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Kadcyla™
ado-trastuzumab emtansine

KADCYLA™ (ado-trastuzumab emtansine) Is the First FDA-Approved Antibody-Drug Conjugate (ADC) for HER2-Positive Metastatic Breast Cancer

DISEASE STATE OVERVIEW

- In 2013, 232,340 women are expected to be diagnosed with breast cancer in the U.S., and 39,630 are expected to die from it.[1]
- Breast cancer is the most frequently diagnosed cancer in women* and is the second leading cancer killer among women.[1] From 2005–2009, the median age at diagnosis for cancer of the breast was 61 years of age.[2] Approximately 5% of breast cancer cases are metastatic at diagnosis.[2] Approximately 25% of breast cancers exhibit overexpression of the HER2 protein, amplification of the HER2 gene, or both.[3,4] Untreated metastatic HER2-positive breast cancer presents with an aggressive disease progression profile and poor patient outcomes.[5]
- In 2013, an estimated 13,000 women may require treatment for HER2-positive metastatic breast cancer following recurrence with first-line treatment.[6]
- 7–8% of HER2-positive adjuvant breast cancer patients (up to 576 patients) are estimated to develop disease recurrence during or within 6 months of completing adjuvant therapy.[7]

*Excluding cancers of the skin

INDICATION AND DOSING

- KADCYLA™ (ado-trastuzumab emtansine) injection, for intravenous use, as a single agent, is indicated for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either:
  - Received prior therapy for metastatic disease, or
  - Developed disease recurrence during or within six months of completing adjuvant therapy.[8]
- The recommended dose of KADCYLA is 3.6 mg/kg given as an intravenous infusion every 3 weeks (21-day cycle).[8] There is no loading dose required.
- KADCYLA should be continued until disease progression or until unacceptable toxicity.[8]

PROPOSED MECHANISM OF ACTION

- KADCYLA is a HER2-targeted ADC that exhibits the mechanisms of trastuzumab and the intracellular cytotoxic activity of DM1.[8]
- Based on preclinical models, KADCYLA has been shown to work via the following steps:[8]
  - HER2 binding: KADCYLA selectively binds to HER2 receptor at subdomain IV
  - Trastuzumab activity: inhibits HER2 signaling, triggers the ADCC* immune response, and inhibits HER2 shedding
  - Internalization: once bound, the KADCYLA/HER2 receptor complex is internalized via endocytosis
  - DM1† release: KADCYLA is degraded inside the cell to release DM1
  - DM1† cytotoxicity: DM1 binds to microtubules and inhibits their polymerization, causing cell-cycle arrest and cell death

*ADCC = antibody-dependent cell-mediated cytotoxicity
†The primary DM1-containing cytotoxic catabolite released is lysine-MCC-DM1

PRODUCT EFFICACY

- EMILIA, a pivotal randomized, multicenter, open-label, Phase III study (N=991), demonstrated statistically significant improvements in overall and progression-free survival in HER2-positive mBC patients previously treated with trastuzumab and a taxane.[8]
- The median age of patients in the pivotal study was approximately 53 years (range 24–84 years).[8]
- KADCYLA demonstrated a 5.8-month improvement in median overall survival (OS) and a 3.2-month improvement in median progression-free survival (PFS) as assessed by an independent review committee (IRC).[8]

Primary Endpoints	KADCYLA (n = 495)	Lapatinib + Capecitabine (n = 496)	HR (95% CI)	*P* value
Overall survival (median months)	30.9	25.1	0.682 (0.548, 0.849)	0.0006
Progression-free survival (median months)	9.6	6.4	0.650 (0.549, 0.771)	< 0.0001

- Patient demographics and baseline tumor characteristics were balanced between treatment arms. A treatment benefit with KADCYLA in terms of PFS and OS was observed in patient subgroups based on stratification factors, key baseline demographic and disease characteristics, and prior treatments.[8]

BOXED WARNINGS

Boxed WARNINGS: HEPATOTOXICITY, CARDIAC TOXICITY, EMBRYO-FETAL TOXICITY

- **Do Not Substitute KADCYLA for or with Trastuzumab**
- **Hepatotoxicity: Serious hepatotoxicity has been reported, including liver failure and death in patients treated with KADCYLA. Monitor serum transaminases and bilirubin prior to initiation of KADCYLA treatment and prior to each KADCYLA dose. Reduce dose or discontinue KADCYLA as appropriate in cases of increased serum transaminases or total bilirubin**
- **Cardiac Toxicity: KADCYLA administration may lead to reductions in left ventricular ejection fraction (LVEF). Evaluate left ventricular function in all patients prior to and during treatment with KADCYLA. Withhold treatment for clinically significant decrease in left ventricular function**
- **Embryo-Fetal Toxicity: Exposure to KADCYLA can result in embryo-fetal death or birth defects. Advise patients of these risks and the need for effective contraception**

Please see reverse for additional important safety information and accompanying full Prescribing Information, including Boxed WARNINGS.

