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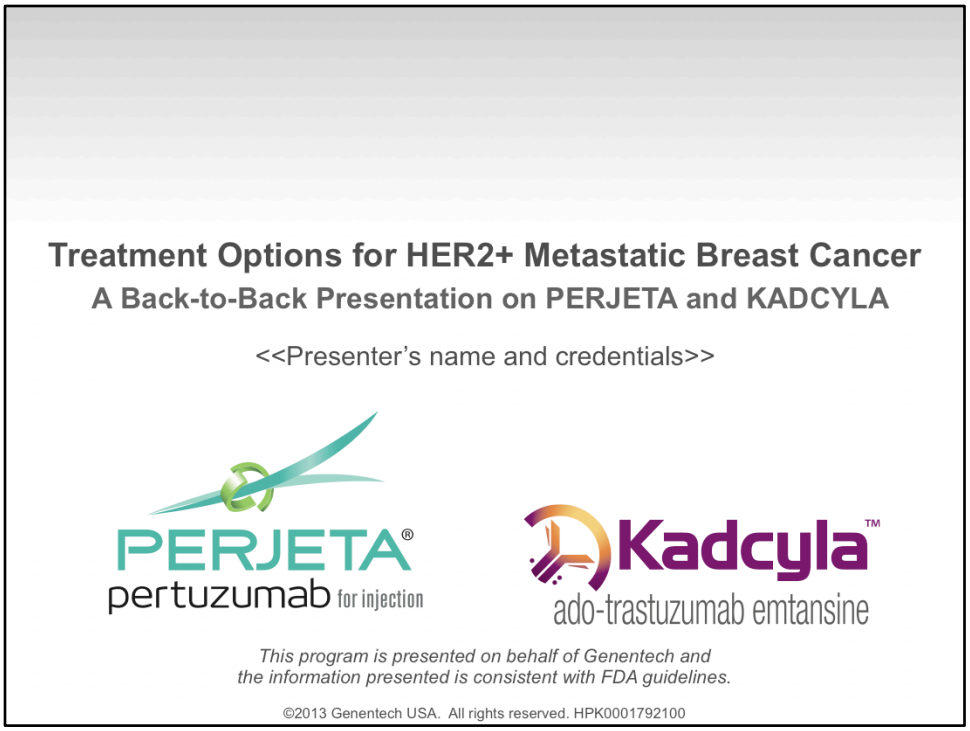

Introduction

Hello. My name is <<name>>. I'm an oncology clinical coordinator (OCC) with Genentech. Today there will be back-to-back presentations focusing on PERJETA and KADCYLA, which are treatment options for human epidermal growth factor receptor 2 positive (HER2+) metastatic breast cancer (MBC).

This program is presented on behalf of Genentech, and the information presented is consistent with FDA guidelines.

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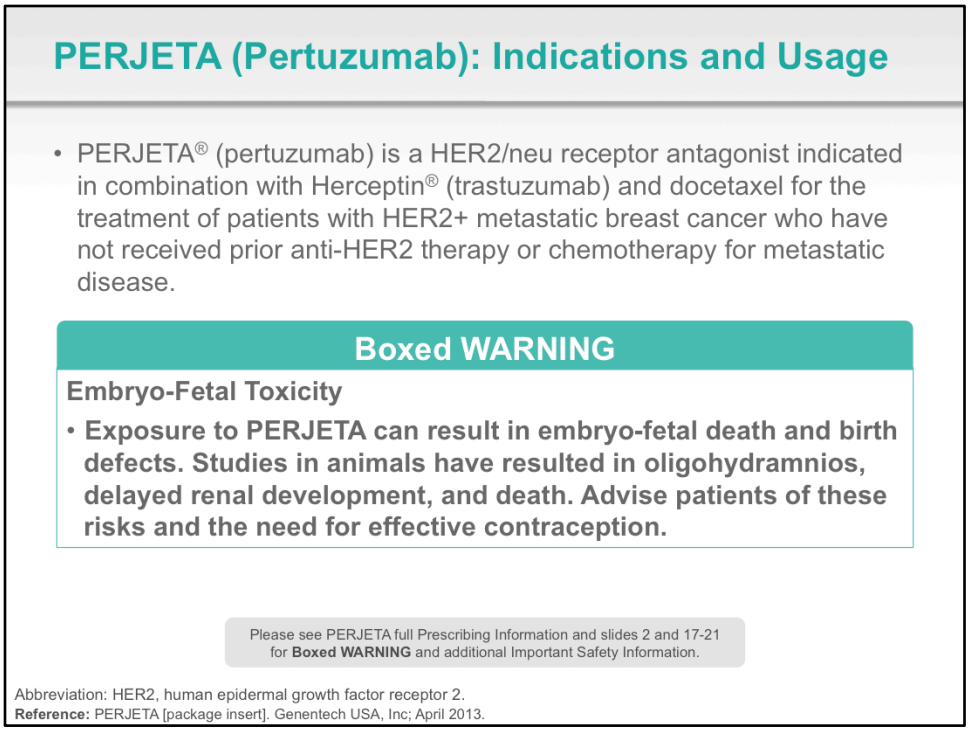
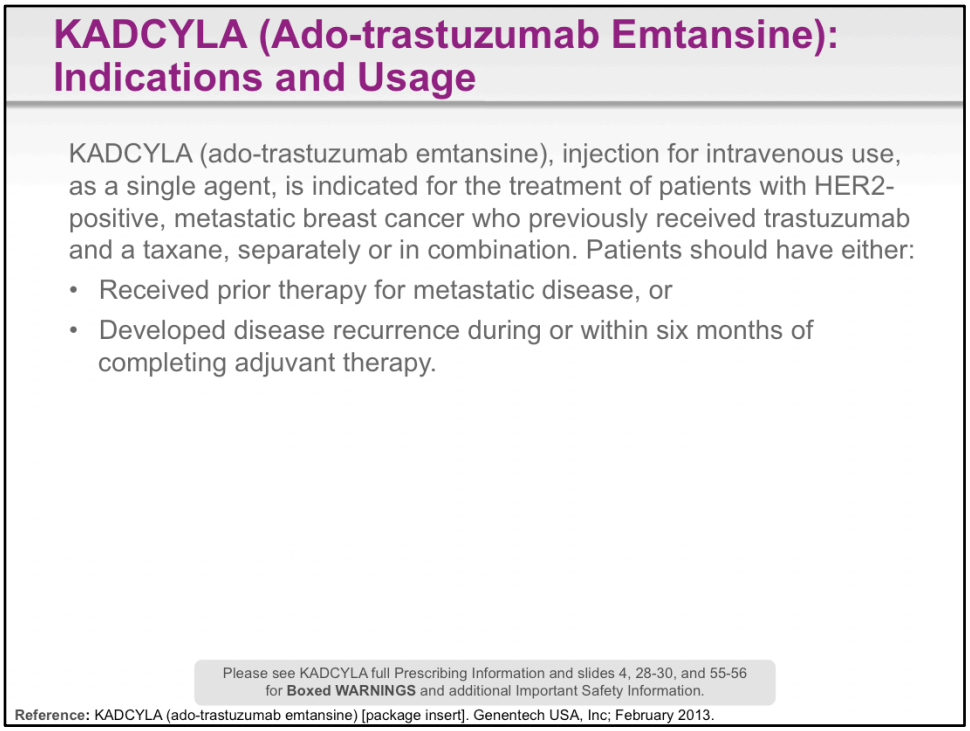


PERJETA (Pertuzumab): Indications and Usage

- Review as stated

Reference: PERJETA [package insert]. South San Francisco, CA: Genentech USA, Inc; April 2013.



KADCYLA (Ado-trastuzumab Emtansine): Indication and Usage

- Review as stated

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.

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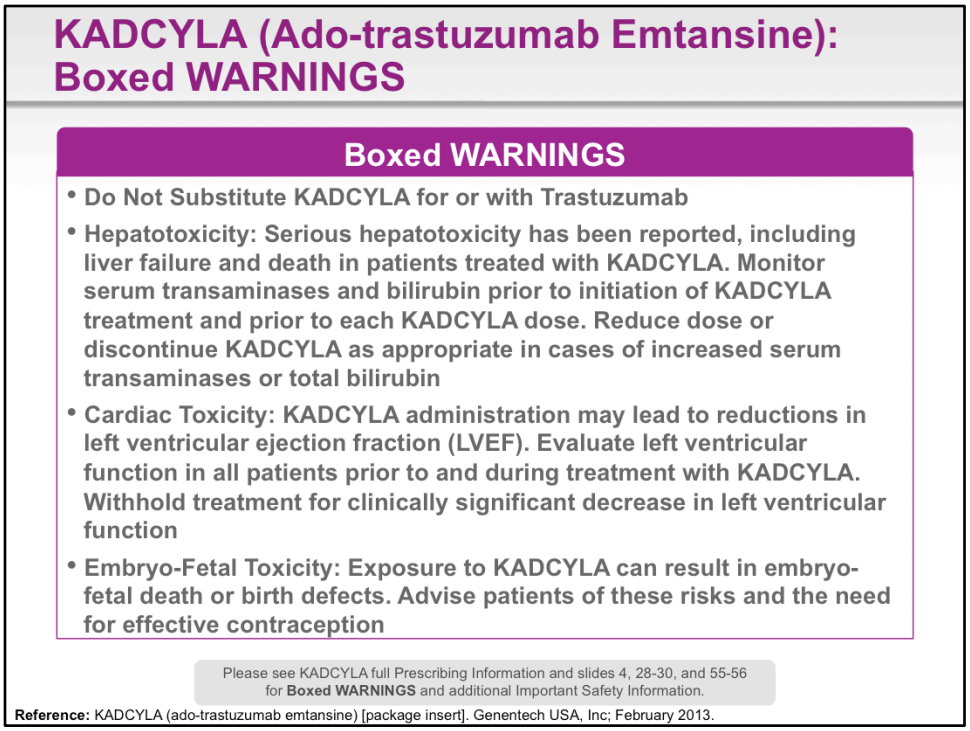

KADCYLA (Ado-trastuzumab Emtansine): Boxed WARNINGS

- Review as stated

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.

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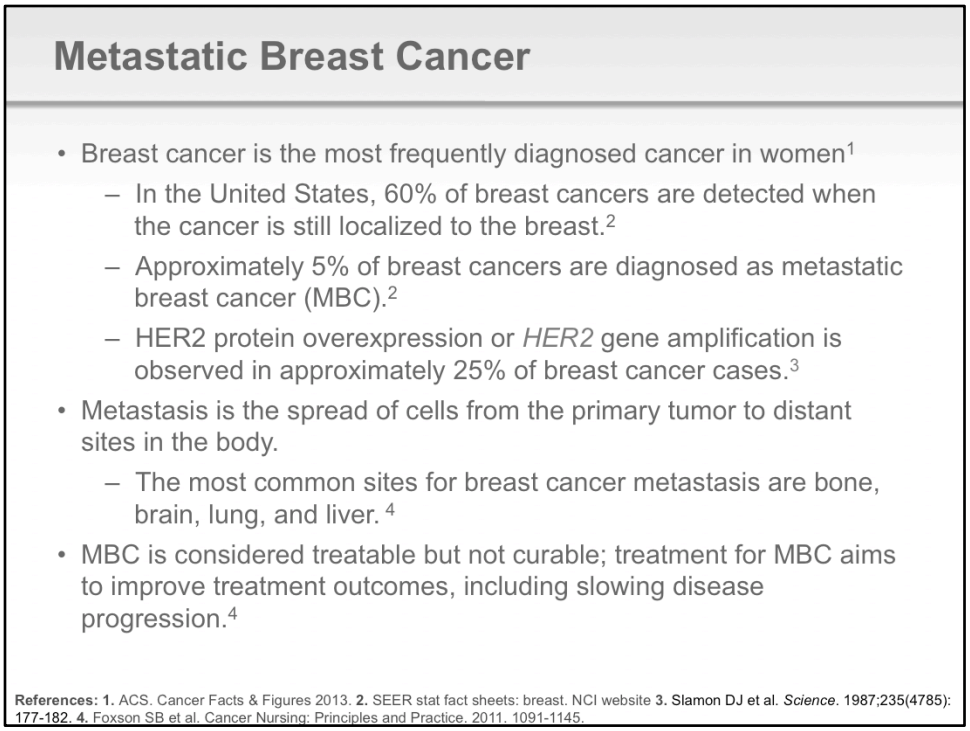

Metastatic Breast Cancer

Breast cancer is the most frequently diagnosed cancer in women.[1] In the United States,

- 60% of breast cancers are detected when the cancer is localized to the breast.[2]
- MBC is the initial diagnosis in approximately 5% of women with breast cancer.[2]
- Regional breast cancer, in which the cancer has spread to regional lymph nodes, is the initial diagnosis in approximately 33% of women with breast cancer. In the remaining 2% of women, the cancer stage/localization is unknown at the time of diagnosis.[2]
- HER2 protein overexpression or HER2 gene amplification is observed in approximately 25% of breast cancer cases.[3]

Metastasis is the spread of tumor cells from the primary tumor to distant sites in the body.

- Breast cancer can spread to almost any organ.[4]
- The most common sites for breast cancer metastasis are bone, brain, lung, and liver.[4]
- HER2+ tumors are most likely to recur in the viscera.[5]

MBC is considered treatable but not curable.[4]

- Treatment for MBC aims to improve treatment outcomes, including slowing disease progression.[4]

References: 1. American Cancer Society. *Cancer Facts & Figures 2013*. Atlanta, GA: American Cancer Society; 2012. **2.** SEER stat fact sheets: breast. NCI website. http://seer.cancer.gov/statfacts/html/breast.html. Updated November 10, 2011. Accessed November 28, 2012. **3.** Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science*. 1987;235(4785):177-182. **4**. Foxson SB, Lattimer JG, Felder B. Breast cancer. In: Yarbro CH, Wujcik D, Gobel BH, eds. *Cancer Nursing: Principles and Practice*. 7th ed. Sudbury, MA: Jones and Bartlett; 2011:1091-1145. **5.** Ross JS, Slodkowska EA, Symmans WF, et al. HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. *Oncologist*. 2009;14:320-368.

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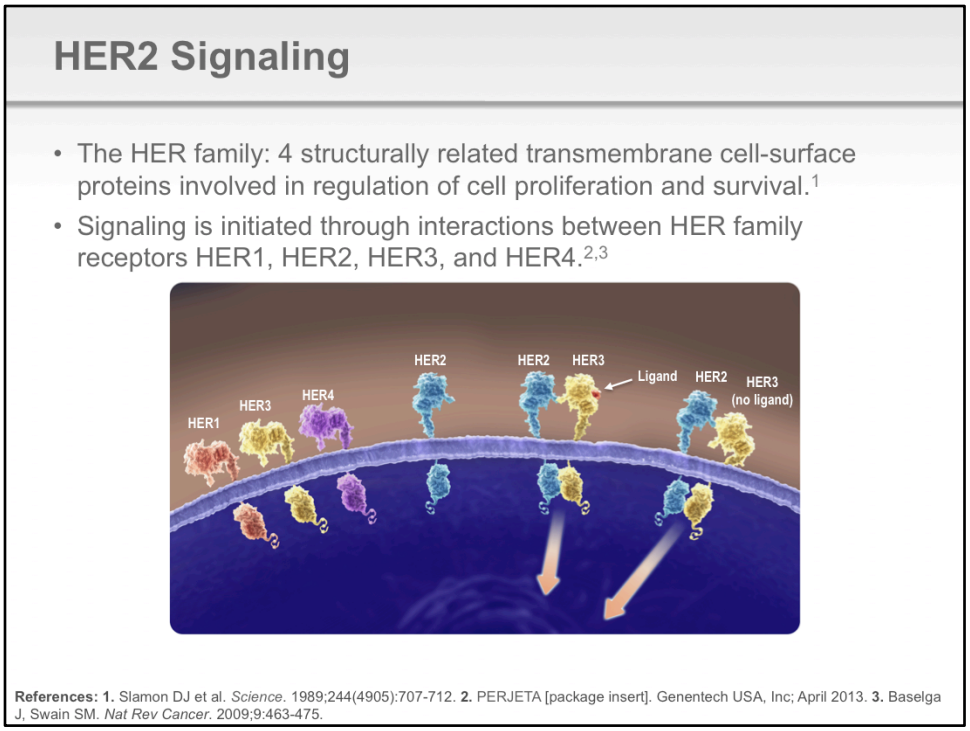

HER2 Signaling

- Review as stated

References: 1. 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. **2.** PERJETA [package insert]. South San Francisco, CA: Genentech USA, Inc; April 2013. **3.** Baselga J, Swain SM. Novel anticancer targets: revisiting ERBB2 and discovering ERBB3. *Nat Rev Cancer*. 2009;9:463-475.

