Kadcyla (Ado-Trastuzumab Emtansine):
First Antibody-Drug Conjugate Approved for the Treatment of HER2-Positive Metastatic Breast Cancer

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Approximately 25% of women who are diagnosed with breast cancer have HER2-positive tumors. The *HER2* gene, which resides on chromosome 17, directs tumor cells to manufacture HER2 protein. This protein is a cell-surface receptor that compels the tumor cell to grow and to divide more frequently than normal, making HER2-positive breast cancer an aggressive phenotype.

Before the advent of HER2-directed therapies, patients diagnosed with HER2-positive disease had significantly shorter disease-free survival compared with patients with other breast cancer subtypes.[1]

Unmet Need in Trastuzumab-Resistant Breast Cancer

The American Cancer Society estimates that approximately 232,340 women will be diagnosed with invasive breast cancer, and approximately 39,620 deaths will occur from the disease in 2013.[2] Since 1989, death rates from breast cancer have declined, with relatively larger decreases in women aged <50 years, in part as a result of earlier detection and increasingly improved treatments.[2]

Much of the increased survival for patients with HER2-positive breast cancer is attributed to the development of HER2-targeted therapies, including trastuzumab (Herceptin), pertuzumab (Perjeta), and lapatinib (Tykerb).[3] The first phase 3 clinical trial that compared trastuzumab plus chemotherapy versus chemotherapy alone in patients with HER2-positive metastatic breast cancer demonstrated robust improvements in response rate (50% vs 32%, respectively), median time to progression (7.4 months vs 4.6 months, respectively), and median overall survival ([OS] 25.1 months vs 20.3 months, respectively) with the addition of trastuzumab.[4] In addition, 2 meta-analyses have confirmed the OS benefit of adding HER2-targeted therapy to standard treatment in patients with early-stage or metastatic HER2-positive breast cancer.[5,6]

However, primary and secondary resistance to trastuzumab occurs in the advanced breast cancer setting: none of these patients is cured. In 2013, approximately 13,000 patients with HER2-positive metastatic breast cancer will have disease recurrence after trastuzumab treatment.[7] Concerted efforts are under way to identify the mechanisms of trastuzumab resistance, as well as novel "druggable" targets for this patient population.[8]

Currently, treatment strategies for patients with trastuzumab-resistant HER2-positive breast cancer are selected on the basis of patient-specific factors (ie, age, comorbidities), disease- related factors, and cost.[9] Therapy alternatives include the combination of pertuzumab, trastuzumab, and a taxane; lapatinib plus trastuzumab; lapatinib plus capecitabine; and the continued use of trastuzumab plus chemotherapy.[10]

FDA Approval of Ado-Trastuzumab Emtansine Fills an Unmet Need

In February 2013, the US Food and Drug Administration (FDA) granted accelerated approval for ado-trastuzumab emtansine (Kadcyla; Genentech, Inc), also known as T-DM1, for the treatment of patients with HER2-positive metastatic breast cancer who were previously treated with trastuzumab and with taxanes.[11] The approval was based on the result of a single, open-label trial of patients with HER2-positive metastatic breast cancer: T-DM1 demonstrated a significant 5.8-month improvement in median OS and a 3.2-month improvement in median progression-free survival (PFS) compared with the combination of lapatinib plus capecitabine.[12]

In an interview regarding T-DM1, Hope S. Rugo, MD, Director, Breast Oncology Clinical Trials Program, University of California, San Francisco, stated, "Use of the immunoconjugate—trastuzumab linked to a microtubule inhibitor [DM1]—was shown in trials to be better in every way: response, progression-free survival, overall survival, and tolerability."[9]

According to the drug manufacturer, 1 cycle (once in 21 days) of T-DM1 costs $9800.

Dosing and Administration

T-DM1 is administered intravenously at 3.6 mg/kg on day 1 of a 21-day cycle. No loading dose or premedica-

tions are required. Treatment with T-DM1 should be continued until disease progression or until unacceptable toxicity occurs.

For the first infusion, T-DM1 should be administered over 90 minutes. Patients should be observed during the infusion and for at least 90 minutes after the initial dose for fever, chills, or other infusion-related reactions. For subsequent infusions, T-DM1 can be administered over 30 minutes if previous infusions were well tolerated. Patients should be observed during the infusion and for at least 30 minutes after.

