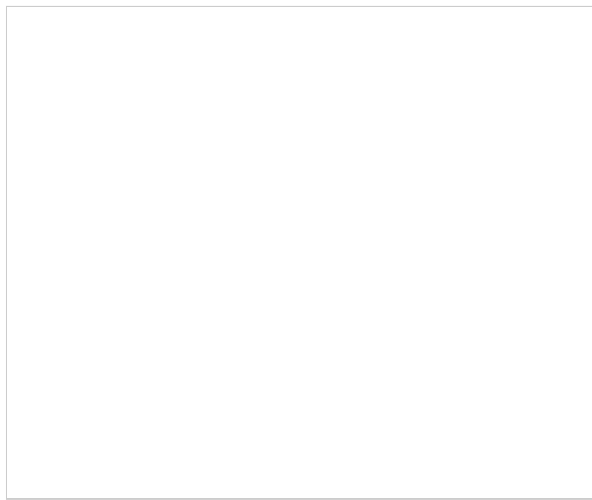
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