Demonstrating the Value of Innovation

ADDITIONAL IMPORTANT SAFETY INFORMATION

- 43.1% of patients experienced ≥ Grade 3 adverse events in the KADCYLA-treated group compared with 59.2% of patients in the lapatinib+capecitabine-treated group.[8]
- 6.5% discontinued KADCYLA due to an adverse event, compared with 8.4% who discontinued lapatinib and 10.5% who discontinued capecitabine due to an adverse event.[8]

Additional Important Safety Information

Pulmonary Toxicity

- Cases of interstitial lung disease (ILD), including pneumonitis, some leading to acute respiratory distress syndrome or fatal outcome have been reported in clinical trials with KADCYLA. In EMILIA the overall frequency of pneumonitis was 1.2%.
- Treatment with KADCYLA should be permanently discontinued in patients diagnosed with ILD or pneumonitis.

Infusion-Related Reactions, Hypersensitivity Reactions

- Treatment with KADCYLA has not been studied in patients who had trastuzumab permanently discontinued due to infusion-related reactions (IRR) and/or hypersensitivity reactions; treatment with KADCYLA is not recommended for these patients.
- In EMILIA, the overall frequency of IRRs in patients treated with KADCYLA was 1.4%.
- KADCYLA treatment should be interrupted in patients with severe IRR and permanently discontinued in the event of a life-threatening IRR.

Thrombocytopenia

- In EMILIA, the incidence of ≥ Grade 3 thrombocytopenia was 14.5% in the KADCYLA-treated group and 0.4% in the comparator group.
- Monitor platelet counts prior to initiation of KADCYLA and prior to each KADCYLA dose. Institute dose modifications as appropriate.

Neurotoxicity

- In EMILIA, the incidence of ≥ Grade 3 peripheral neuropathy was 2.2% in the KADCYLA-treated group and 0.2% in the comparator group.
- Monitor for signs or symptoms of neurotoxicity. KADCYLA should be temporarily discontinued in patients experiencing Grade 3 or 4 peripheral neuropathy until resolution to ≤ Grade 2.

HER2 Testing

- Detection of HER2 protein overexpression or gene amplification is necessary for selection of patients appropriate for KADCYLA. Perform using FDA approved tests by laboratories with demonstrated proficiency.

Extravasation

- In KADCYLA clinical studies, reactions secondary to extravasation have been observed and were generally mild. The infusion site should be closely monitored for possible subcutaneous infiltration during drug administration.

Nursing Mothers

- Discontinue nursing or discontinue KADCYLA taking into consideration the importance of the drug to the mother.

Pregnancy Registry

- Encourage women who may be exposed to KADCYLA during pregnancy to enroll in the MotHER Pregnancy Registry by contacting 1-800-690-6720.

Adverse Reactions

- The most common ADRs seen with KADCYLA in EMILIA (frequency > 25%) were nausea, fatigue, musculoskeletal pain, thrombocytopenia, increased transaminases, headache, and constipation. The most common NCI-CTCAE (version 3) ≥ Grade 3 ADRs (frequency >2%) were thrombocytopenia, increased transaminases, anemia, hypokalemia, peripheral neuropathy and fatigue.

You are encouraged to report side effects to Genentech and the FDA. You may contact Genentech by calling 1-888-835-2555. You may contact the FDA by visiting www.fda.gov/medwatch or calling 1-800-FDA-1088.

SUPPLY AND DISTRIBUTION

- KADCYLA (ado-trastuzumab emtansine) is available through authorized specialty distributors and wholesalers.
- KADCYLA is supplied as a lyophilized powder in single-use vials: 100 mg per vial (NDC 50242-088-01) or 160 mg per vial (NDC 50242-087-01). Store vials in a refrigerator at 2-8°C (36-46°F) until time of use.[8]

Please see KADCYLA full Prescribing Information including Boxed WARNINGS for additional Important Safety Information.

References: 1. American Cancer Society. Cancer Facts & Figures 2013. Atlanta, GA: American Cancer Society; 2013. **2.** SEER Stat Fact Sheets: Breast. National Cancer Institute Web site. http://seer.cancer.gov/statfacts/html/breast.html. Accessed February 14, 2013. **3.** Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science.* 1987;235(4785):177-182. **4.** Slamon DJ, Godolphin W, Jones LA, et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science.* 1989;244(4905):707-712. **5.** Wolff AC, Hammond ME, Schwartz JN, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *J Clin Oncol.* 2007;25(1):118-145. **6.** Data on file, Genentech, Inc. **7.** Slamon DJ, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med.* 2011;365(14):1273-83. **8.** KADCYLA™ (ado-trastuzumab emtansine) full prescribing information. Genentech, Inc., February 2013.

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