T-DM1 should not be administered at doses greater than 3.6 mg/kg. T-DM1 should not be substituted for or coadministered with trastuzumab.[12]

Dose Modifications Based on Toxicity

The dose of T-DM1 may be modified if hematologic or nonhematologic toxicities occur, including grade 3 or 4 cytopenias; cardiac, hepatic, or renal toxicities; pulmonary complications; neurotoxicity; or other toxicities. In general, T-DM1 is withheld until resolution, followed by restarting therapy at the same dose or at a reduced dose, depending on the type of toxicity and whether it was attributable to T-DM1.[12]

Mechanism of Action

T-DM1 is a HER2-targeted antibody drug conjugate. The antibody is the humanized anti-HER2 immunoglobulin G1, ado-trastuzumab. The small-molecule drug DM1 is a microtubule inhibitor. On binding to subdomain IV of the HER2 receptor, T-DM1 undergoes receptor-mediated internalization and lysosomal degradation, resulting in intracellular release of DM1-containing cytotoxic catabolites. Binding of DM1 to tubulin disrupts microtubule networks in the cell, resulting in cell-cycle arrest and cell death. In vitro studies have shown that similar to 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 the *HER2* gene.[12]

The availability of an antibody drug conjugate for selected patients with breast cancer offers an exciting and novel approach, particularly for women who wish to avoid the side effects of chemotherapy. According to Julie R. Gralow, MD, Director, Breast Medical Oncology, Seattle Cancer Care Alliance, WA, T-DM1 "is a true magic bullet. For the 20% to 25% of breast cancer patients that have HER2-positive breast cancer (HER2-expressing breast cancer), this is an antibody that can take chemotherapy directly to the tumor cell and deliver it inside the cell. Then the bulk of the body does not get exposed to the chemotherapy."[13]

EMILIA: A Phase 3 Clinical Trial

T-DM1 was approved by the FDA based on the results of the EMILIA trial, a randomized, multicenter, open-label trial of 991 patients with HER2-positive, unresectable, locally advanced or metastatic breast cancer.[15] Previous taxane- and trastuzumab- based therapies were required before trial enrollment. Patients who had only received previous adjuvant therapy were required to have disease recurrence during or within 6 months of completing adjuvant therapy. Tumor samples were required to show evidence of HER2 overexpression, defined as 3+ immunohistochemistry by Dako's HercepTest, or evidence of HER2 overexpression defined as a fluorescence in situ hybridization (FISH) amplification ratio of ≥2.0 by Dako's HER2 FISH pharmDx test kit.[12,14]

Trial Design and Patient Population. Patients in the EMILIA trial were randomized to T-DM1 or to lapatinib plus capecitabine.[12] Randomization was stratified by world region (ie, United States, Western Europe, or other), the number of previous chemotherapy regimens used for unresectable locally advanced or metastatic disease, and by visceral versus nonvisceral disease as determined by the investigators.

T-DM1 was given intravenously at 3.6 mg/kg on day 1 of a 21-day cycle. Lapatinib was administered orally at 1250 mg once daily in a 21-day cycle. Capecitabine was administered orally at 1000 mg/m^2 twice daily on days 1 through 14 of a 21-day cycle.

Patients were treated with T-DM1 or with lapatinib plus capecitabine until disease progression, consent withdrawal, or until reaching an unacceptable toxicity level.[12]

The patient demographics and baseline tumor characteristics were balanced between treatment arms in the EMILIA trial.[12] All patients had metastatic disease at study entry. The median age was approximately 53 years (range, 24-84 years); 74% of patients were white, 18% were Asian, and 5% were black. All but 5 patients were women. Tumor prognostic characteristics, including hormone receptor status (positive, 55%; negative, 43%), presence of visceral disease (68%) and nonvisceral disease only (33%), and the number of metastatic sites (<3, 61%; ≥3, 37%), were similar in the study arms.[12]

Efficacy. Of the 991 patients who were enrolled in the EMILIA trial, 978 received treatment.[15] The median dose intensity was 99.9% for patients receiving T-DM1, 77.2% for patients receiving capecitabine, and 93.4% for patients treated with lapatinib. The key study findings are summarized in **Table 1**.

