Ann Surg Oncol (2024) 31:1423–1427
https://doi.org/10.1245/s10434-023-14766-9

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ASO PERSPECTIVES

Adjuvant Trastuzumab Emtansine Versus Paclitaxel and Trastuzumab in Stage I HER2-Positive Breast Cancer: The ATEMPT Trial

Monica N. Khattak, DO, Anna M. Chichura, MD, and Julie E. Lang, MD

Division of Breast Services, Cleveland Clinic Foundation, Cleveland, OH

ABSTRACT This ASO perspective reviews the findings of a randomized, phase II clinical trial evaluating adjuvant trastuzumab emtansine (T-DM1) compared with paclitaxel and trastuzumab (TH) in stage I human epidermal growth factor receptor 2-positive breast cancer, as reported recently by the ATEMPT trial investigators. Patients treated with T-DM1 had better disease-free survival but did not have fewer treatment toxicities. The T-DM1-treated group had higher rates of treatment discontinuations, therefore long-term follow-up will be required to evaluate survival differences between T-DM1 and TH.

Human epidermal growth factor receptor 2 (HER2) is overexpressed in 20–25% of invasive breast cancers and is associated with aggressive tumor growth.[1] Although the overexpression of HER2 was initially recognized as a poor prognostic factor, the discovery of anti-HER2 monoclonal antibodies drastically improved prognosis and survival.[1,2] Moreover, stage I breast cancer has an excellent prognosis, with a survival rate of over 95% regardless of molecular subtype.[2]

Trastuzumab is a humanized monoclonal antibody that binds to the extracellular domain of HER2, preventing dimerization and extracellular domain cleavage.[3] Trastuzumab was approved in 1998 by the US FDA for the treatment of HER2-positive metastatic breast cancer, and was subsequently approved for the adjuvant treatment of surgically resectable HER2-positive breast cancer in 2006[4] following publication of the North Central Cancer Treatment Group trial N9831 and NSABP B 31 pivotal phase III trials, which demonstrated that the addition of trastuzumab to adjuvant chemotherapy significantly improved disease-free survival (DFS) and overall survival (OS) in patients with operable HER2-positive breast cancer.[5] Prior to the use of trastuzumab, patients with HER2-positive disease were treated with paclitaxel or anthracycline/cyclophosphamide-based chemotherapy regimens.[6]

In 2015, the results of the Adjuvant Paclitaxel and Trastuzumab (APT) trial were published, demonstrating that patients with HER2-positive, node-negative cancers up to 3 cm treated with APT had a 3-year interval invasive DFS (iDFS) of 98.7%, a 7-year iDFS of 93%, and a 7-year recurrence-free interval (RFI) of 97.5%.[7,8] Per the current National Comprehensive Cancer Network (NCCN) guidelines, the standard of care for HER2-positive breast cancers that are pT1N0, especially if the tumor is hormone receptor (HR)-negative, includes adjuvant chemotherapy with weekly paclitaxel and trastuzumab. They recommended *consideration* of adjuvant chemotherapy for tumors that are <10 mm (pT1a and pT1b) or do not involve lymph nodes (pN0 or pN1mi), stating that the toxicity of treatment with trastuzumab must be balanced with the uncertain absolute benefit from treatment.[9] Low-intensity regimens such as weekly paclitaxel and trastuzumab are commonly used in patients with T1a/T1b tumors, especially if the tumor displays high-risk features such as high-grade or HR-negative status or occurs in patients of younger age. Paclitaxel and trastuzumab (TH) is an example of a de-escalated regimen for HER2-positive breast cancer.

