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FDA Approval Summary: Ado-Trastuzumab Emtansine for the Adjuvant Treatment of HER2-positive Early Breast Cancer

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ABSTRACT

On May 3, 2019, the FDA granted regular approval to ado-trastuzumab emtansine (KADCYLA), for the adjuvant treatment of patients with HER2-positive early-breast cancer (EBC) who have residual invasive disease after neoadjuvant taxane-based chemotherapy and trastuzumab-based treatment. Approval was based on data from the KATHERINE trial, which randomized patients to receive ado-trastuzumab emtansine or trastuzumab. At 3 years, the event-free rate for invasive disease-free survival in the ado-trastuzumab emtansine arm was 88.3% [95% confidence interval (CI), 85.8–90.7] compared with 77.0% (95% CI, 73.8–80.7) in the trastuzumab arm, (HR, 0.50; 95% CI, 0.39–0.64; $P < 0.0001$). Results from secondary endpoints, subgroup analyses, and sensitivity analyses generally supported the primary efficacy endpoint results. Common adverse reactions (>25% and higher incidence in ado-trastuzumab emtansine arm) with ado-trastuzumab emtansine were fatigue, nausea, increased transaminases, musculoskeletal pain, hemorrhage, thrombocytopenia, headache, peripheral neuropathy, and arthralgia. Ado-trastuzumab emtansine is the first drug approved for the treatment of patients with residual disease after neoadjuvant treatment and surgery. This article summarizes the FDA review and the data supporting the approval of ado-trastuzumab emtansine as a component of treatment for patients with HER2-positive EBC with residual disease.

Introduction

Approximately 15%–20% of human breast cancers overexpress HER2 (1). The overexpression of HER2 is associated with more aggressive disease (2, 3). Patients with early-breast cancers (EBC) that overexpress HER2 are more likely to experience local and distant recurrences in the setting of residual invasive disease following initial treatment with preoperative chemotherapy in combination with HER2-targeted therapy and surgery (4). However, the treatment paradigm of patients with both residual invasive disease and pathologic complete response (pCR) had previously been similar in the types of agents used and the duration of therapy, and consisted of continuation of the HER2-targeted therapy in the adjuvant setting to complete 1 year (18 cycles; ref. 5).

Ado-trastuzumab emtansine is a HER2-targeted antibody–drug conjugate containing the humanized anti-HER2 IgG1, trastuzumab, covalently linked to the microtubule inhibitory drug DM1, which is a maytansine derivative via the stable thioether linker MCC (4-[N-maleimidomethyl] cyclohexane-1-carboxylate). Ado-trastuzumab emtansine was first approved in the United States on February 22, 2013, for the treatment of patients with HER2-positive metastatic breast cancer who have received prior treatment with trastuzumab and a taxane, separately or in combination (6). As previously described, the approval was based primarily on the results of the primary analysis of efficacy and safety data from the EMILIA trial, which demonstrated a statistically significant improvement in progression-free survival (PFS) in the ado-trastuzumab emtansine–treated group, compared with the lapatinib plus capecitabine–treated group [HR, 0.65; 95% confidence interval (CI), 0.55–0.77; $P < 0.0001$], and an increase in estimated median PFS of 3.2 months (median PFS of 9.6 months in the ado-trastuzumab emtansine–treated group vs. 6.4 months in the lapatinib plus capecitabine group; refs. 7, 8). In an analysis of overall survival (OS) following the primary analysis of PFS, OS was significantly improved in patients receiving ado-trastuzumab emtansine (HR, 0.68; 95% CI, 0.55–0.85; $P = 0.0006$). The estimated median duration of survival was 30.9 months in the ado-trastuzumab emtansine arm compared with 25.1 months in the lapatinib plus capecitabine arm.