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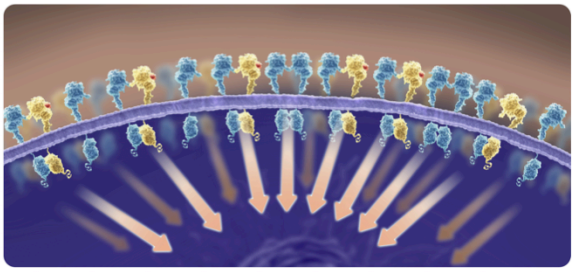
HER2 Overexpression in MBC

- HER2 protein overexpression or *HER2* gene amplification is observed in approximately 25% of breast cancer cases.[1]
  - HER2 overexpression results in overactive cellular signaling that leads to abnormal cell proliferation and survival and to tumor growth.[2,3]
- HER2-positive (HER2+) status is associated with more aggressive tumor behavior and poorer patient outcomes in untreated breast cancer.[4]
  - HER2+ status correlates with decreased survival in patients with metastatic disease.
- HER2 is a predictive biomarker of response to HER2-targeted therapy.[5]



References: 1. Foxson SB et al. *Cancer Nursing: Principles and Practice*. 2011:1091-1145. **2.** PERJETA [package insert]. Genentech USA, Inc; April 2013. **3.** Baselga J, Swain SM. *Nat Rev Cancer*. 2009;9:463-475. **4.** Witton CJ et al. *J Pathol.* 2003;200(3):290-197. **5.** Wolff AC et al. *J Clin Oncol*. 2007;25(1):1-28.

HER2 Overexpression in MBC

- Review as stated

References: 1. Foxson SB, Lattimer JG, Felder B. Breast cancer. In: Yarbro CH, Wujcik D, Gobel BH, eds. *Cancer Nursing: Principles and Practice*. 7th ed. Sudbury, MA: Jones and Bartlett; 2011:1091-1145. **2.** PERJETA [package insert]. South San Francisco, CA: Genentech USA, Inc; April 2013. **3.** Baselga J, Swain SM. Novel anticancer targets: revisiting ERBB2 and discovering ERBB3. *Nat Rev Cancer*. 2009;9:463-475. **4.** Witton CJ, Reeves JR, Going JJ, Cooke TG, Bartlett JM. Expression of the HER1-4 family of receptor tyrosine kinases in breast cancer. *J Pathol.* 2003;200(3):290-297. **5.** Wolff AC, Hammond EH, Schwarz 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):1-28.

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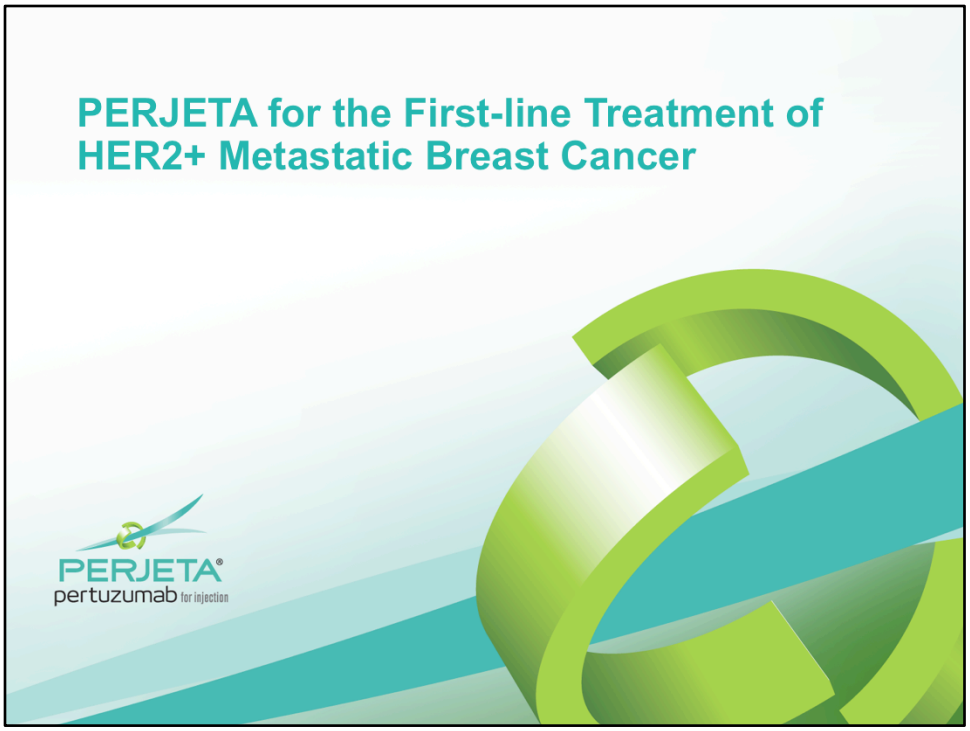
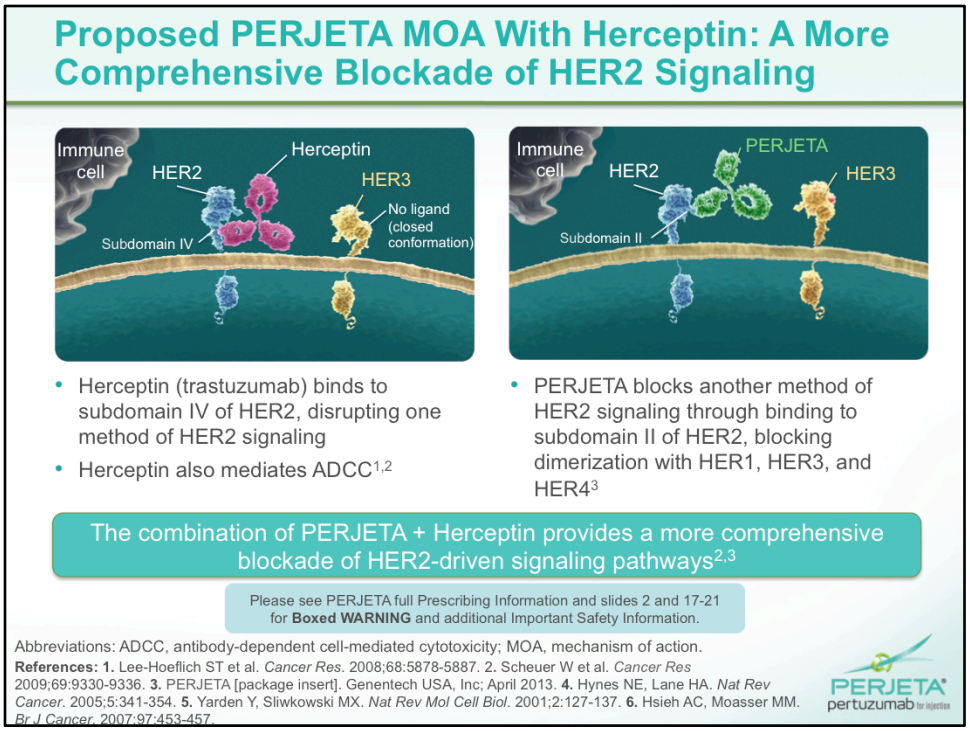


Introduction

This portion of the presentation will discuss PERJETA, a first-line treatment for HER2-positive metastatic breast cancer (MBC).



Proposed Mechanism of Action of PERJETA With Herceptin: A More Comprehensive Blockade of HER2 Signaling

- Review as stated

References: 1. Lee-Hoeflich ST, Crocker L, Yao E, et al. A central role for HER3 in *HER2*-amplified breast cancer: implications for targeted therapy. *Cancer Res*. 2008;68:5878-5887. **2.** Scheuer W, Friess T, Burtscher H, Bossenmaier B, Endl J, Hasmann M. Strongly enhanced antitumor activity of Herceptin and pertuzumab combination treatment on HER2-positive human xenograft tumor models. *Cancer Res*. 2009;69:9330-9336. **3.** PERJETA [package insert]. South San Francisco, CA: Genentech USA, Inc; April 2013. **4.** Hynes NE, Lane HA. ERBB receptors and cancer: the complexity of targeted inhibitors. *Nat Rev Cancer*. 2005;5:341-354. **5.** Yarden Y, Sliwkowski MX. Untangling the ErbB signalling network. *Nat Rev Mol Cell Biol*. 2001;2:127-137. **6.** Hsieh AC, Moasser MM. Targeting HER proteins in cancer therapy and the role of the non-target HER3. *Br J Cancer*. 2007;97:453-457.

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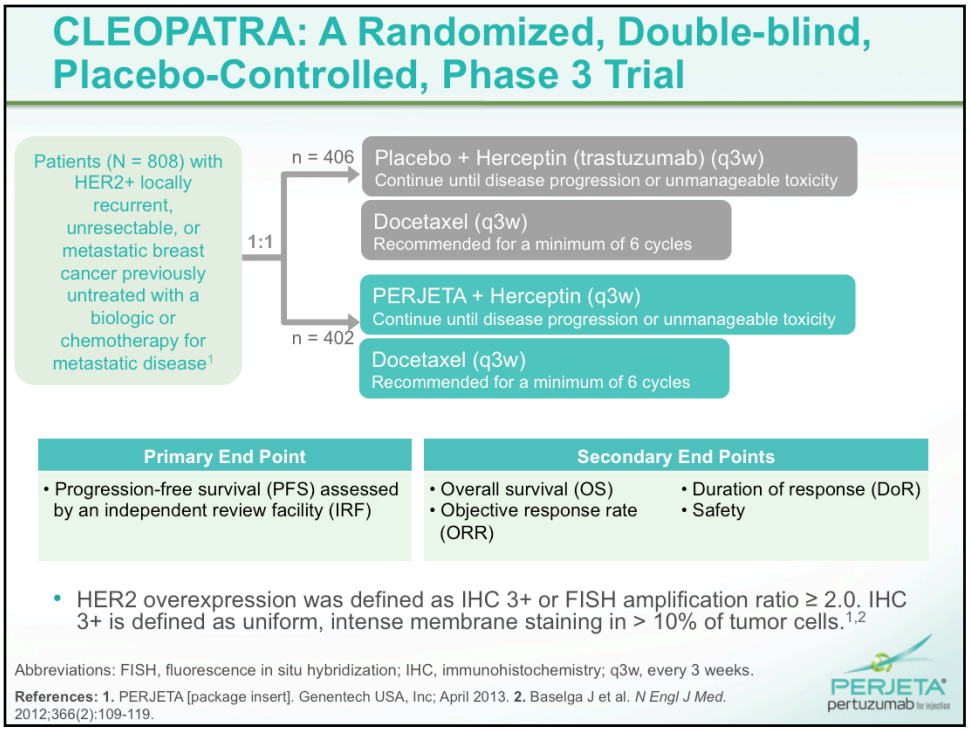

KEY POINT: The results of the pivotal phase 3 trial CLEOPATRA supported the approval of PERJETA as a first-line treatment for MBC.

CLEOPATRA was a randomized, double-blind, placebo-controlled, phase 3 clinical trial that compared PERJETA plus Herceptin plus docetaxel to placebo plus Herceptin plus docetaxel.

- It was conducted in 808 patients with HER2+ locally recurrent, unresectable, or metastatic breast cancer
    - Patients with prior adjuvant or neoadjuvant therapy were required to have a disease-free interval of ≥ 12 months before enrollment into the trial
    - Patients were required to have evidence of HER2 overexpression defined as IHC 3+ by Dako HercepTest™ or FISH amplification ratio ≥ 2.0 by Dako *HER2* FISH pharmDx™ Kit
    - Patients were stratified by prior treatment status (de novo vs prior adjuvant/neoadjuvant therapy) and geographic region
- Patients were treated with either PERJETA plus Herceptin plus docetaxel or placebo plus Herceptin plus docetaxel every 3 weeks
- Treatment continued until disease progression, unmanageable toxicity, or withdrawal of consent
- The primary end point was progression-free survival (PFS), assessed by an independent review facility (IRF)
- Additional end points were overall survival (OS), objective response rate (ORR), duration of response (DoR), and safety

HER2 overexpression was defined as IHC 3+ or FISH amplification ratio of 2.0 or greater. IHC 3+ is defined as uniform, intense membrane staining in more than 10% of tumor cells.[1,2]

[click] Per protocol, one prior hormonal treatment for MBC was allowed.1,2 Adjuvant treatment with chemotherapy and/or Herceptin was also allowed. Patients with prior adjuvant or neoadjuvant therapy were required to have a disease-free interval of ≥ 12 months to be eligible for enrollment in the trial.[1,2]

Randomization was stratified by prior treatment status (de novo or prior adjuvant/neoadjuvant therapy) and geographic region (Europe, North America, South America, and Asia).

References: 1. PERJETA [package insert]. South San Francisco, CA: Genentech USA, Inc; April 2013. **2.** Baselga J, Cortés J, Kim S-B, et al; CLEOPATRA Study Group. Pertuzumab plus Herceptin plus docetaxel for metastatic breast cancer. *N Engl J Med*. 2012;366:109-119.