Given the success of anti-HER2 therapies, interest developed in creating HER2-targeted antibody-drug conjugates (ADCs) that could directly deliver highly potent chemotherapeutic agents directly to cancer cells, thereby

First Received: 27 October 2023
Accepted: 27 November 2023
Published online: 21 December 2023

J. E. Lang, MD
e-mail: LANGJ2@ccf.org

minimizing off-target toxicities associated with the administration of systemic chemotherapy. Ado-trastuzumab emtansine, or T-DM1, is an ADC of trastuzumab and a cytotoxic agent, a derivative of maytansine (DM1), that works by inhibiting microtubule assembly. The trastuzumab component allows for delivery of DM1 directly to HER2-positive breast cancer cells where it binds to the extracellular domain of HER2, stimulates receptor-mediated endocytosis, and results in cell death after the DM1 domain is released.[10] T-DM1 was FDA-approved in 2013 for individuals with HER2-positive metastatic breast cancer who had progressed on trastuzumab and a taxane.[11]

Tolaney and colleagues recently reported the results of the ATEMPT trial (Fig. 1), a randomized, phase II clinical trial at 24 institutions within the United States (US) evaluating adjuvant T-DM1 compared with TH in stage I HER2-positive breast cancer.[12] T-DM1 was administered at a dose of 3.6 mg/kg intravenously every 3 weeks for 17 cycles, and T was administered at a dose of 80 mg/m^2 intravenously with H once every week × 12 weeks (4 mg/kg load → 2 mg/kg), followed by H × 39 weeks (6 mg/kg once every 3 weeks) [Fig. 1]. The authors hypothesized that T-DM1 would be as effective as TH in reducing the risk of invasive recurrence in stage I HER2-positive breast cancer with less clinically relevant toxicity (CRT). CRT was defined as grade ≥3 non-hematologic toxicity, grade ≥2 neurotoxicity, grade ≥4 hematologic toxicity, febrile neutropenia, any serious adverse event, or any toxicity that required dose delay or discontinuation of treatment.[12]

Overall, 512 patients were recruited between 17 May 2013, and 13 December 2016. Patients were randomized in a 3:1 ratio to compare toxicity from receiving either T-DM1 or TH. Randomization was stratified by age (<55 years, ≥55 years), planned use of RT (yes, no), and planned use of endocrine therapy (yes, no). After excluding patients who withdrew consent, an intention-to-treat analysis was performed on 383 patients in the T-DM1 arm and 114 in the TH arm. The median follow-up time was 3.9 years, precluding definitive assessment of iDFS. There was no difference in the composite CRT rate between the T-DM1 and TH arms (46% vs. 47%; $p = 0.83$).[12]

Despite no observed difference in the *composite* rate of CRT, grade ≥2 adverse events were significantly more common among patients receiving TH compared with those receiving T-DM1, including neuropathy (23% vs. 11%; $p = 0.003$), neutropenia (12% vs. 3%; $p = 0.0003$), alopecia (41% vs. 0%; $p < 0.0001$), diarrhea (9% vs. 4%; $p = 0.04$), gastroesophageal reflux disease (9% vs. 4%; $p = 0.04$), decreased WBC (6% vs. 2%; $p = 0.02$), and infusion-related reactions (11% vs. 5%; $p = 0.04$). In contrast, thrombocytopenia (11% vs. 1%; $p = 0.0001$) and elevated bilirubin (5% vs. 1%; $p = 0.04$) were more common with T-DM1 compared with TH. Of the patients receiving TH, 23% experienced at least one grade 3 adverse event compared with 16% of patients receiving T-DM1; however, 29% of patients