Clinical Trial Design

The adjuvant approval of ado-trastuzumab emtansine was based on a randomized, multicenter, multinational, open label study (KATHERINE; NCT01772472) in patients with HER2-positive primary breast cancer who had residual invasive disease in the breast or axillary lymph nodes after receiving preoperative chemotherapy and HER2-targeted therapy, including taxane and trastuzumab, followed by surgery (9). The primary objective was to compare invasive disease-free survival (IDFS) in patients randomized to receive ado-trastuzumab emtansine versus trastuzumab, within 12 weeks of surgery. IDFS was defined as the time between randomization and date of first occurrence of any one of the following events: invasive breast tumor recurrence in the breast, axilla, regional lymph nodes, chest wall, and/or skin; distant recurrence; or death attributable to any cause. Secondary objectives were to compare IDFS including second primary

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nonbreast cancers, disease-free survival (DFS) including ductal carcinoma *in situ*, and OS.

Eligible patients were randomized (1:1) to receive ado-trastuzumab emtansine 3.6 mg/kg given intravenously every 3 weeks, or trastuzumab 6 mg/kg given intravenously every 3 weeks (an 8 mg/kg loading dose was given in cases where there was an interval greater than 6 weeks since the last dose of trastuzumab). Treatment was administered for 14 cycles; treatment was discontinued prior to 14 cycles in the event of disease recurrence or unacceptable toxicity.

The trial planned to enroll a total of 1,486 patients. The final analysis of IDFS was to occur at 384 events with one interim analysis of IDFS planned at 67% information. An O'Brien-Fleming stopping boundary was used for the interim analysis of IDFS. A total of four analyses of OS were also planned: at the interim IDFS analysis (if the IDFS crossed the boundary), at final IDFS analysis, at approximately 2 years after the second OS interim analysis, and at the end of 10 years of follow-up. An O'Brien-Fleming boundary was used to control type I error for the interim OS analyses.

Patient reported outcomes were assessed using the EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires.

Results

Efficacy

KATHERINE enrolled 1,486 patients. The demographic and baseline disease characteristics of the intent-to-treat (ITT) population of the KATHERINE trial are shown in **Table 1** and **Table 2**.

The trial met the primary endpoint and demonstrated a statistically significant and clinically meaningful improvement in IDFS for ado-trastuzumab emtansine arm compared with the trastuzumab arm, in the ITT population, as shown in **Table 3** and **Fig. 1**.

Results from secondary endpoints, subgroup analyses, and sensitivity analyses generally supported the primary efficacy endpoint results. While there was a small numeric increase in the rate of central nervous system (CNS) recurrence that occurred as first site of distant recurrence (5.8% ado-trastuzumab emtansine arm vs. 4.0% trastuzumab arm), when limited to patients with a CNS recurrence, those taking ado-trastuzumab emtansine typically had longer time to a CNS recurrence event than those taking trastuzumab.

Data for OS were immature at the time of IDFS analysis [98 deaths (6.6%) occurred in 1,486 patients] but did not indicate a detrimental effect on this endpoint. The OS results for patients with a CNS event were similar between the two treatment arms.

Safety

Overall, the safety findings in the KATHERINE trial were consistent with the known safety profile of ado-trastuzumab emtansine. More patients receiving ado-trastuzumab emtansine experienced all-grade adverse events (AE), serious AEs (SAE), Grade ≥3 AEs, and AEs leading to discontinuation compared with trastuzumab.

The most common adverse drug reactions occurring in the ado-trastuzumab emtansine arm (>25%) included fatigue, nausea, increased transaminases, musculoskeletal pain, hemorrhage, thrombocytopenia, headache, peripheral neuropathy, and arthralgia. A higher incidence of AEs leading to treatment discontinuation was reported in the ado-trastuzumab emtansine arm (18.0%) compared with the trastuzumab arm (2.1%). The most commonly reported AEs leading to discontinuation in the ado-trastuzumab emtansine arm (≥1% patients) were: platelet count decreased (4.2%), blood bilirubin increased (2.6%), ejection fraction decreased (1.2%), aspartate aminotransferase (AST) increased (1.6%), alanine aminotransferase (ALT) increased (1.5%), and peripheral sensory neuropathy (1.5%).