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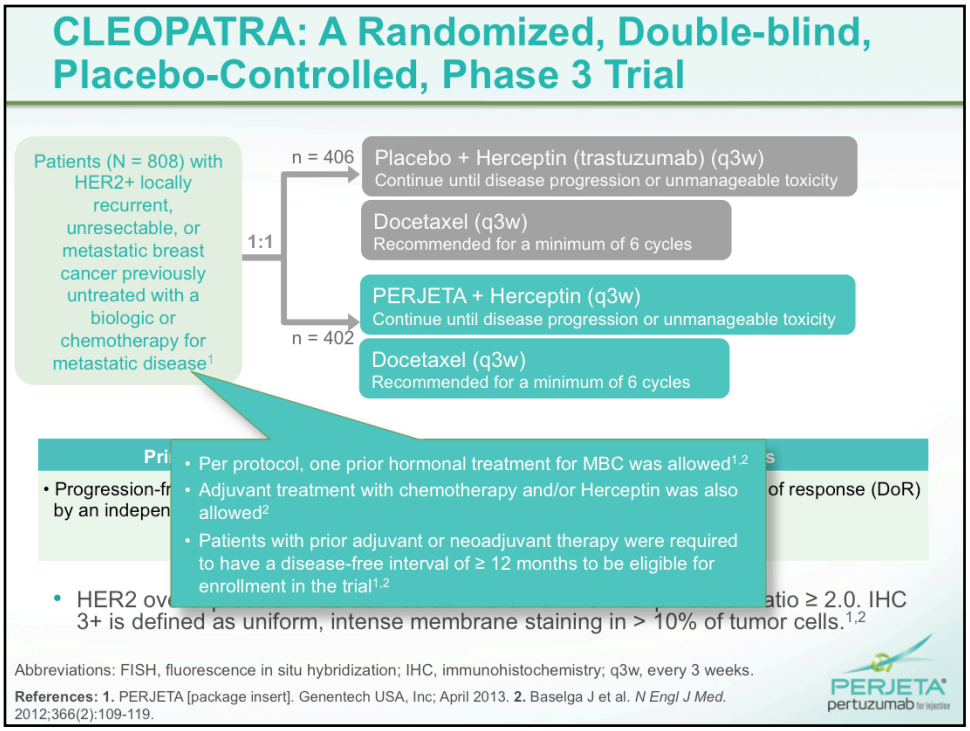

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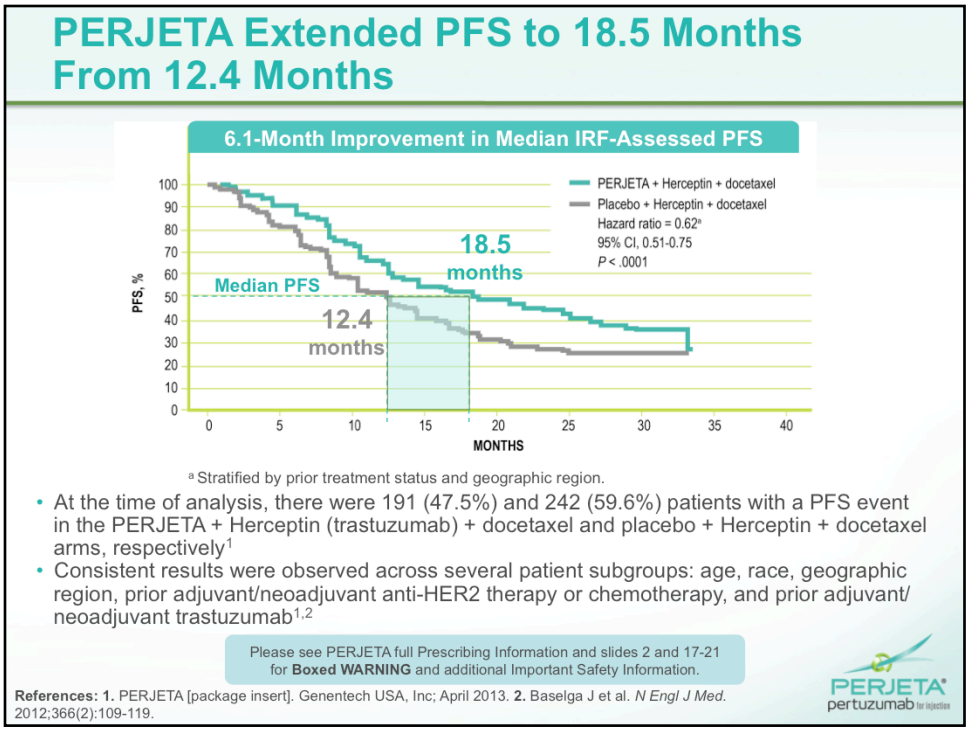


PERJETA Extended PFS to 18.5 Months From 12.4 Months

The primary end point in CLEOPATRA was PFS, as assessed by an IRF. (PFS is the time from when the patient was randomly assigned to a treatment arm in CLEOPATRA until death or disease progression.)

- Median PFS, the time when 50% (half) of patients have progressed or died in a specified arm of the study and half continue to be progression-free or alive, was 12.4 months in the placebo plus Herceptin plus docetaxel arm vs 18.5 months in the PERJETA-containing arm, an increase of 6.1 months.

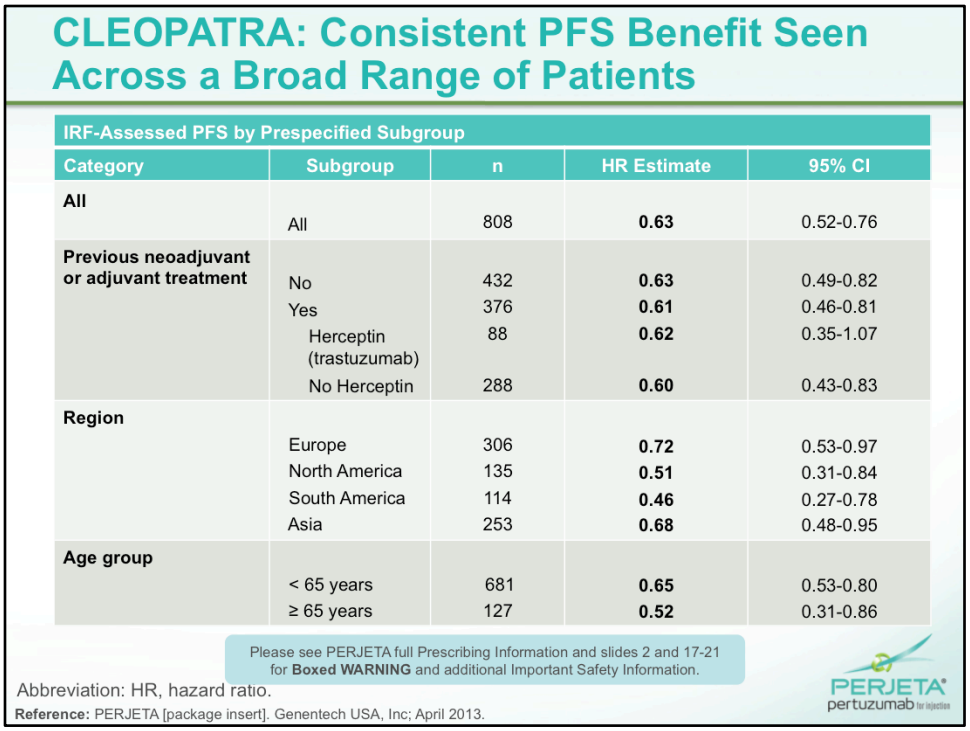
At the time of the final PFS analysis OS was not mature and the first interim OS analysis results did not meet the pre-specified stopping boundary for statistical significance.

At the time of PFS analysis, 191 patients (47.5%) had experienced a PFS event in the PERJETA plus Herceptin plus docetaxel arm, compared with 242 patients (59.6%) in the placebo plus Herceptin plus docetaxel arm.

- The hazard ratio for PFS with the addition of PERJETA was 0.62.

Consistent results were observed across several patient subgroups including age (< 65 or ≥ 65 years), race, geographic region, prior adjuvant/neoadjuvant anti-HER2 therapy or chemotherapy (yes or no), and prior adjuvant/neoadjuvant trastuzumab (yes or no).[1,2]

References: 1. PERJETA [package insert]. South San Francisco, CA: Genentech USA, Inc; April 2013. **2.** Baselga J, Cortés J, Kim S-B, et al; CLEOPATRA Study Group. Pertuzumab plus Herceptin plus docetaxel for metastatic breast cancer. *N Engl J Med*. 2012;366:109-119.



CLEOPATRA: Consistent PFS Benefit Seen Across a Broad Range of Patients

- Review as stated

Reference: PERJETA [package insert]. South San Francisco, CA: Genentech USA, Inc; April 2013.

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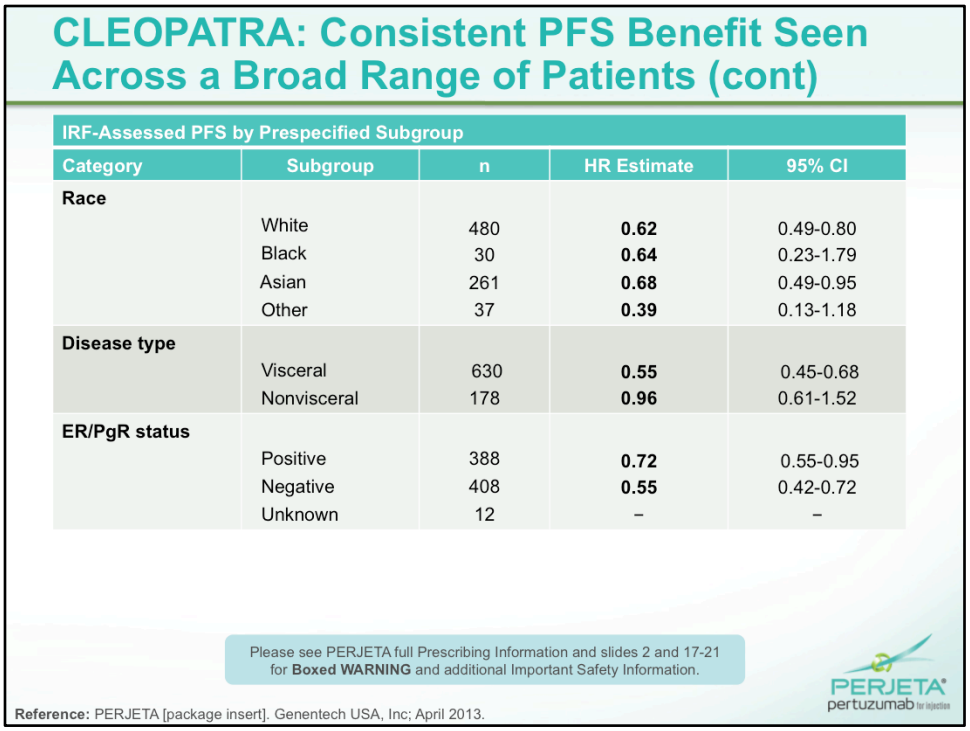
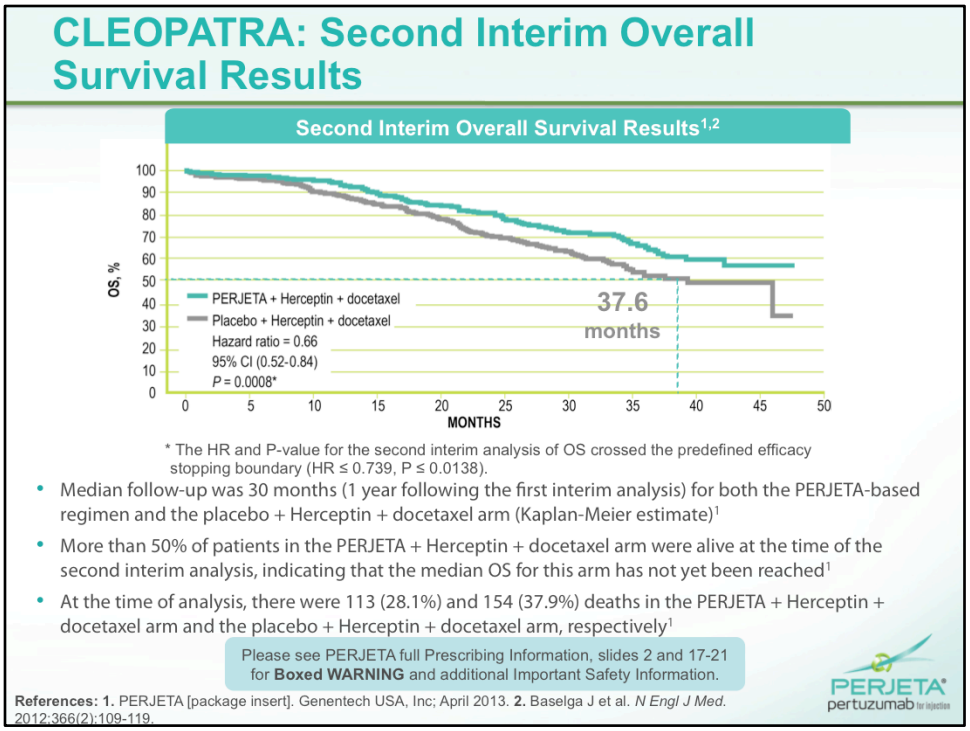


CLEOPATRA: Consistent PFS Benefit Seen Across a Broad Range of Patients (cont)

- Review as stated

Reference: PERJETA [package insert]. South San Francisco, CA: Genentech USA, Inc; April 2013.



KEY POINT: At the time of the second interim analysis, median OS had not been reached in the PERJETA + Herceptin + docetaxel arm because more than half of the patients were still alive.

The graph shows the Kaplan-Meier curves for OS data at the second interim analysis, conducted 1 year following the first interim analysis

- Median follow-up was 30 months (1 year following the first interim analysis) for both the PERJETA-based regimen and the placebo + Herceptin + docetaxel arm (Kaplan-Meier estimate)[1]
- More than 50% of patients in the PERJETA + Herceptin + docetaxel arm were alive at the time of the second interim analysis, thereby indicating that the median OS for this arm has not yet been reached[1]
- At the time of the second interim analysis, there were 113 (28.1%) and 154 (37.9%) deaths in the PERJETA + Herceptin + docetaxel arm and the placebo + Herceptin + docetaxel arm, respectively[1]
- The hazard ratio and *P* value demonstrated a statistically significant improvement in OS (HR = 0.66; *P* = .0008).[1,2] The hazard ratio and *P* value for the second interim analysis of OS crossed the pre-defined efficacy stopping boundary.

References: 1. PERJETA [package insert]. South San Francisco, CA: Genentech USA, Inc; April 2013. **2.** Baselga J, Cortés J, Kim S-B, et al; CLEOPATRA Study Group. Pertuzumab plus Herceptin plus docetaxel for metastatic breast cancer. *N Engl J Med*. 2012;366:109-119.

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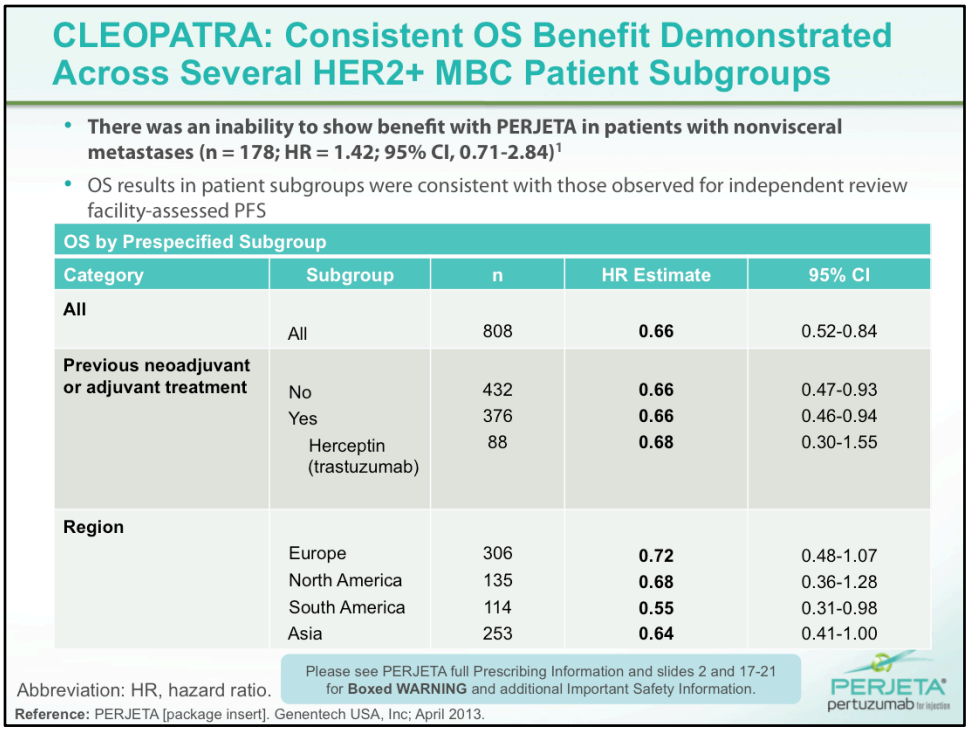


CLEOPATRA: Consistent OS Benefit Demonstrated Across Several HER2+ MBC Patient Subgroups

- **There was an inability to show benefit with PERJETA in patients with nonvisceral metastases (n = 178; HR = 1.42; 95% CI, 0.71-2.84)[1]**
- OS results in patient subgroups were consistent with those observed for independent review facility-assessed PFS

OS by Prespecified Subgroup

Category	Subgroup	n	HR Estimate	95% CI
All	All	808	**0.66**	0.52-0.84
Previous neoadjuvant or adjuvant treatment	No	432	**0.66**	0.47-0.93
	Yes	376	**0.66**	0.46-0.94
	Herceptin (trastuzumab)	88	**0.68**	0.30-1.55
Region	Europe	306	**0.72**	0.48-1.07
	North America	135	**0.68**	0.36-1.28
	South America	114	**0.55**	0.31-0.98
	Asia	253	**0.64**	0.41-1.00

Abbreviation: HR, hazard ratio.