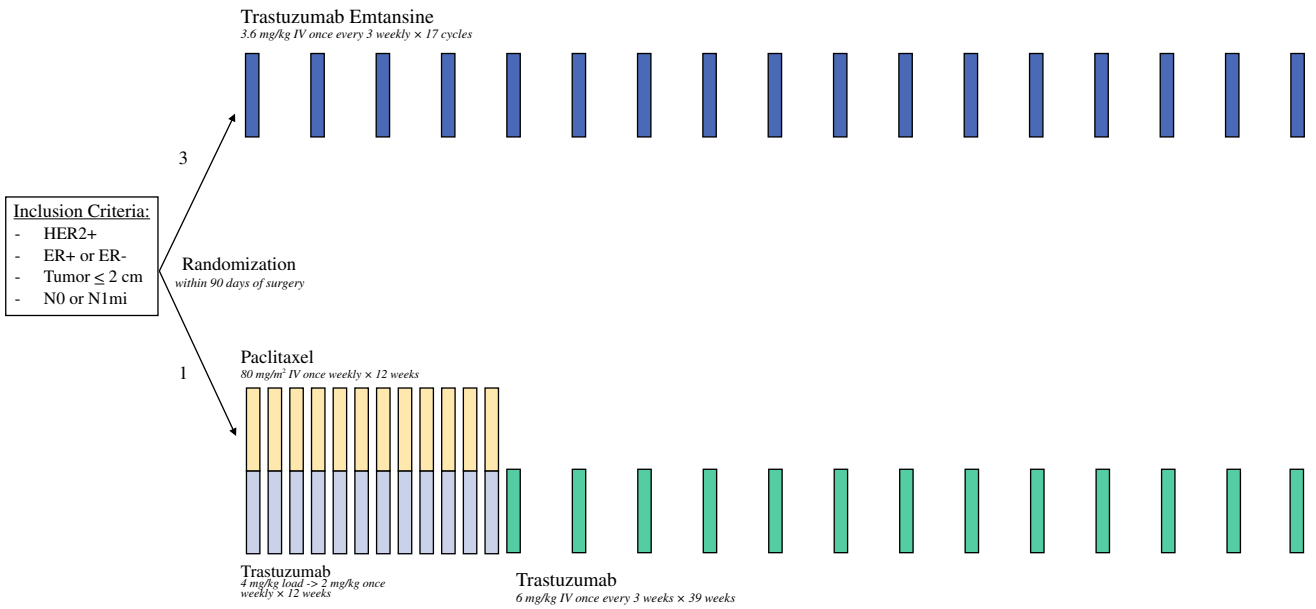

FIG. 1 Schematic of ATEMPT trial treatment arms. Ado-trastuzumab emtansine was administered at a dose of 3.6 mg/kg intravenously every 3 weeks for 17 cycles (dark blue boxes). Paclitaxel was administered at a dose of 80 mg/m^2 intravenously with H once every week × 12 weeks (4 mg/kg load → 2 mg/kg) [yellow and light blue boxes, respectively], followed by H × 39 weeks (6 mg/kg once every 3 weeks) [green boxes]. Each rectangle represents 1 week. *H* trastuzumab, *HER2+* human epidermal growth factor receptor 2-positive, *ER+* estrogen receptor-positive, *ER−* estrogen receptor-negative, *IV* intravenously

in the T-DM1 arm had at least one dose reduction compared with 17% of patients in the TH arm.[12]

The adverse events observed in the ATTEMPT trial did impact the treatment discontinuation rate. While T-DM1 was discontinued for protocol-mandated indications in 8% of patients, the overall discontinuation rate of T-DM1 in the study, as dictated by the treating physician, was 17% as compared with 8% in the TH arm. The most common indications for discontinuation of T-DM1 were elevated liver enzymes or bilirubin (28%), neuropathy (19%), and thrombocytopenia (19%).[12]

One of the major adverse effects of HER-2-targeted drugs is cardiovascular adverse events (CVAEs) such as heart failure, cardiomyopathy, and arrhythmias, which can occur in up to 13.5% of patients treated with HER-2 inhibitors.[13] Data from large adjuvant trastuzumab trials suggest that the proportion of patients who experience asymptomatic declines in left ventricular ejection fraction (LVEF) during or after trastuzumab therapy in the curative-intent setting ranges from 4.1 to 30.1%, but rates of symptomatic congestive heart failure (CHF) are much lower (0.6–3.8%).[14] While CVAEs induced by HER-2 inhibitors are reversible after discontinuation, the risk of cardiotoxicity cannot be ignored. Trastuzumab-induced cardiotoxicity causes most treatment interruptions. Shorter duration of trastuzumab therapy (6 months vs. 1 year) is associated with favorable cardiac outcomes, however there are conflicting results regarding DFS. In fact, interruption to trastuzumab treatment has been associated with three times worse DFS and OS rates when compared with a 1-year therapy with <14 days of treatment interruption.[15]