Cardiac event rates were low in both treatment arms, with a numerically lower rate in the ado-trastuzumab emtansine arm (3.1%) than in the trastuzumab arm (5.6%). The increased incidence of hepatotoxicity was primarily driven by increases in ALT and AST. There were two nodular regenerative hyperplasia cases in patients receiving ado-trastuzumab emtansine, which is a known toxicity with ado-trastuzumab emtansine. Decreased platelet count was the most common SAE and Grade ≥3 AE in patients receiving ado-trastuzumab

Table 1. KATHERINE baseline demographics.

	Trastuzumab ($N = 743$)	Ado-trastuzumab emtansine ($N = 743$)
Age (years), median (range)	49 (23–80)	49 (24–79)
Female, *n* (%)	740 (99.6%)	741 (99.7%)
Race, *n* (%)		
American Indian or Alaskan native	50 (6.7%)	36 (4.8%)
Asian	64 (8.6%)	65 (8.7%)
Black	19 (2.6%)	21 (2.8%)
White	531 (71.5%)	551 (74.2%)
Other or unknown	79 (10.6%)	70 (9.4%)
Region, *n* (%)		
North America	164 (22.1%)	170 (22.9%)
Western Europe	403 (54.2%)	403 (54.2%)
Rest of World	176 (23.7%)	170 (22.9%)
Hormone receptor (positive), *n* (%)	210 (28.3%)	213 (28.7%)
Preoperative HER2 therapy, *n* (%)		
Trastuzumab	596 (80.2%)	600 (80.8%)
Trastuzumab + additional HER2 therapy	147 (19.8%)	143 (19.2%)
Preoperative pertuzumab (yes), *n* (%)	139 (18.7%)	133 (17.9%)
Prior anthracycline use (yes), *n* (%)	564 (75.9%)	579 (77.9%)
Menopausal status (post), *n* (%)	330 (44.4%)	344 (46.3%)
ECOG status (0), *n* (%)	613 (82.5%)	597 (80.3%)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

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Table 2. KATHERINE baseline disease characteristics.

	Trastuzumab (*N* = 743)	Ado-trastuzumab emtansine (*N* = 743)
Histologic subtype, *n* (%)		
Ductal	679 (91.4%)	688 (92.6%)
Lobular	38 (5.1%)	21 (2.8%)
Not otherwise specified	17 (2.3%)	16 (2.2%)
Other	9 (1.2%)	18 (2.4%)
Histologic grade, *n* (%)		
Well differentiated	56 (7.5%)	57 (7.7%)
Moderately differentiated	263 (35.4%)	276 (37.1%)
Poorly differentiated	283 (38.1%)	282 (38.0%)
Unknown	141 (19.0%)	128 (17.2%)
Primary tumor stage (at surgery), *n* (%)		
ypT0, ypT1a, ypT1b, ypT1mic, ypT1is	306 (41.2%)	331 (44.5%)
ypT1, ypT1c	184 (24.8%)	175 (23.6%)
ypT2	185 (24.9%)	174 (23.4%)
ypT3	57 (7.7%)	51 (6.9%)
ypT4, ypT4a, ypT4b, ypT4c	9 (1.2%)	7 (0.9%)
ypTd	1 (0.1%)	5 (0.7)
ypTX[a]	1 (0.1%)	0 (0.0%)
Lymph node stage (at surgery), *n* (%)		
cN0	335 (45.1%)	344 (46.3%)
cN1	213 (28.7%)	220 (29.6%)
cN2	103 (13.9%)	86 (11.6%)
cN3	30 (4.0%)	37 (5.0%)
cNX[b]	62 (8.3%)	56 (7.5%)

[a]Primary tumor stage unknown.
[b]Lymph node stage unknown.

emtansine. Three patients (0.4%) in the ado-trastuzumab emtansine arm and 2 patients (0.3%) in the trastuzumab arm had at least one Grade ≥3 AE hemorrhage. Four of these patients had resolution of their AE; 1 patient in the ado-trastuzumab emtansine arm had a fatal AE of intracranial hemorrhage associated with a traumatic fall and Grade 2 platelet count decreased.