Please see PERJETA full Prescribing Information and slides 2 and 17-21 for **Boxed WARNING** and additional Important Safety Information.

PERJETA pertuzumab for injection

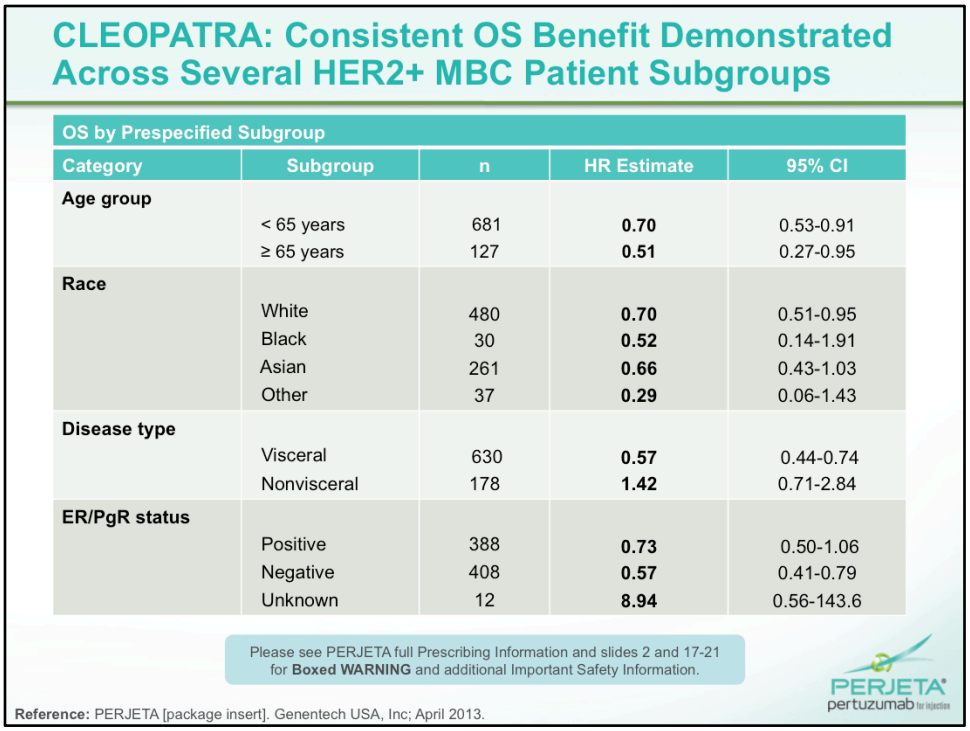
Reference: PERJETA [package insert]. Genentech USA, Inc; April 2013.

CLEOPATRA: Consistent OS Benefit Demonstrated Across Several HER2+ MBC Patient Subgroups

- Review as stated

OS results in patient subgroups were consistent with those observed for IRF-assessed PFS with the exception of the subgroup of patients with disease limited to nonvisceral metastasis (HR = 1.42; 95% CI, 0.71-2.84).

Reference: PERJETA [package insert]. South San Francisco, CA: Genentech USA, Inc; April 2013.



CLEOPATRA: Consistent OS Benefit Demonstrated Across Several HER2+ MBC Patient Subgroups (cont)

- Review as stated

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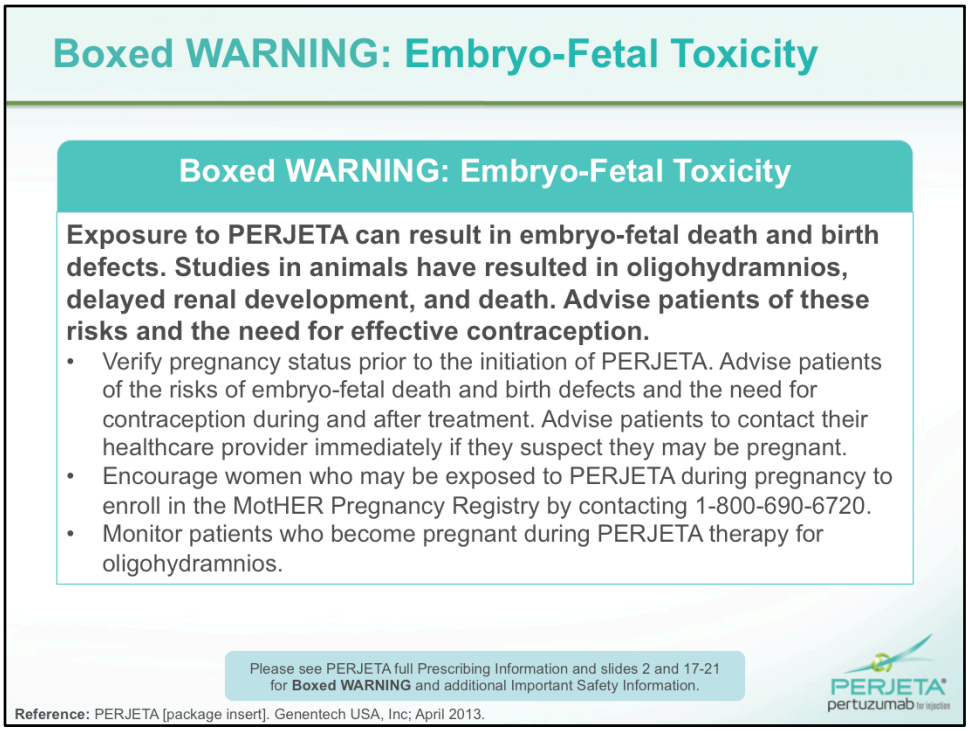

Boxed WARNING: Embryo-Fetal Toxicity

- Review as stated

Reference: PERJETA [package insert]. South San Francisco, CA: Genentech USA, Inc; April 2013.

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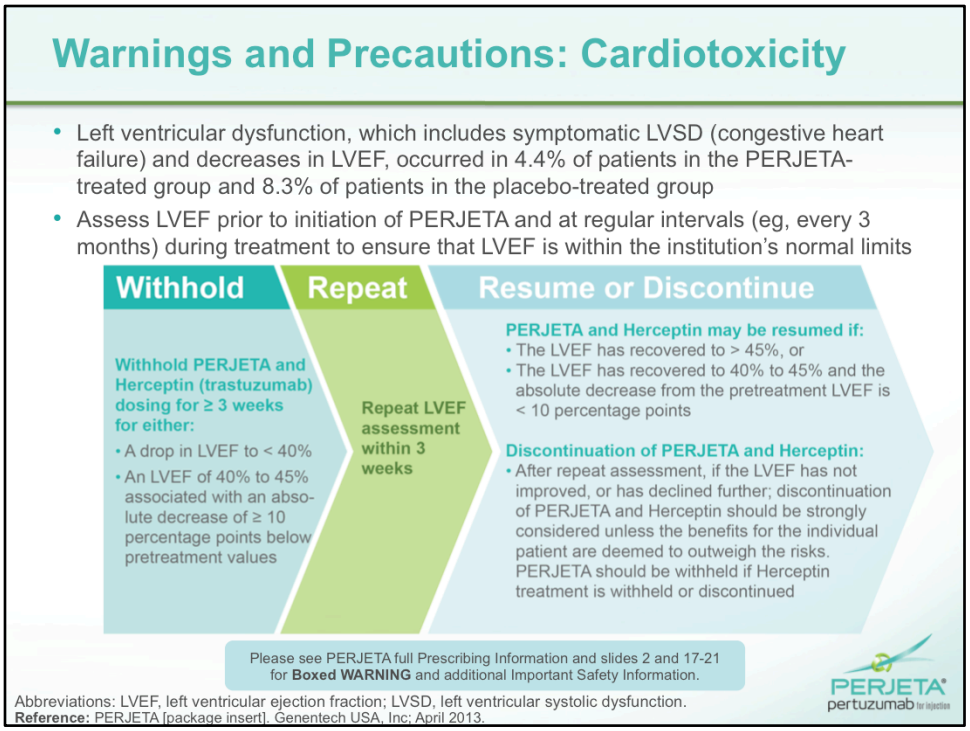

Warnings and Precautions: Cardiotoxicity

Decreases in left ventricular ejection fraction (LVEF) have been reported with drugs that block HER2 activity, including PERJETA.

In CLEOPATRA, the addition of PERJETA to the combination of Herceptin and docetaxel was not associated with increases in left ventricular dysfunction, including cases of congestive heart failure (CHF). The incidence of left ventricular dysfunction in the PERJETA-based arm was 4.4%, compared with 8.3% in the arm with Herceptin + docetaxel alone.

It is important to carefully select patients for PERJETA therapy and monitor them closely.

Assess LVEF prior to initiation of PERJETA and at regular intervals (eg, every 3 months) during treatment to ensure that LVEF is within the institution's normal limits.

- ***[click]*** Withhold PERJETA and Herceptin for at least 3 weeks if LVEF is less than 40% or if LVEF is 40% to 50% and is 10 percentage points or more below baseline value.
- Repeat LVEF assessment within 3 weeks.
- You can resume PERJETA and Herceptin if LVEF is greater than 45% or if LVEF is 40% to 45% and is less than 10 percentage points below baseline. Discontinuation should be strongly considered if LVEF has not improved or has declined further, unless the benefits for the individual are deemed to outweigh the risks.
- PERJETA should be withheld or discontinued if Herceptin treatment is withheld or discontinued.

Reference: PERJETA [package insert]. South San Francisco, CA: Genentech USA, Inc; April 2013.

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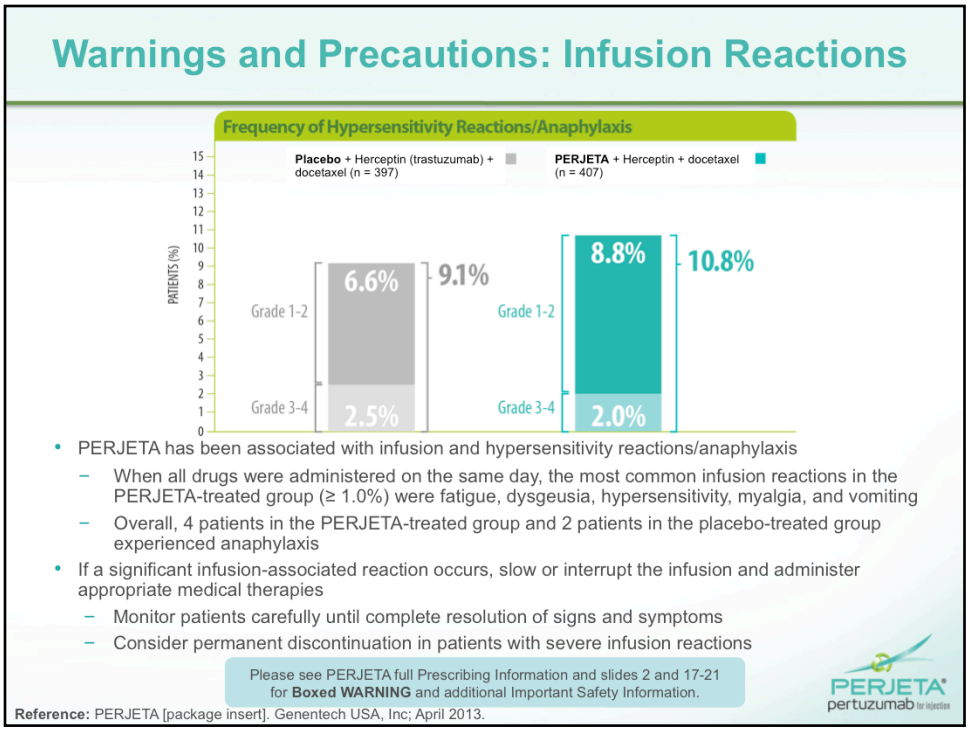

Warnings and Precautions: Infusion Reactions

- Review as stated

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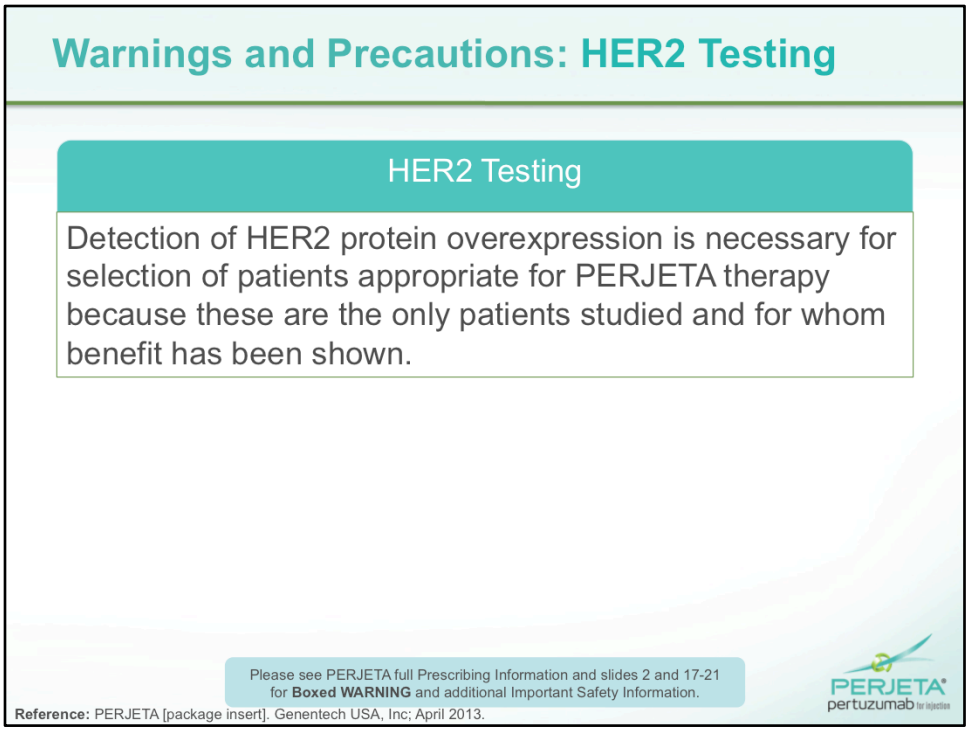

Warnings and Precautions: HER2 Testing

- Review as stated

Reference: PERJETA [package insert]. South San Francisco, CA: Genentech USA, Inc; April 2013.