Dose reduction was necessary for 16.3% of patients in the T-DM1 arm; capecitabine doses and lapatinib doses were reduced for 53.4% and 27.3% of the patients, respectively.[15]

At the time of the primary efficacy analysis, median

time with therapy was 5.7 months for T-DM1, 4.9 months for lapatinib, and 4.8 months for capecitabine.[12] The coprimary efficacy end points were PFS based on tumor response assessments by an independent review committee and on OS.

PFS was defined as the time from the date of randomization to the date of disease progression or death from any cause (whichever occurred earlier). OS was defined as the time from the date of randomization to the date of death from any cause.

Secondary end points included PFS based on investigator tumor response assessments, objective response rate, duration of response, and time to symptom progression.[12]

Subgroup analyses using baseline patient characteristics indicated that the use of single-agent T-DM1 was superior to lapatinib plus capecitabine for all patient subsets except those aged ≥65 years.[14] A subsequent biomarker analysis demonstrated that patients in EMILIA whose tumors expressed high HER2 messenger RNA levels derived more benefit from T-DM1 than patients with lower levels of expression. In high HER2 expressors, the median PFS was 34.1 months with T-DM1 versus 24.8 months with lapatinib plus capecitabine.[16]

Safety Profile

Single-agent T-DM1 has been evaluated in 884 patients with HER2-positive metastatic breast cancer.[12] These patients received a median of 7.6 months of T-DM1 treatment. The most common (frequency, ≥25%) drug-related adverse events (AEs) seen in patients receiving T-DM1 were fatigue, nausea, musculoskeletal pain, thrombocytopenia, headache, increased transaminases, and constipation. Grades 3 and 4 AEs were reported in 43.1% of patients receiving T-DM1 and in 59.2% of patients receiving lapatinib plus capecitabine.

Overall, 32 (6.5%) patients discontinued T-DM1 as a result of an AE. The most common AEs leading to T-DM1 withdrawal were thrombocytopenia and increased transaminases.

Eighty (16.3%) patients receiving T-DM1 experienced AEs leading to dose reductions. These AEs included thrombocytopenia, increased transaminases, and peripheral neuropathy.

AEs that led to dose delays occurred in 23.7% of patients receiving T-DM1 and included neutropenia, thrombocytopenia, leukopenia, fatigue, increased transaminases, and pyrexia.[12]

Hepatotoxicity. Serious hepatotoxicity has been reported, including liver failure and death, in patients receiving T-DM1. Serum transaminases and bilirubin should be monitored before the initiation of T-DM1 treatment and before each T-DM1 dose. The dose of

Table 1	EMILIA: Efficacy End Points of Ado-Trastuzumab Emtansine versus Lapatinib plus Capecitabine	
Outcome parameter	Ado-trastuzumab emtansine (N = 495)	Lapatinib plus capecitabine (N = 496)
PFS (independent review) Patients, N (%) Median PFS, mo	265 (53.5) 9.6	304 (61.3) 6.4
Hazard ratio, stratified[a] (95% CI) P value (log-rank test, stratified[a])	0.650 (0.549-0.771) <.001	
Overall survival[b] Patients, N (%) Median survival, mo	149 (30.1) 30.9	182 (36.7) 25.1
Hazard ratio, stratified[a] (95% CI) P value (log-rank test[a])	0.682 (0.548-0.849) .006	
OR rate (independent review) Patients with measurable disease, N Patients with OR, N (%)	397 173 (43.6)	389 120 (30.8)
Difference (95% CI)	12.7 (6.0-19.4)	
Duration of OR, mo Patients with OR, N Median duration, mo (95% CI)	173 12.6 (8.4-20.8)	120 6.5 (5.5-7.2)

[a]Stratified by world region (ie, United States, Western Europe, or other), number of previous chemotherapeutic regimens for locally advanced or metastatic disease (0-1 vs >1), and visceral versus nonvisceral disease.
[b]The second interim analysis for OS was conducted when 331 events were observed. The results are presented in this table.
CI indicates confidence interval; OR, objective response; PFS, progression- free survival.
Source: Kadcyla (ado-trastuzumab emtansine) for injection [prescribing information]. South San Francisco, CA: Genentech, Inc; February 2013.