KATHERINE permitted patients who prematurely discontinued ado-trastuzumab emtansine, for reasons other than disease recurrence, to receive trastuzumab for the remainder of their treatment course, if considered appropriate. Seventy-one of the 196 patients (26.4%) who met this criterion received trastuzumab.

Adjuvant radiotherapy with ado-trastuzumab emtansine was permitted as part of standard-of-care treatment, and, thus, the majority of patients (84.2%) in the study had concurrent radiation with ado-trastuzumab emtansine. Pulmonary toxicity was 2.8% in the ado-trastuzumab emtansine arm compared with 0.8% in the trastuzumab arm. The most commonly reported pulmonary toxicity AEs (in at least 1% of patients) were radiation pneumonitis (1.5% for ado-trastuzumab

Table 3. Efficacy results from KATHERINE.

	Trastuzumab (*N* = 743)		Ado-trastuzumab emtansine (*N* = 743)
IDFS			
Events, *n* (%)	165 (22.2%)		91 (12.2%)
HR (95% CI)		0.50 (0.39–0.64)	
P		<0.0001	
3-year event-free rate, (95% CI)	77.0 % (73.8%–80.7%)		88.3% (85.8%–90.7%)
IDFS including second primary nonbreast cancer			
Events, *n* (%)	167 (22.5%)		95 (12.8%)
HR (95% CI)		0.51 (0.40–0.66)	
3-year event-free rate (95% CI)	76.9% (73.7%–80.1%)		87.7% (85.2%–90.2%)
DFS			
Events, *n* (%)	167 (22.5%)		98 (13.2%)
HR (95% CI)		0.53 (0.41–0.68)	
3-year event-free rate (95% CI)	76.9% (73.7%–80.1%)		87.4% (84.9%–89.9%)

Note: Results of IDFS were obtained from the prespecified interim analysis (67% of the number of events for the planned final analysis) with the *P* value compared with the allocated alpha of 0.0124; HR and *P* values were obtained from unstratified analyses; 3-year event-free rates were obtained from Kaplan–Meier estimates.

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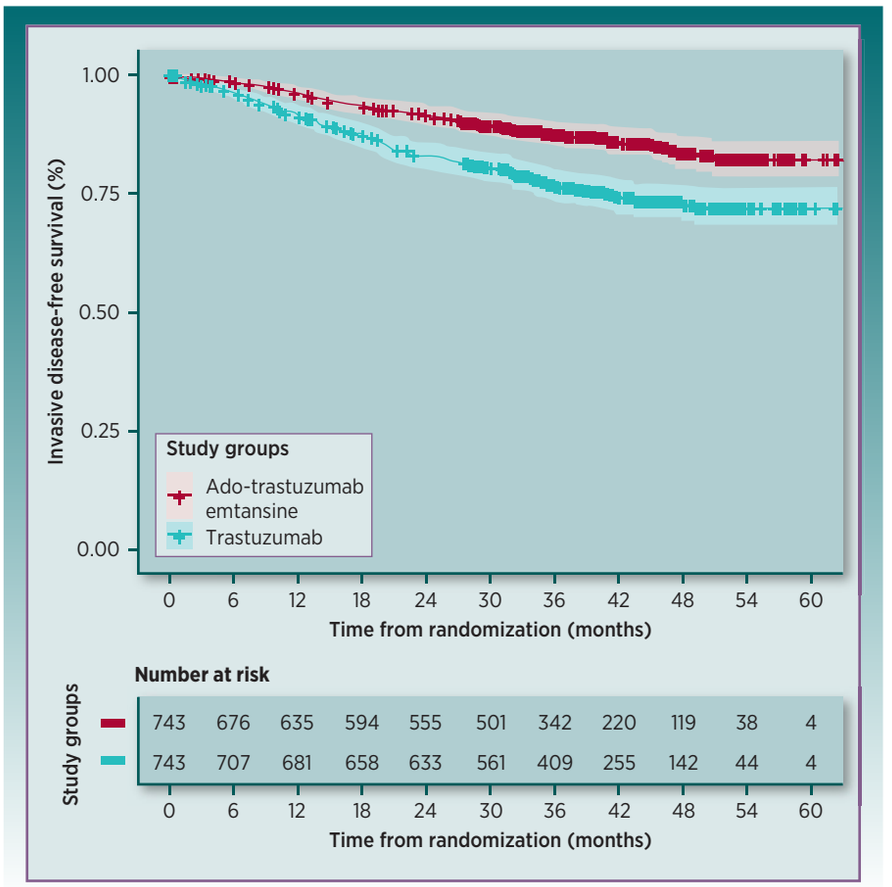
Figure 1.
KATHERINE IDFS Kaplan–Meier plot.