A recent subanalysis of the ATEMPT trial aimed to determine the cardiac safety of adjuvant T-DM1 as compared with TH. The incidence of grade 3–4 left ventricular systolic dysfunction (LVSD) was found to be 0.8% in the T-DM1 arm and 1.8% in the TH arm. Additionally, only 0.8% of patients in the T-DM1 arm and 5.3% in the TH arm experienced a significant asymptomatic LVEF decline that required T-DM1 or trastuzumab to be held.[16]

A post hoc analysis of the ATEMPT trial was performed 18 months post-enrollment to compare the rates of quality of life, drug toxicity, and treatment discontinuation in patients <50 years of age versus patients >50 years of age. Overall, 366 patients were studied, with 34% in the younger age group <50 years) and 66% in the older age group (>50 years). Overall, treatment discontinuation was higher and time to discontinuation was shorter in the older group. Toxicity was listed as the main reason for T-DM1 discontinuation in the older patients, primarily due to elevated liver and bilirubin enzymes, neuropathy, and thrombocytopenia. Interestingly, older patients receiving T-DM1 therapy were noted to have better physical well-being and less activity impairment than those receiving TH therapy. Although T-DM1 was associated with a higher rate of discontinuation due to the toxicities mentioned above, patient-reported outcomes and quality of life were superior in the T-DM1 group versus the TH group, specifically among younger patients. Younger patients are often overtreated and at risk for an impaired quality of life. This post hoc analysis suggests that a de-escalated chemotherapy approach for younger patients with T-DM1 may allow for an improved health-related quality of life.[17]

A subsequent publication reported that patients in both the T-DM1 and TH arms tolerated radiation therapy (RT) well. The radiation protocol included whole breast or partial breast RT that occurred concurrently with T-DM1 treatment or concurrently with trastuzumab therapy (but after paclitaxel completion). In the ATEMPT trial, 289 patients received RT—40% of patients in the T-DM1 arm and 41.5% in the TH arm. Overall, there was no difference in the rate of skin toxicity (grade ≥2) in patients undergoing either therapy (T-DM1 33.9% vs. TH 23.2%; $p = 0.11$).[18]

Chemotherapy-related amenorrhea (CRA) is a known consequence of chemotherapy in premenopausal breast cancer patients and can be used as a surrogate to measure ovarian toxicity. Seventy-six premenopausal women from both arms of the ATEMPT trial were surveyed to determine CRA at 18 months. Overall, there appeared to be less CRA in premenopausal patients enrolled in the T-DM1 arm as compared with the TH arm (24% vs. 50%; $p = 0.045$). However, CRA rates appeared to increase over time in the T-DM1 group, suggesting a delayed CRA attributed to the increased length of treatment duration (T-DM1 treatment of 1 year vs. TH treatment of 12 weeks).[19]

Other secondary outcomes in addition to adverse events included the invasive DFS (iDFS), RFI and patient-reported outcomes. iDFS was defined to include local or regional recurrence, contralateral invasive breast cancer, distant recurrence, or death from any cause. The observed 3-year iDFS for the T-DM1 cohort was 97.8% (95% confidence interval [CI] 96.3–99.3), which exceeded the protocol specified 3-year iDFS rate of 95%. The RFI was defined as invasive local or regional recurrences, distant recurrences, and any death from breast cancer. At 3 years, the RFI for patients receiving T-DM1 was 99.2% (95% CI 98.2–100). Three deaths were observed in the T-DM1 group secondary to diabetic coma, stroke, and Creutzfeldt–Jakob disease, respectively, whereas no deaths were observed in the TH arm. Patient-reported outcomes, including quality of life, general symptomatology, neurotoxicity, alopecia, and work productivity and activity, were all worse in patients in the TH arm as compared with patients in the T-DM1 arm.[12]

In weighing the risks and benefits of these interventions, it is also important to consider the cost to the patient and healthcare system. The average wholesale price of T-DM1 in the US is $11,129.28 per cycle, while trastuzumab is

$5714.19 per cycle.[20] Given a treatment duration of 17 cycles for T-DM1 and 25 cycles for trastuzumab, as seen in the ATEMPT trial, the total treatment cost with T-DM1 is approximately $189,197.76 versus $142,854.75 with trastuzumab.