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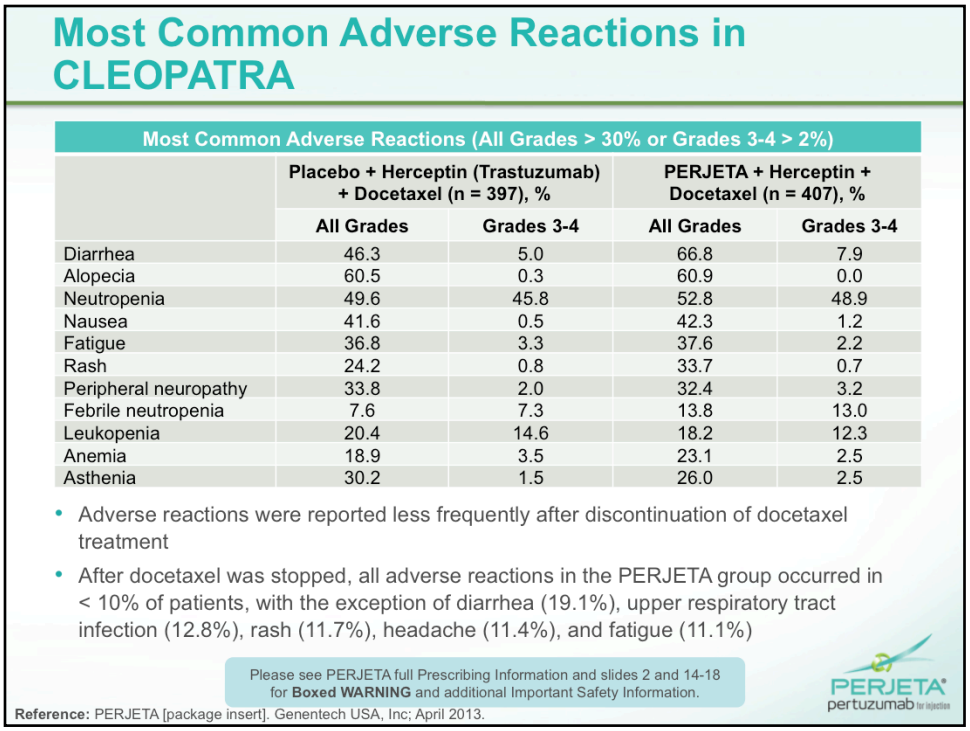
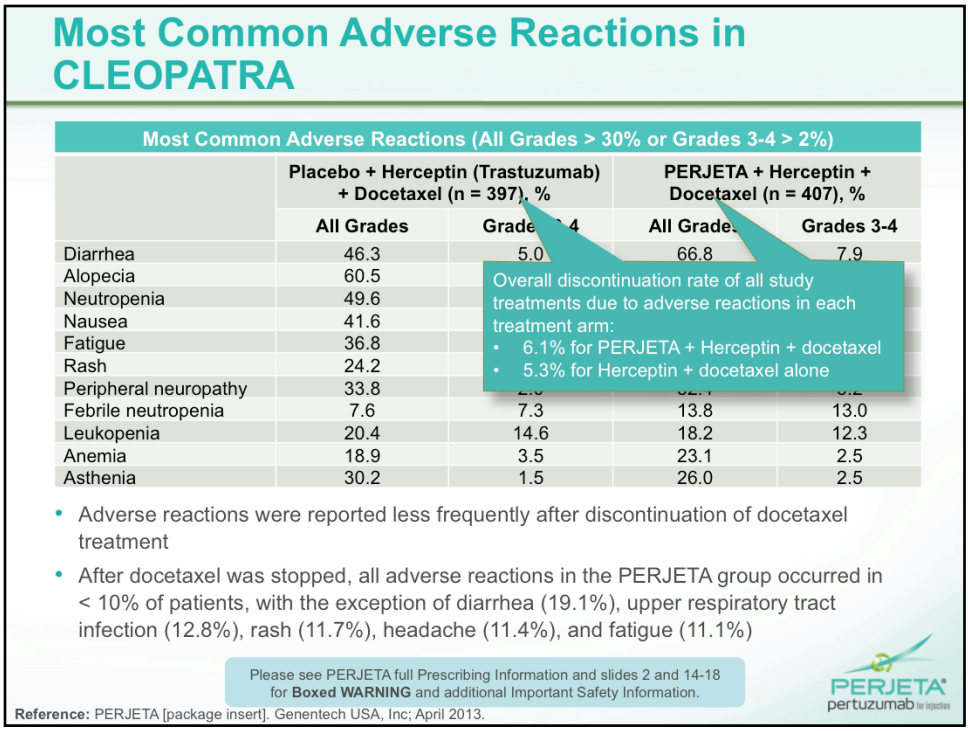


Most Common Adverse Reactions (All Grades > 30% or Grades 3-4 > 2%) in CLEOPATRA

- Review as stated

Reference: PERJETA [package insert]. South San Francisco, CA: Genentech USA, Inc; April 2013.

21b



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Reference: PERJETA [package insert]. South San Francisco, CA: Genentech USA, Inc; April 2013.

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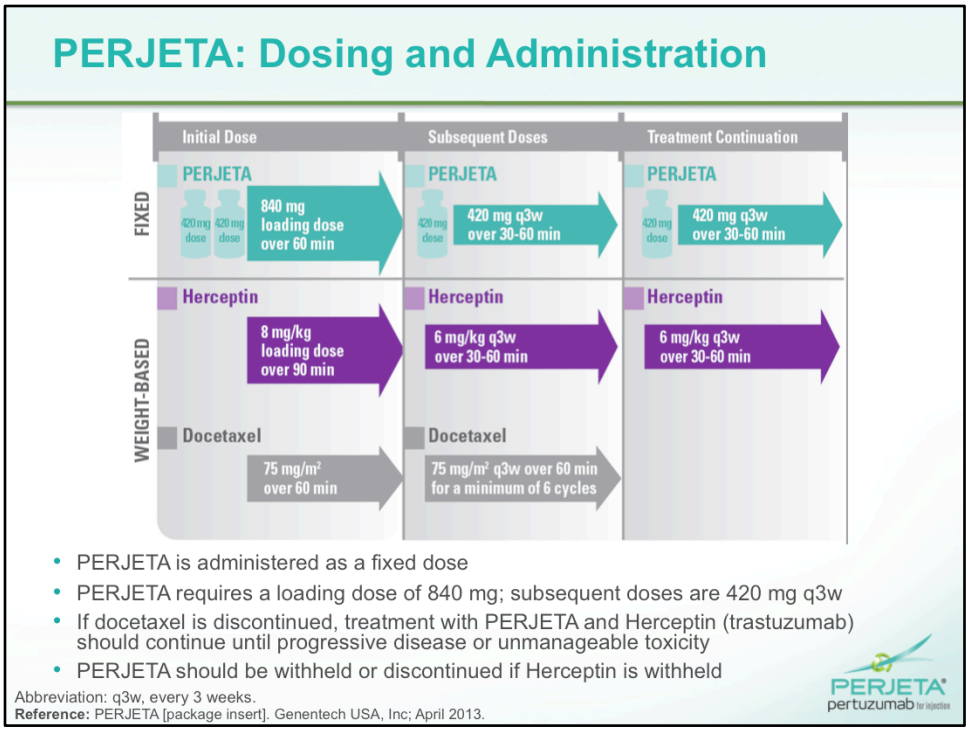


PERJETA Dosing and Administration

PERJETA is administered as a fixed dose.

PERJETA requires a loading dose of 840 mg, given intravenously over 60 minutes; subsequent doses are 420 mg every 3 weeks (q3w) given over a 30 to 60 minute period. Close observation of the patient for 60 minutes after first infusion and 30 minutes after subsequent infusions is recommended.

Herceptin (trastuzumab) also requires a loading dose. For Herceptin, the loading dose is 8 mg/kg given intravenously over 90 minutes; subsequent doses are 6 mg/kg q3w given intravenously over a 30 to 60 minute period.

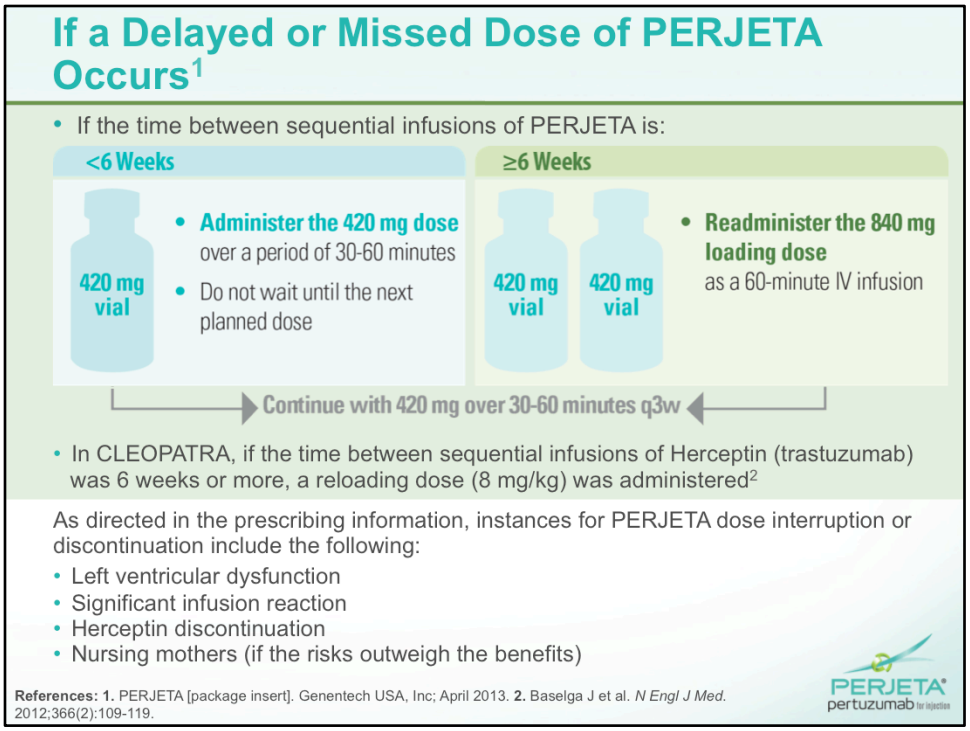
[click]

If docetaxel is discontinued, treatment with PERJETA and Herceptin should continue until progressive disease or unmanageable toxicity.

PERJETA should be withheld or discontinued if Herceptin is withheld.

PERJETA, trastuzumab, and docetaxel should be administered sequentially. PERJETA and trastuzumab can be given in any order. Docetaxel should be administered after PERJETA and trastuzumab. An observation period of 30 to 60 minutes is recommended after each PERJETA infusion and before commencement of any subsequent infusion of trastuzumab or docetaxel [see Warnings and Precautions (5.3)].

Reference: PERJETA [package insert]. South San Francisco, CA: Genentech USA, Inc; April 2013.



If a Delayed or Missed Dose of PERJETA Occurs

For delayed or missed doses of PERJETA, if the time between 2 sequential infusions is less than 6 weeks, the 420-mg dose of PERJETA should be administered. Do not wait until the next planned dose.

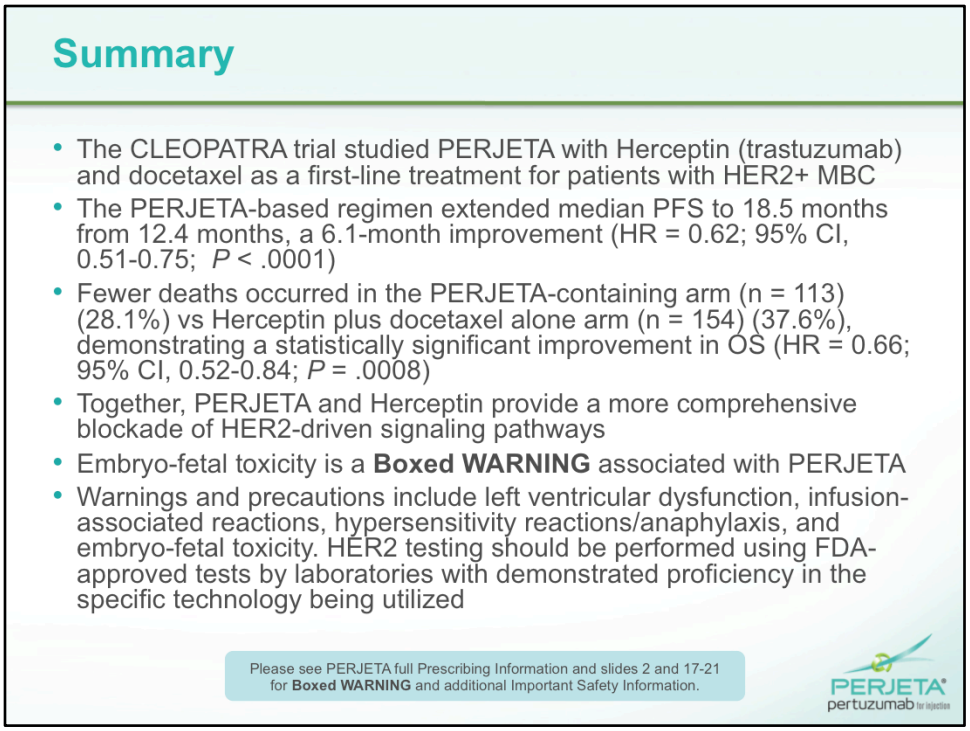
If the time between 2 sequential infusions is 6 weeks or more, the initial dose of 840 mg of PERJETA should be readministered as a 60-minute IV infusion followed every 3 weeks thereafter by a dose of 420 mg administered over 30 to 60 minutes.[1]

[click] In CLEOPATRA, if the time between sequential infusions of Herceptin (trastuzumab) was 6 weeks or more, a reloading dose (8 mg/kg) was administered.[2]

[click] As directed in the prescribing information, instances for PERJETA dose interruption or discontinuation include the following:

- Left ventricular dysfunction
- Significant infusion reaction
- Herceptin: If Herceptin is discontinued, PERJETA should be discontinued
- Nursing mothers: In this situation, assess the importance of PERJETA to the mother and advise her to either discontinue nursing or discontinue PERJETA

References: 1. PERJETA [package insert]. South San Francisco, CA: Genentech USA, Inc; April 2013. **2.** Baselga J, Cortés J, Kim S-B, et al; CLEOPATRA Study Group. Pertuzumab plus Herceptin plus docetaxel for metastatic breast cancer. *N Engl J Med*. 2012;366:109-119.



Summary

- Review as stated

Reference: 1. PERJETA [package insert]. South San Francisco, CA: Genentech USA, Inc; April 2013.


THANK YOU & QUESTIONS

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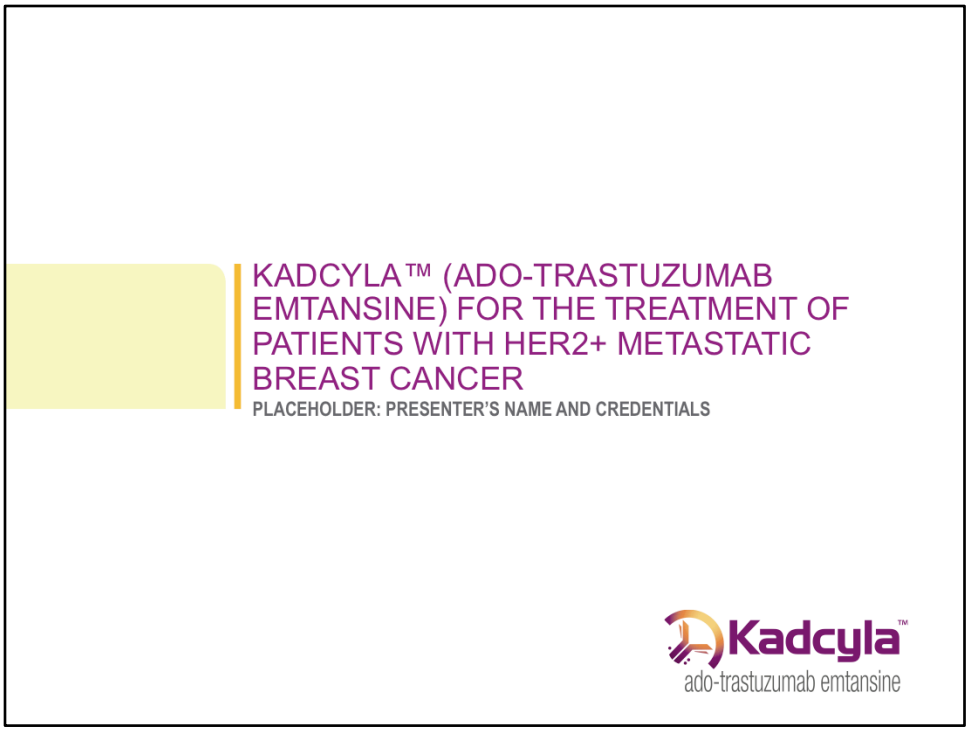

Introduction

This portion of the presentation will discuss KADCYLA, a treatment for HER2-positive metastatic breast cancer (MBC).