emtansine vs.0.7% for trastuzumab) and pneumonitis (0.1% vs. 1.1%). No AE of Grade 4 or 5 was reported. The majority of pneumonitis/radiation pneumonitis events were of Grade 1–2 and reversible.

Patient-reported outcomes

Patient-reported outcomes (PRO) were assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and EORTC QLQ-BR23 (breast module). The scales measuring function and global health status/health-related quality of life (GHS/QoL) are transformed onto a 0–100 scoring scale, where higher scores indicate better functioning, whereas for symptoms, higher scores indicate the symptom is worse (10, 11). Patients completed a PRO assessment at baseline, cycles 5, and 11, and at the end of treatment. The completion rates for EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires were similar between the treatment arms at baseline (>84%). Completion rates were maintained above 83% through cycle 11 for both arms.

Analysis of PRO endpoints was not prespecified with type I error allocation. Exploratory objectives were to evaluate PRO measures of GHS/QoL, function, and disease/treatment-related symptoms associated with both treatment arms. With regard to the physical functioning subscale: for patients who completed a baseline PRO assessment and a follow-up PRO assessment, small mean changes in physical functioning were observed at cycles 5 and 11 and were similar in both arms (cycle 5 mean change ado-trastuzumab −1.6 and trastuzumab 0.3; cycle 11 mean change ado-trastuzumab −0.6 and trastuzumab 1.9). There did not appear to be large differences for treatment-related symptoms including nausea, vomiting, diarrhea, constipation, and fatigue between the treatment arms. However, more patients reported a dry mouth in the ado-trastuzumab emtansine arm compared with the trastuzumab arm (ado-trastuzumab emtansine 71.9% vs. trastuzumab 39.1% at cycle 5; ado-trastuzumab emtansine 66.4% vs. trastuzumab 39.5% at cycle 11).

Regulatory Insights

Historically, drug development trials in early-stage breast cancer were conducted in the adjuvant setting, adding drugs to standard systemic therapy. Realizing challenges with lengthy follow-up and particularly high unmet medical need in certain early-stage breast cancer populations, FDA proposed using pCR rate as a new endpoint to facilitate drug development (12). The use of pCR as a regulatory endpoint was supported by a meta-analysis of 11,955 patients with EBC demonstrating, at an individual level, an improvement in clinical outcomes when pCR is achieved (13). However, to date, FDA has only granted accelerated approval to one drug, pertuzumab, based on improvement of pCR rate in the neoadjuvant setting. This approval was based on the totality of evidence, including results from the neoadjuvant study demonstrating a near doubling of the pCR rate, the significant OS improvement seen with pertuzumab treatment in the metastatic setting, known safety profile, and fully enrolled confirmatory trial in the adjuvant setting (14, 15). Despite the magnitude

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Table 4. FDA risk-benefit assessment.