Efforts to discover the optimal adjuvant regimen for patients with HER2-positive stage I breast cancer are ongoing. The ATEMPT 2 trial is currently investigating adjuvant T-DM1 followed by trastuzumab as compared with TH in this patient population.[21] This phase II randomized control trial is estimated to end in 2025. Unlike in the ATEMPT trial, the T-DM1 treatment arm will have participants receiving T-DM1 every 3 weeks for six cycles (totaling 18 weeks) followed by trastuzumab every 3 weeks for 11 cycles (totaling 33 weeks). Patients in the ATEMPT trial received T-DM1 every 3 weeks for 17 cycles (51 weeks). The discontinuation rate of T-DM1 treatment due to adverse effects within the first 6 months was 8.2%, and 10.7% within 6–12 months. We are interested in following the results of ATEMPT 2 to see how a shorter course of T-DM1 is tolerated.

The 2019 KATHERINE trial showed that individuals who had residual invasive HER2-positive disease after neoadjuvant taxane and trastuzumab-based treatment had a 50% lower risk of recurrence of invasive breast cancer or death when treated with adjuvant T-DM1 as compared with trastuzumab alone.[22] T-DM1 was subsequently FDA approved for HER2-positive early breast cancer in the post-neoadjuvant setting.[23] It is noteworthy that while the ATEMPT trial focuses on the role of T-DM1 as adjuvant therapy, KATHERINE showed the potential benefit for adjuvant T-DM1 if residual disease is present after neoadjuvant therapy with taxane and trastuzumab-based treatment.

The results from ATEMPT and KATHERINE suggest that novel treatment regimens currently approved for advanced HER2-positive breast cancer may also be appropriate for adjuvant use in specific populations of patients with early-stage breast cancer. However, when deciding to administer regimens other than TH, it is important to balance iDFS, adverse effects, treatment discontinuation, financial toxicity, and quality of life. Multidisciplinary management of breast cancer is evolving based on RCTs evaluating de-escalation of therapy based on identifying populations that may be overtreated with current oncology regimens. We look forward to updates from the ATEMPT trial, results from the ATEMPT 2 trial, and any future phase III trials to potentially achieve a level of evidence sufficient to consider adopting this approach as standard of care. For this population of relatively low-risk patients with stage I HER2-positive breast cancer, results from the phase II ATEMPT trials are of interest but treatment discontinuations could be problematic in regard to recurrences. Long-term follow-up for the ATEMPT trial will be helpful to better understand the iDFS of this regimen.