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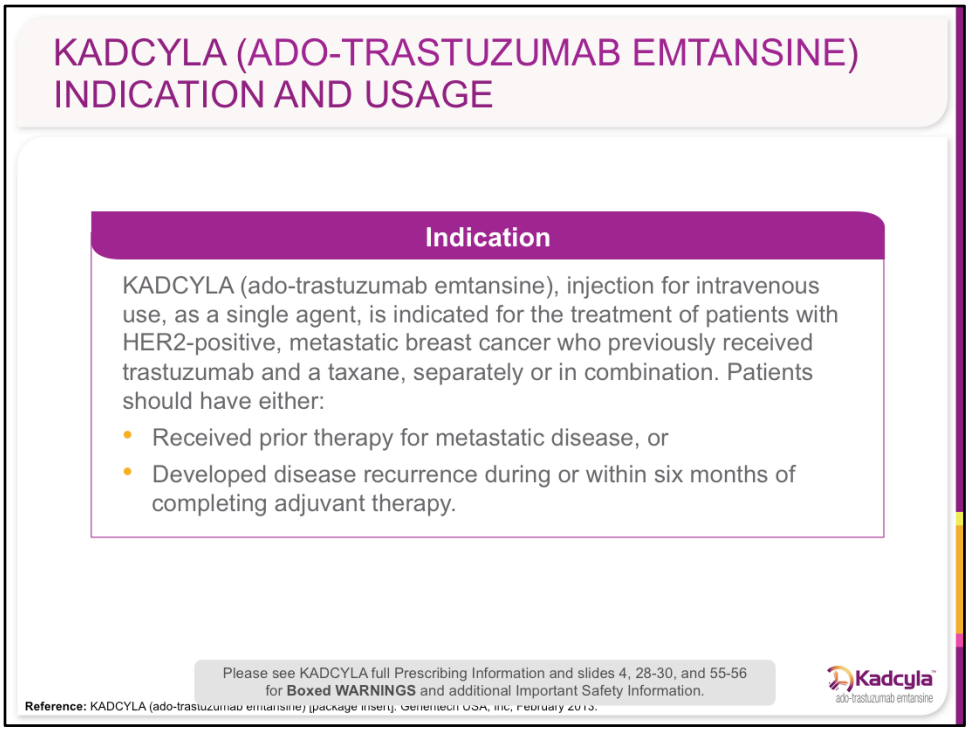

KADCYLA (Ado-trastuzumab Emtansine) Indication and Usage

Review as stated.

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.

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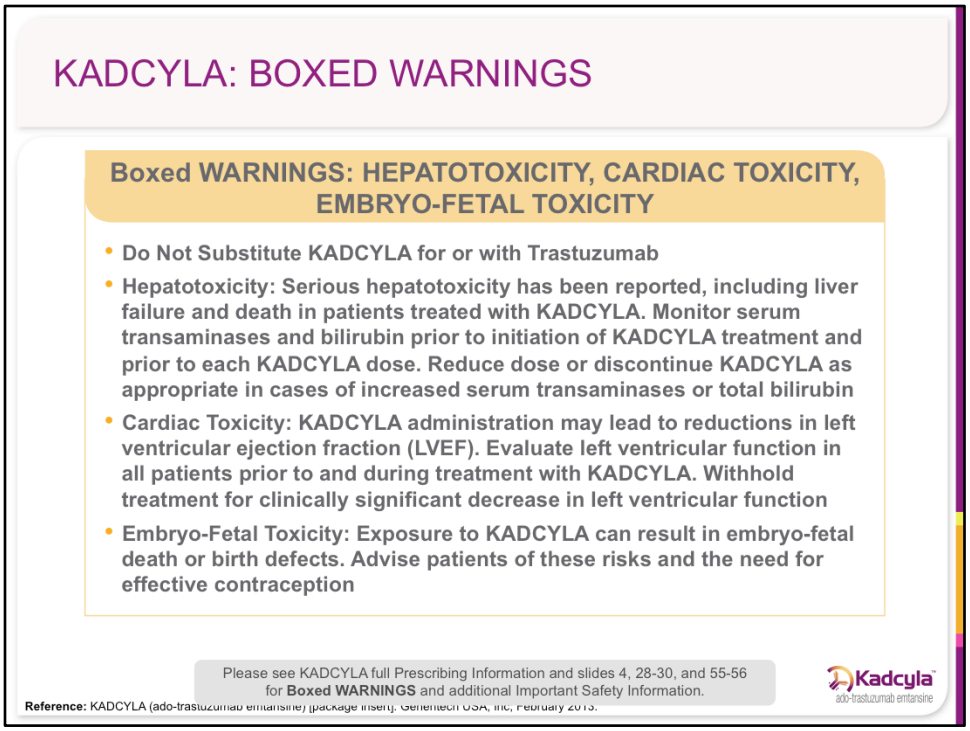

KADCYLA: Boxed WARNINGS

Review as stated.

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.

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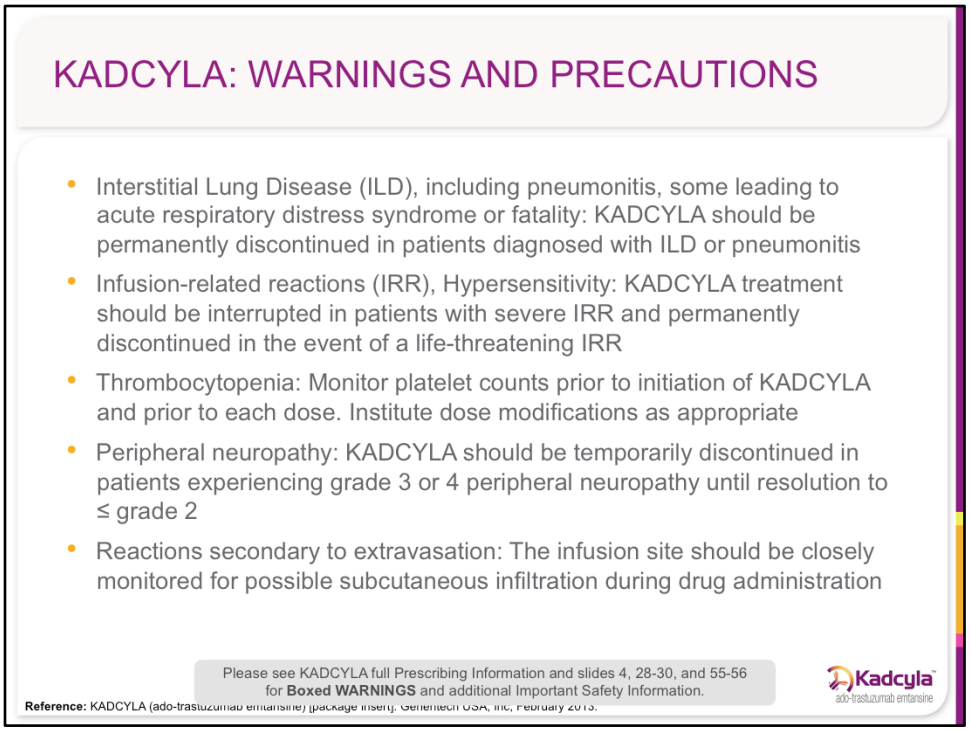

KADCYLA: Warnings and Precautions

Review as stated.

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.

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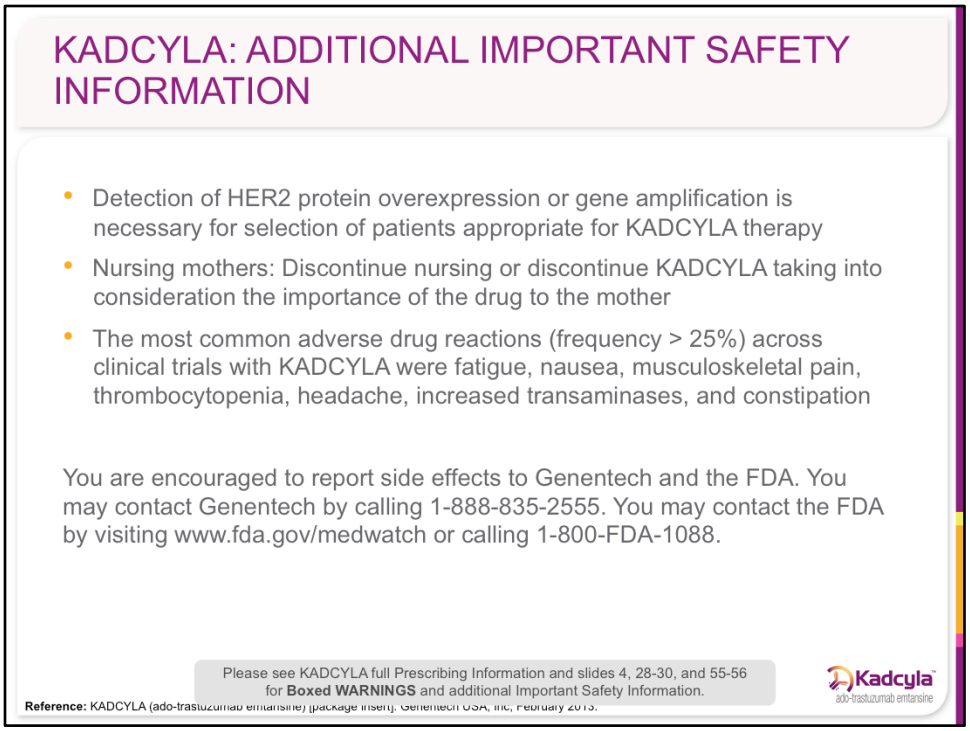

KADCYLA: Additional Important Safety Information

Review as stated.

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.

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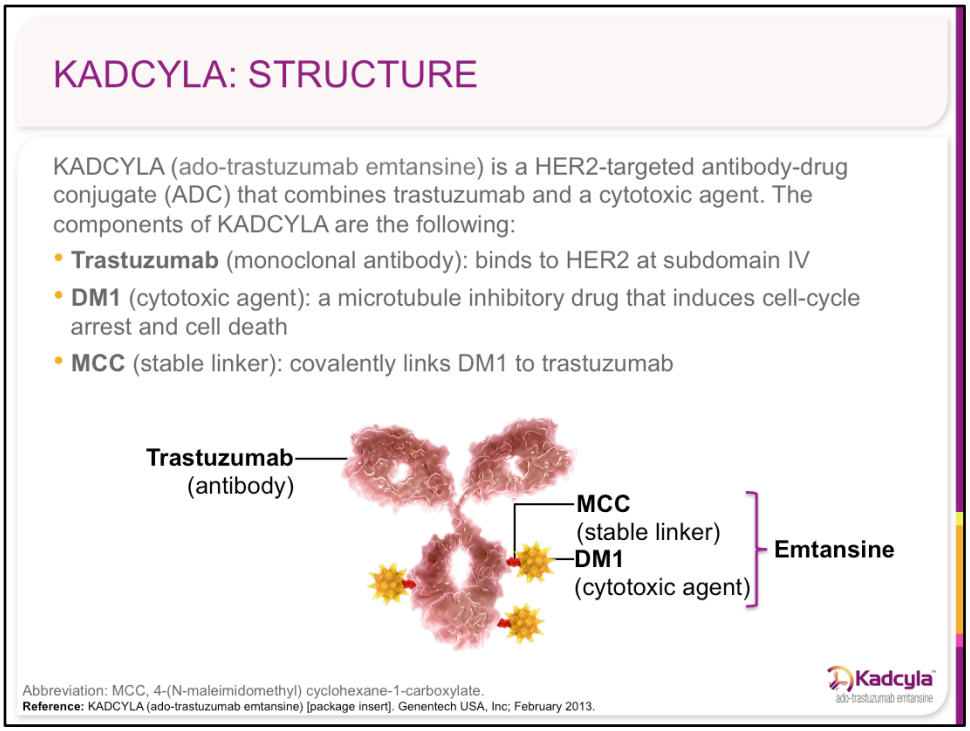

[[Slide builds]]

KADCYLA: Structure

KADCYLA (ado-trastuzumab emtansine) is a HER2-targeted antibody-drug conjugate (ADC).

[[Click]] KADCYLA contains the anti-HER2 antibody trastuzumab.

[[Click]] In KADCYLA, trastuzumab is covalently linked to a microtubule inhibitory drug, DM1.

- KADCYLA contains an average of 3.5 DM1 molecules per antibody.

[[Click]] DM1 is linked to trastuzumab with the stable linker MCC (4-[N-maleimidomethyl] cyclohexane-1-carboxylate).

[[Click]] The MCC-DM1 complex is referred to as emtansine.

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.

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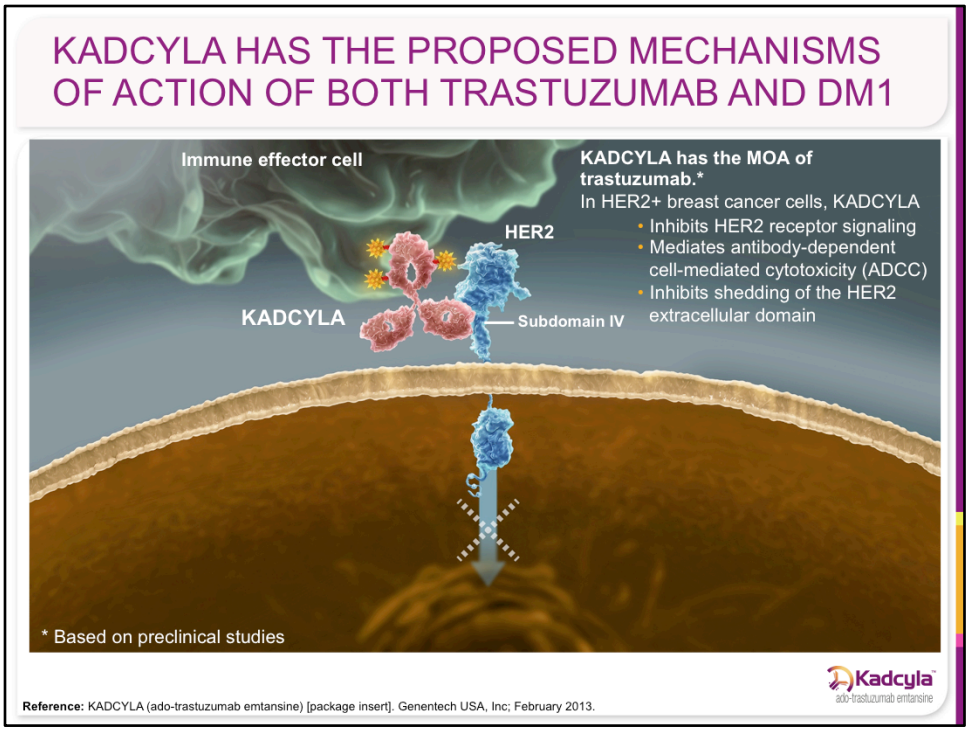

KADCYLA: Proposed Mechanism of Action

KADCYLA has the mechanisms of action of both trastuzumab and DM1.

KADCYLA, like trastuzumab, binds to subdomain IV of the HER2 extracellular domain (ECD).

In vitro studies have shown that KADCYLA, like trastuzumab, inhibits HER2 receptor signaling, mediates antibody-dependent cell-mediated cytotoxicity (ADCC), and inhibits shedding of the HER2 ECD in human breast cancer cells that overexpress HER2.

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.