T-DM1 should be reduced or discontinued as appropriate in cases of increased serum transaminases or increased total bilirubin.[12]

Cardiac Toxicity. T-DM1 administration may lead to reductions in left-ventricular ejection fraction. Left-ventricular function should be evaluated in all patients before and during treatment with T-DM1. Treatment should be withheld if a clinically significant decrease in left-ventricular function is detected.[12]

Warnings and Precautions

A number of adverse reactions associated with T-DM1 are discussed in the "Warnings and Precautions" section of the prescribing information and are summarized in **Table 2**.[12]

Table 2	Ado-Trastuzumab Emtansine: Warnings and Precautions
Warnings and precautions	**Description**
Infusion reactions	• Occurred in 1.4% of patients receiving the drug; 1 case of a serious, allergic/anaphylactic-like reaction was reported • Characterized by flushing, chills, pyrexia, dyspnea, hypotension, wheezing, bronchospasm, tachycardia • Monitor patients closely for infusion reactions, particularly during first infusion
Extravasation	• Occurs within 24 hours of infusion • Characterized by mild erythema, tenderness, skin irritation, pain, swelling at the infusion site • Monitor the infusion site closely for possible subcutaneous infiltration during administration
Thrombocytopenia	• Occurred in 31.2% of patients; 14.5% were grade 3/4 • Higher incidence and severity of thrombocytopenia were noted in Asian patients • Monitor platelet counts frequently
Peripheral neuropathy	• Occurred in 21.2% of patients; 2.2% were grade 3/4 • Monitor frequently for signs and symptoms of neurotoxicity
Hepatic toxicity and hepatic failure	• Mainly asymptomatic transient increases in serum transaminase concentrations • Because T-DM1 can cause elevated serum transaminases and bilirubin, liver enzymes should be monitored frequently • Serious hepatobiliary disorders, including ≥2 deaths resulting from severe drug-induced liver injury and associated hepatic encephalopathy, were reported • Of 884 patients in T-DM1 clinical trials, 3 had NRH of the liver identified from liver biopsies; consider NRH in patients with clinical symptoms of portal hypertension, normal transaminases, and no manifestations of cirrhosis
Left-ventricular dysfunction	• A decrease of LVEF to <40% has been observed in patients treated with T-DM1 • Left-ventricular dysfunction occurred in 1.8% of patients receiving T-DM1 and in 3.3% of patients treated with lapatinib plus capecitabine in the randomized trial • Assess LVEF before initiation of T-DM1 and at regular intervals (eg, every 3 months) during treatment to ensure LVEF is within the institution's normal limits
Pulmonary toxicity	• Cases of interstitial lung disease (eg, pneumonitis), including some leading to acute respiratory distress syndrome or death, have been reported • Pneumonitis incidence was 0.8% in clinical trials, including 1 case of grade 3
Embryo-fetal toxicity	• Exposure to T-DM1 can result in embryo-fetal death or birth defects • Patients should be advised of this risk and the need for effective contraception

LVEF indicates left-ventricular ejection fraction; NRH, nodular regenerative hyperplasia; T-DM1, ado-trastuzumab emtansine.
Source: Kadcyla (ado-trastuzumab emtansine) for injection [prescribing information]. South San Francisco, CA: Genentech, Inc; February 2013.

The FDA has issued a warning to prescribers advising that they should add "ado-" to the nonproprietary name "trastuzumab" when discussing T-DM1 to avoid confusion between Herceptin and Kadcyla, which was reported in clinical trials.[17]

Conclusion

T-DM1, which several experts have called a "magic bullet," combines trastuzumab and DM1 without causing traditional chemotherapy side effects, such as alopecia, neutropenia, or vomiting. For first-, second-, and third-line patients with HER2-positive metastatic breast cancer who are resistant to trastuzumab and to taxanes, single-agent T-DM1 offers clinically and statistically significant OS and PFS benefits, with a favorable tolerability profile on a convenient, once-every-3-week dosing schedule. ■

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