REFERENCES

1. Slamon DJ, Godolphin W, Jones LA, Holt JA, Wong SG, Keith DE, et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science*. 1989;244(4905):707–12.
2. Howlader N, Cronin KA, Kurian AW, Andridge R. Differences in breast cancer survival by molecular subtypes in the United States. *Cancer Epidemiol Biomark Prev*. 2018;27(6):619–26.
3. Hudis CA. Trastuzumab—mechanism of action and use in clinical practice. *N Engl J Med*. 2007;357(1):39–51.
4. Mahtani R, Hineman L. Advances in HER2-positive breast cancer: novel therapies and adverse event management. *J Adv Practitioner Oncol*. 2019;10(2):136.
5. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, Davidson NE, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med*. 2005;353(16):1673–84.
6. Patel A, Unni N, Peng Y. The changing paradigm for the treatment of HER2-positive breast cancer. *Cancers*. 2020;12(8):2081.
7. Tolaney SM, Barry WT, Dang CT, Yardley DA, Moy B, Marcom PK, et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. *N Engl J Med*. 2015;372(2):134–41.
8. Tolaney SM, Guo H, Pernas S, Barry WT, Dillon DA, Ritterhouse L, et al. Seven-year follow-up analysis of adjuvant paclitaxel and trastuzumab trial for node-negative, human epidermal growth factor receptor 2–positive breast cancer. *J Clin Oncol*. 2019;37(22):1868.
9. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Breast Cancer, Version 4.2023. National Comprehensive Cancer Network; May 2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
10. Barok M, Joensuu H, Isola J. Trastuzumab emtansine: mechanisms of action and drug resistance. *Breast Cancer Res*. 2014;16(2):1–12.
11. Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med*. 2012;367(19):1783–91.
12. Tolaney SM, Tayob N, Dang C, Yardley DA, Isakoff SJ, Valero V, et al. Adjuvant trastuzumab emtansine versus paclitaxel in combination with trastuzumab for stage I HER2-positive breast cancer (ATEMPT): a randomized clinical trial. *J Clin Oncol*. 2021;39(21):2375–85.
13. Zhao M, Chen C, Zhang C, Xu X, Tian F, Wu B, et al. Cardiotoxicity with human epidermal growth factor receptor-2 inhibitors in breast cancer: Disproportionality analysis of the FDA adverse event reporting system. *Int J Cardiol*. 2023;375:87–93.
14. Nowsheen S, Viscuse PV, O'Sullivan CC, Sandhu NP, Haddad TC, Blaes A, et al. Incidence, diagnosis, and treatment of cardiac toxicity from trastuzumab in patients with breast cancer. *Curr Breast Cancer Rep*. 2017;9:173–82.
15. Sardesai S, Sukumar J, Kassem M, Palettas M, Stephens J, Morgan E, et al. Clinical impact of interruption in adjuvant Trastuzumab therapy in patients with operable HER-2 positive breast cancer. *Cardio-Oncology*. 2020;6(1):1–9.
16. Barroso-Sousa R, Tarantino P, Tayob N, Dang C, Yardley DA, Isakoff SJ, et al. Cardiac outcomes of subjects on adjuvant trastuzumab emtansine vs paclitaxel in combination with trastuzumab for stage I HER2-positive breast cancer (ATEMPT) study (TBCRC033): a randomized controlled trial. *NPJ Breast Cancer*. 2022;8(1):18.
17. Sella T, Zheng Y, Tayob N, Ruddy KJ, Freedman RA, Dang C, et al. Treatment discontinuation, patient-reported toxicities and quality-of-life by age following trastuzumab emtansine

or paclitaxel/trastuzumab (ATEMPT). *NPJ Breast Cancer*. 2022;8(1):127.
18. Bellon JR, Tayob N, Yang DD, Tralins J, Dang CT, Isakoff SJ, et al. Local therapy outcomes and toxicity from the ATEMPT trial (TBCRC 033): a phase II randomized trial of adjuvant trastuzumab emtansine versus paclitaxel in combination with trastuzumab in women with stage I HER2-positive breast cancer. *Int J Radiat Oncol Biol Phys*. 2022;113(1):117–24.
19. Ruddy KJ, Zheng Y, Tayob N, Hu J, Dang CT, Yardley DA, et al. Chemotherapy-related amenorrhea (CRA) after adjuvant ado-trastuzumab emtansine (T-DM1) compared to paclitaxel in combination with trastuzumab (TH)(TBCRC033: ATEMPT Trial). *Breast Cancer Res Treat*. 2021;189(1):103–10.
20. MagalhãesFilho MA, Aguiar PN Jr, Neves MB, et al. Cost-effectiveness analysis of Ado-trastuzumab emtansine for the treatment of residual invasive HER2-positive breast cancer. *Einstein (São Paulo)*. 2022;20:eGS6655.
21. Tolaney SM. ATEMPT 2.0: Adjuvant T-DM1 vs TH. ClinicalTrials.gov identifier: NCT04893109. Updated March 13, 2023. Available at: https://clinicaltrials.gov/study/NCT04893109. Accessed 12 Oct 2023.
22. Von Minckwitz G, Huang CS, Mano MS, Loibl S, Mamounas EP, Untch M, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med*. 2019;380(7):617–28.
23. US FDA. FDA approves ado-trastuzumab emtansine for early breast cancer. Silver Spring, MD: US FDA; 2019.