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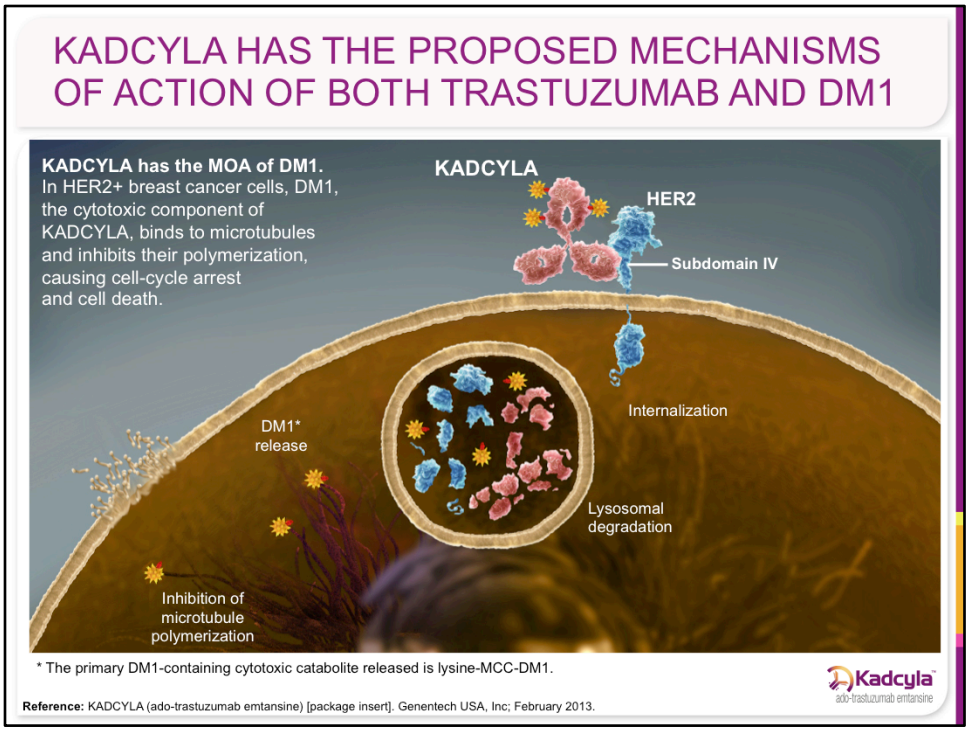

KADCYLA: Proposed Mechanism of Action

KADCYLA has the mechanisms of action of both trastuzumab and DM1.

After binding to the HER2 protein, KADCYLA is internalized by receptor-mediated endocytosis.

KADCYLA then undergoes lysosomal degradation, resulting in intracellular release of DM1-containing cytotoxic catabolites (primarily lysine-MCC-DM1).

DM1, the cytotoxic component of KADCYLA, binds to tubulin. Binding of DM1 to tubulin disrupts microtubule networks in the cell, which results in cell-cycle arrest and apoptotic cell death.

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.

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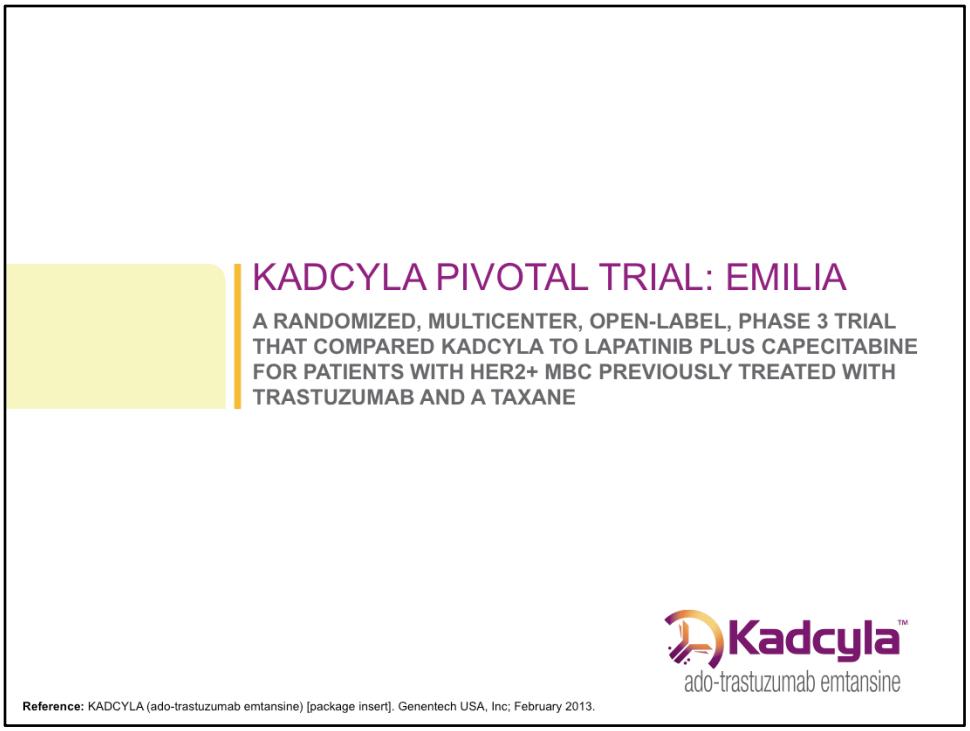

EMILIA Was the Pivotal Trial for KADCYLA

The efficacy and safety profile of KADCYLA were evaluated in a randomized, multicenter, open-label trial of 991 patients with HER2-positive, unresectable locally advanced breast cancer (LABC) or MBC. Prior taxane- and trastuzumab-based therapy was required before trial enrollment.

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.

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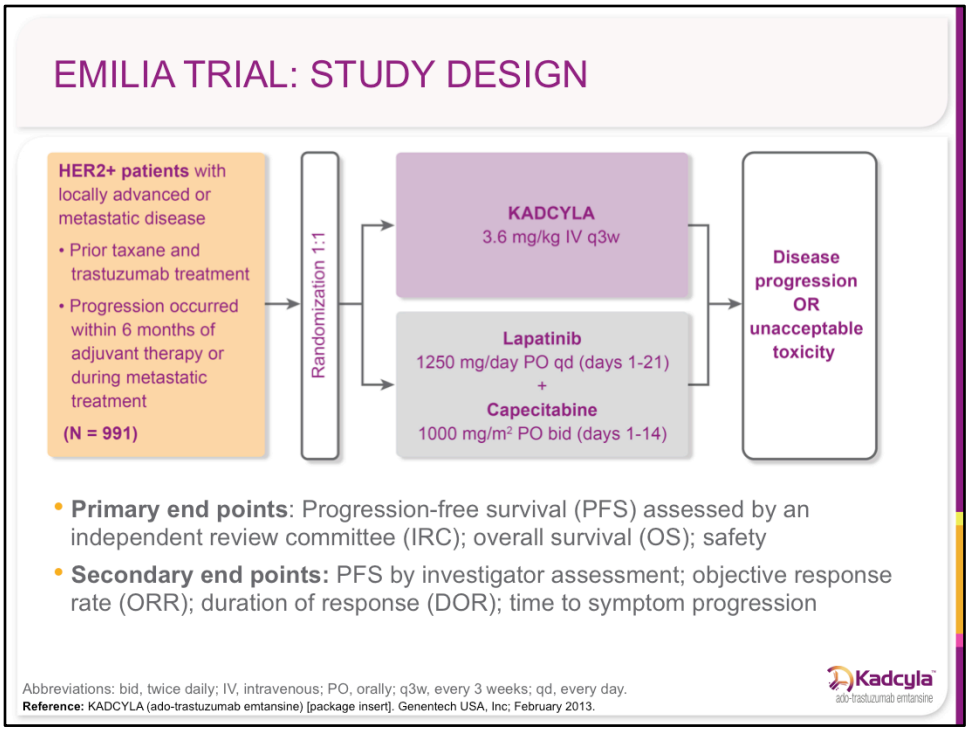


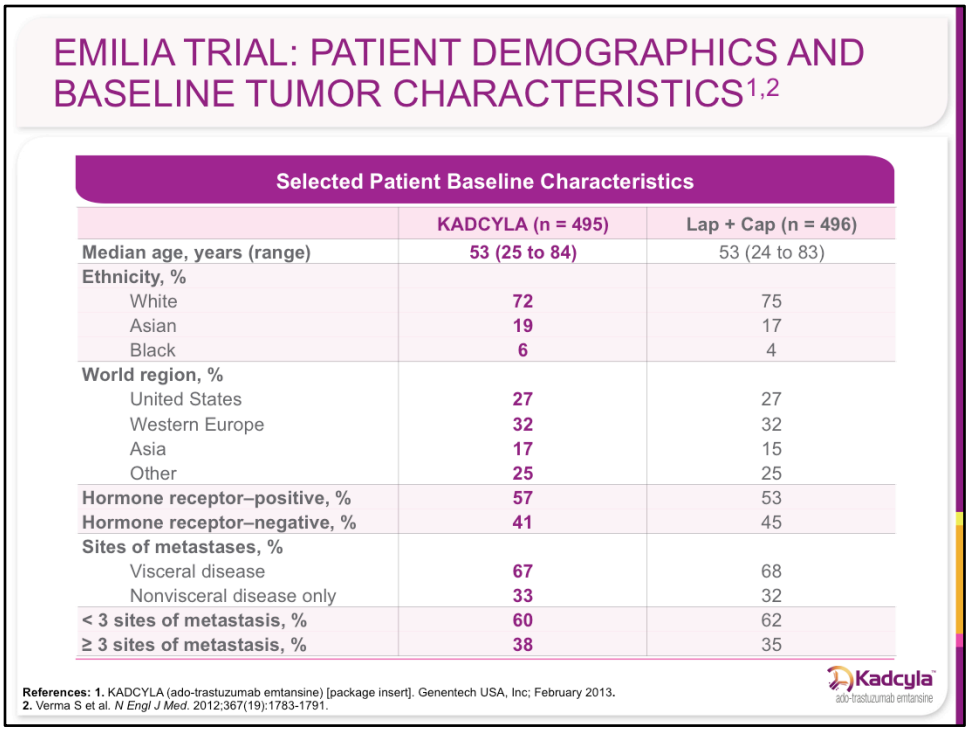
EMILIA Trial: Study Design

- Enrolled patients had
  - Unresectable LABC or MBC.
  - Prior taxane- and trastuzumab-based therapy, including prior therapy with trastuzumab and a taxane in the neoadjuvant or adjuvant setting, and relapse within 6 months of completing adjuvant therapy.
  - HER2+ cancer based on a central laboratory assay result.
    - Breast tumor samples were required to show HER2 overexpression defined as 3+ immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH) amplification ratio greater than or equal to 2.0.
- Patients were randomized 1:1 to receive either lapatinib plus capecitabine or KADCYLA.
  - Randomization was stratified by world region, number of prior chemotherapy regimens for unresectable locally advanced or metastatic disease (0 to 1, or more than 1), and visceral vs nonvisceral disease.
- The primary end points were progression-free survival (PFS) based on tumor-response assessments by an independent review committee (IRC), overall survival (OS), and safety.
  - 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 (ORR), duration of response (DOR), and time to symptom progression.

Dosing information

- KADCYLA was given intravenously at 3.6 mg/kg on day 1 of a 21-day cycle. There were no recommended premedications.
- Lapatinib was administered at 1250 mg orally once per day of a 21-day cycle, and capecitabine was administered at 1000 mg/m^2 orally twice daily on days 1 through 14 of a 21-day cycle.
- Patients were treated with either KADCYLA or lapatinib plus capecitabine until progression of disease, withdrawal of consent, or unacceptable toxicity.

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.



EMILIA Trial: Selected Patient Demographics and Baseline Tumor Characteristics[1,2]

Patient demographics and baseline tumor characteristics were balanced between treatment arms.

- All but 5 patients were women.

References: 1. KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013. **2**. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med*. 2012;367(19):1783-1791.

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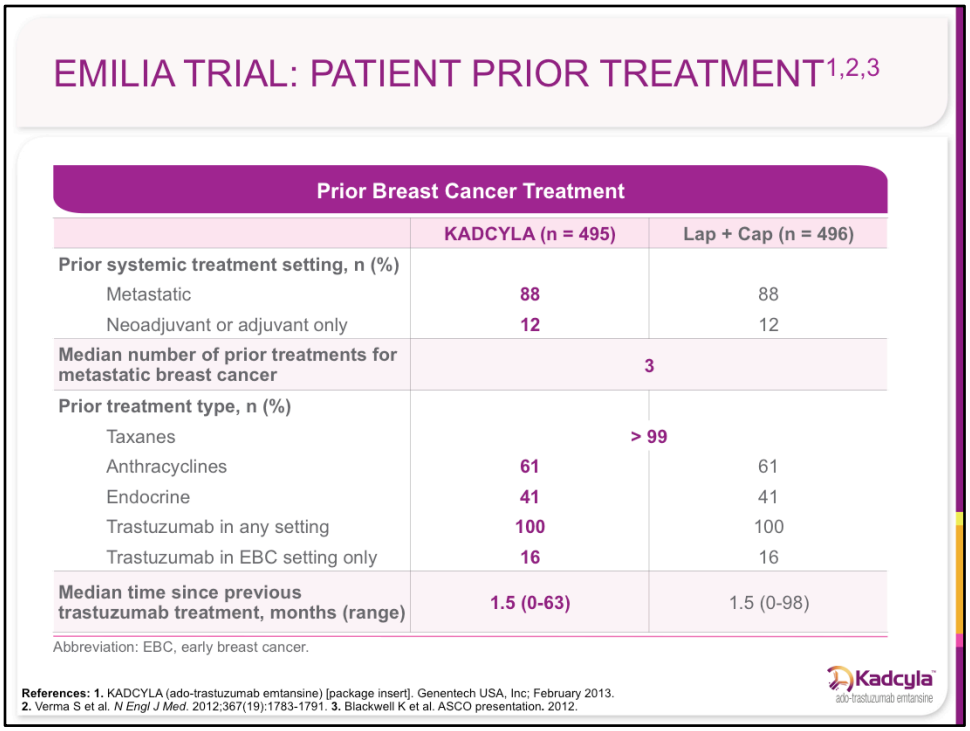

EMILIA Trial: Patient Prior Treatment[1,2,3]

Patients were balanced between treatment arms with respect to factors including type, number, and setting of prior systemic treatments for breast cancer.

References: 1. KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013. **2**. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med*. 2012;367(19):1783-1791. **3.** Blackwell K, Miles D, Gianni L, et al. Primary results from EMILIA, a phase III study of trastuzumab emtansine (T-DM1) versus capecitabine (X) and lapatinib (L) in HER2-positive locally advanced or metastatic breast cancer (MBC) previously treated with trastuzumab (T) and a taxane. Abstract presented at: ASCO 2012 Annual Meeting; June 1-5, 2012; Chicago, IL.