Dimension	Evidence and uncertainties	Conclusions and reasons
Analysis of condition	• Approximately 15%–20% of human breast cancers overexpress the HER2. • Local and distant breast cancer recurrence remains a major health concern for patients with HER2-positive EBC.	• Patients with HER2-positive disease without pCR after preoperative treatment are at increased risk of disease recurrence.
Current treatment options	• Patients with HER2-positive EBC are recommended to complete a total of 1 year of trastuzumab-containing treatment, regardless of the presence of residual disease after preoperative treatment.	• There is an unmet medical need to develop therapies for patients with HER2-positive EBC and residual invasive disease after preoperative therapy and surgery.
Benefit	• Ado-trastuzumab emtansine demonstrated an improvement in IDFS (HR, 0.50; 95% CI, 0.39–0.64; $P < 0.0001$) compared with trastuzumab for patients with residual invasive disease following treatment preoperative chemotherapy and HER2-targeted therapy followed by surgery.	• Evidence of effectiveness was supported by a statistically significant and clinically meaningful improvement in IDFS.
Risk and risk management	• AEs, SAEs, and dose modifications were more common with ado-trastuzumab emtansine. • The most common NCI CTCAE Grade ≥3 AEs (>2%) were thrombocytopenia and hypertension. • Two new AEs included in the United States Package Insert (USPI) include radiation pneumonitis and blood bilirubin increased.	• The safety profile of ado-trastuzumab emtansine is acceptable for the intended population, and manageable with current labeling and routine oncology care. Warnings and precautions in labeling detail the serious risks of the drug.

of pCR improvement, results from primary analysis of the confirmatory trial, although statistically significant, demonstrated only a small absolute difference in IDFS at 3 years in the ITT population (16). Residual uncertainty remains regarding the magnitude of pCR improvement that would lead to a meaningful improvement in long term outcomes.

In contrast, the approval of ado-trastuzumab emtansine was the first breast cancer approval based on treatment of a high-risk population following standard neoadjuvant therapy and surgery. This trial utilizes pCR in a novel way to select for a high-risk population and minimize potential overtreatment and resultant serious toxicities. Using residual invasive disease to target a high-risk population expected to have an increased event rate allows for an enrichment design that would lend to smaller and faster trials (17).

There are some limitations to the KATHERINE study design. Although a strength of the study involved the ability to enrich the trial with a high-risk population, an inherent limitation is that ado-trastuzumab emtansine was not studied in patients who developed a pCR and thus the potential to also improve efficacy in that population was not assessed. The optimal duration of therapy was also not investigated, and it is not known whether a shorter course of ado-trastuzumab emtansine would be beneficial. Finally, this study was initiated before pertuzumab was approved in the adjuvant setting and neratinib was approved for extended adjuvant therapy in the United States. Less than 20% of patients on the KATHERINE study received pertuzumab in the neoadjuvant setting and no patients received neratinib leaving residual uncertainties about use in clinical practice.

Conclusions

In summary, treatment with adjuvant ado-trastuzumab emtansine demonstrated a statistically significant and clinically meaningful improvement in IDFS in patients with HER2-positive EBC who had residual invasive disease after preoperative therapy. In general, FDA's assessment of clinical meaningfulness is context-dependent and takes into account many factors including the clinical setting, trial design, and medical need, while weighing the risks/toxicities with the benefit of the drug. In this population at higher risk of recurrence, these results indicate a substantial benefit compared with trastuzumab. More patients receiving ado-trastuzumab emtansine experienced all-grade AEs, SAEs, Grade ≥3 AEs, and AEs leading to discontinuation compared with trastuzumab, as would be expected of ado-trastuzumab emtansine given its cytotoxic component. The OS data were immature at the time of IDFS analysis and will be followed up as part of a post-marketing commitment. Overall, the safety profile of this agent was deemed acceptable for this patient population with a serious and life-threatening disease in the curative setting and given the large improvement in IDFS, the benefit/risk profile was favorable to recommend approval of ado-trastuzumab emtansine for this indication (**Table 4**). The post-neoadjuvant residual disease setting provides an excellent opportunity for high-risk trial enrichment and potential for efficient drug development particularly for HER2-positive and triple-negative breast cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The Editor handling the peer review and decision-making process for this article has no relevant employment associations to disclose.

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