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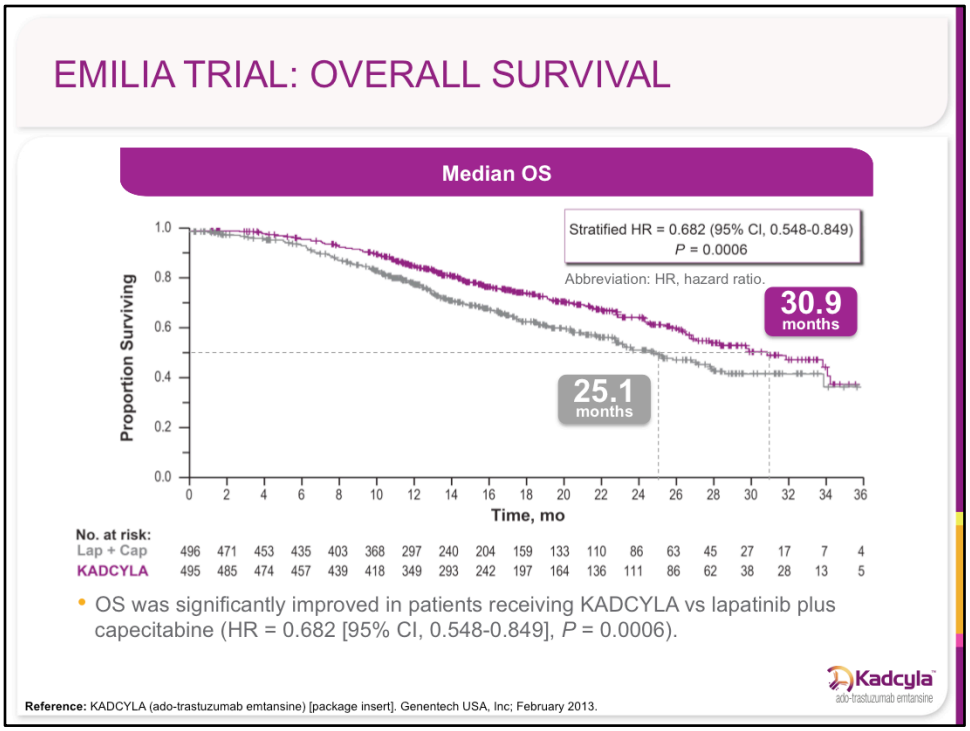

EMILIA Trial: Primary Efficacy End Point, OS

At the time of PFS analysis, 223 patients had died. More deaths occurred in the lapatinib-plus-capecitabine arm (26%) compared with the KADCYLA arm (19%); however, the results of this interim OS analysis did not meet the prespecified boundary for statistical significance.

At the time of the second interim OS analysis, 331 events had occurred. The coprimary end point of OS was met; OS was significantly improved in patients receiving KADCYLA vs lapatinib plus capecitabine (HR = 0.682 [95% CI, 0.548-0.849], *P* = 0.0006). The median duration of survival was 30.9 months in the KADCYLA arm vs 25.1 months in the lapatinib-plus-capecitabine arm.

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.

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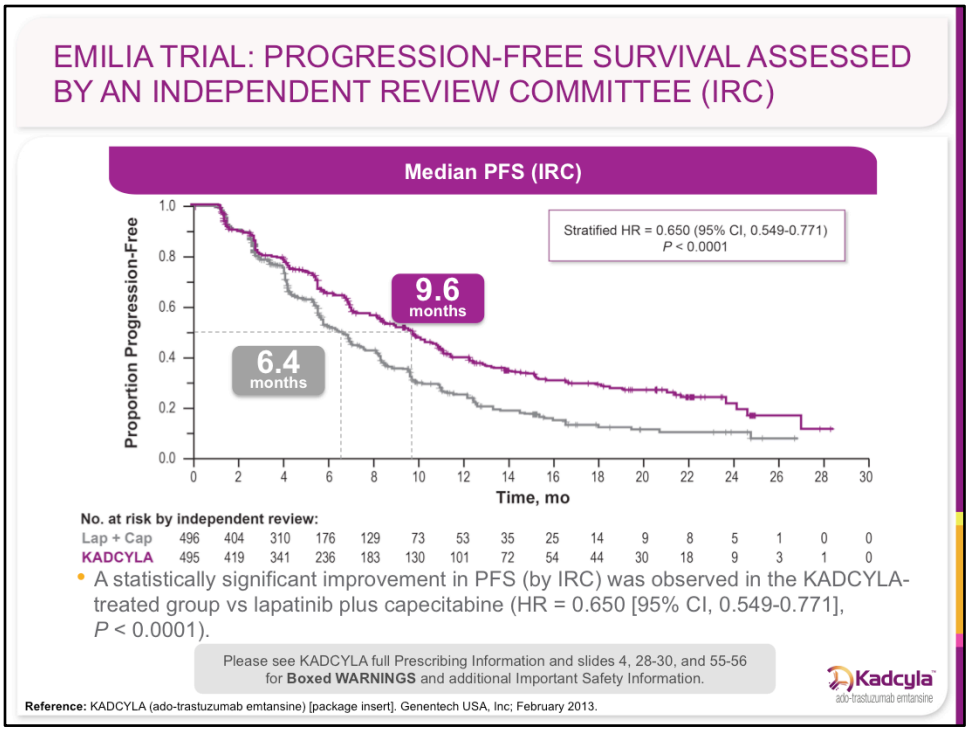

EMILIA Trial: Primary Efficacy End Point, PFS by IRC

In the EMILIA trial, a statistically significant improvement in IRC-assessed PFS was observed in the KADCYLA-treated group vs the lapatinib-plus-capecitabine-treated group (HR = 0.650 [95% CI, 0.549-0.771], *P* < 0.0001), with an increase in median PFS of 3.2 months (median PFS of 9.6 months in the KADCYLA-treated group vs 6.4 months in the lapatinib-plus-capecitabine group).

The results for PFS based on investigator assessments were similar to those observed for IRC-assessed PFS.

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.

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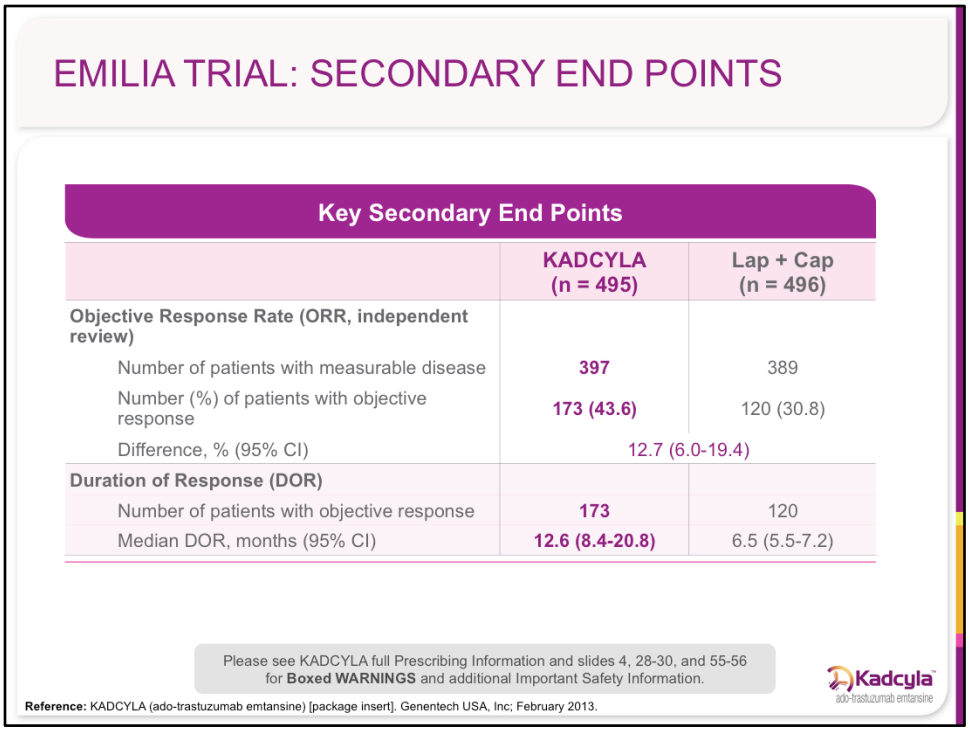

EMILIA Trial: Secondary End Points (ORR, DOR)

Review as stated.

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.

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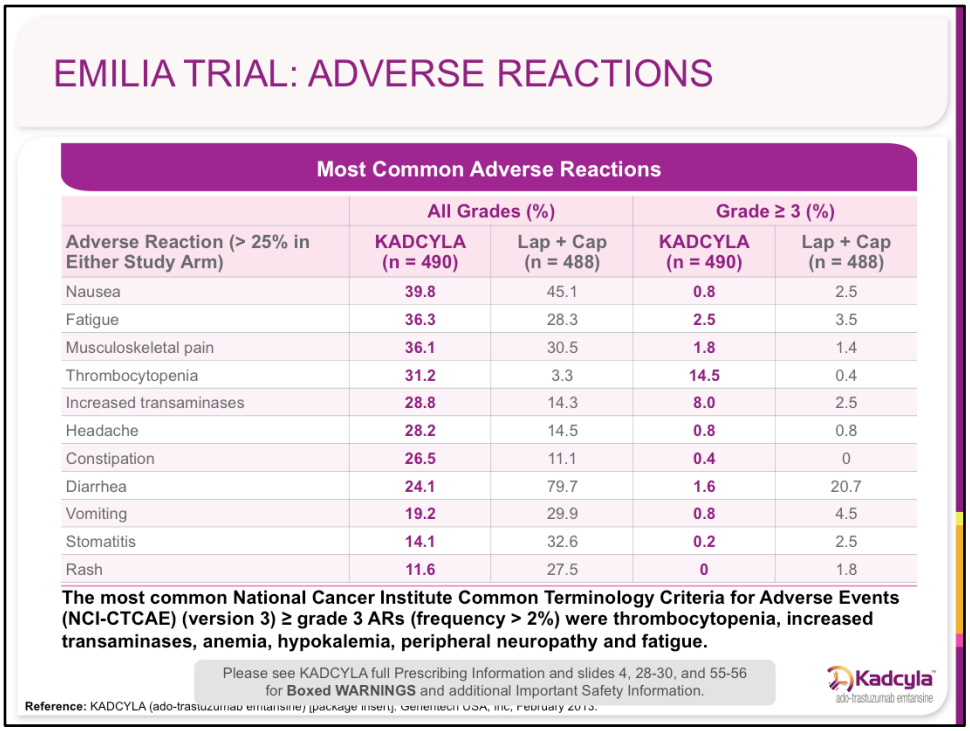

EMILIA TRIAL: ADVERSE REACTIONS

Most Common Adverse Reactions

	All Grades (%)		Grade ≥ 3 (%)	
Adverse Reaction (> 25% in Either Study Arm)	KADCYLA (n = 490)	Lap + Cap (n = 488)	KADCYLA (n = 490)	Lap + Cap (n = 488)
Nausea	**39.8**	45.1	**0.8**	2.5
Fatigue	**36.3**	28.3	**2.5**	3.5
Musculoskeletal pain	**36.1**	30.5	**1.8**	1.4
Thrombocytopenia	**31.2**	3.3	**14.5**	0.4
Increased transaminases	**28.8**	14.3	**8.0**	2.5
Headache	**28.2**	14.5	**0.8**	0.8
Constipation	**26.5**	11.1	**0.4**	0
Diarrhea	**24.1**	79.7	**1.6**	20.7
Vomiting	**19.2**	29.9	**0.8**	4.5
Stomatitis	**14.1**	32.6	**0.2**	2.5
Rash	**11.6**	27.5	**0**	1.8

The most common National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (version 3) ≥ grade 3 ARs (frequency > 2%) were thrombocytopenia, increased transaminases, anemia, hypokalemia, peripheral neuropathy and fatigue.

Please see KADCYLA full Prescribing Information and slides 4, 28-30, and 55-56 for **Boxed WARNINGS** and additional Important Safety Information.

Kadcyla ado-trastuzumab emtansine

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. Genentech USA, Inc; February 2013.

EMILIA Trial: Most Common Adverse Reactions

Review as stated.

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.

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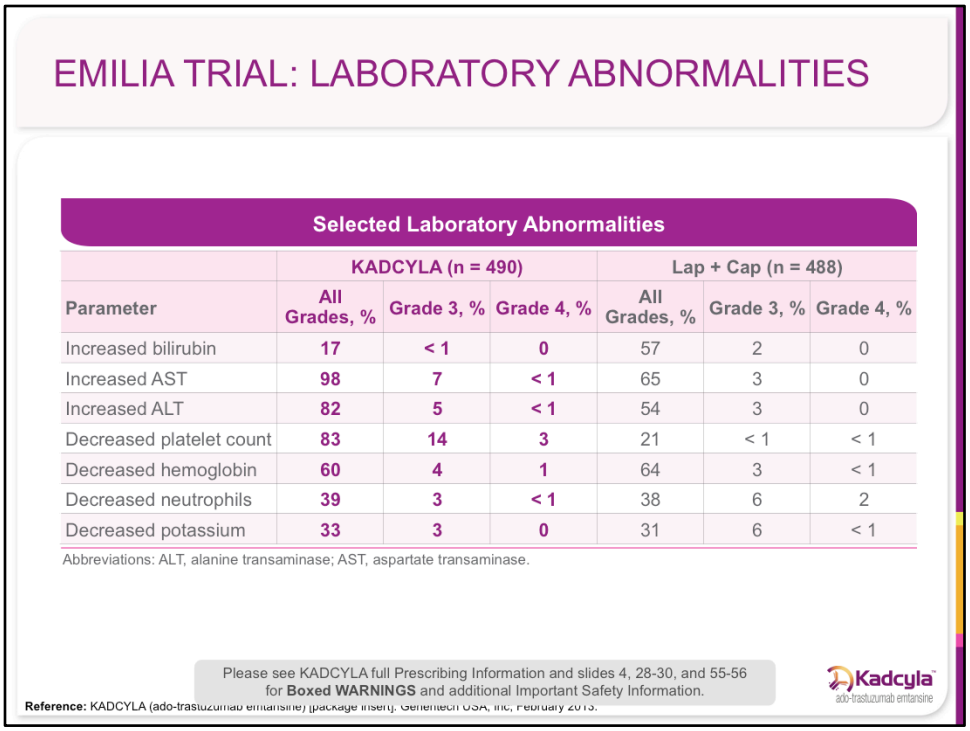

EMILIA Trial: Selected Laboratory Abnormalities

Review as stated.

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.

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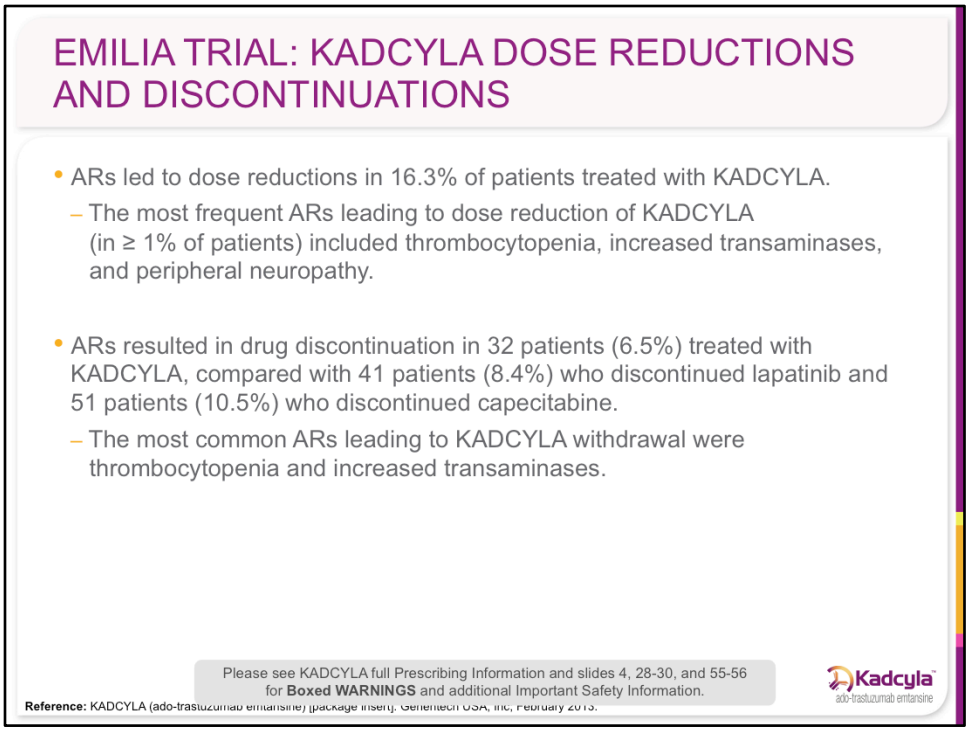

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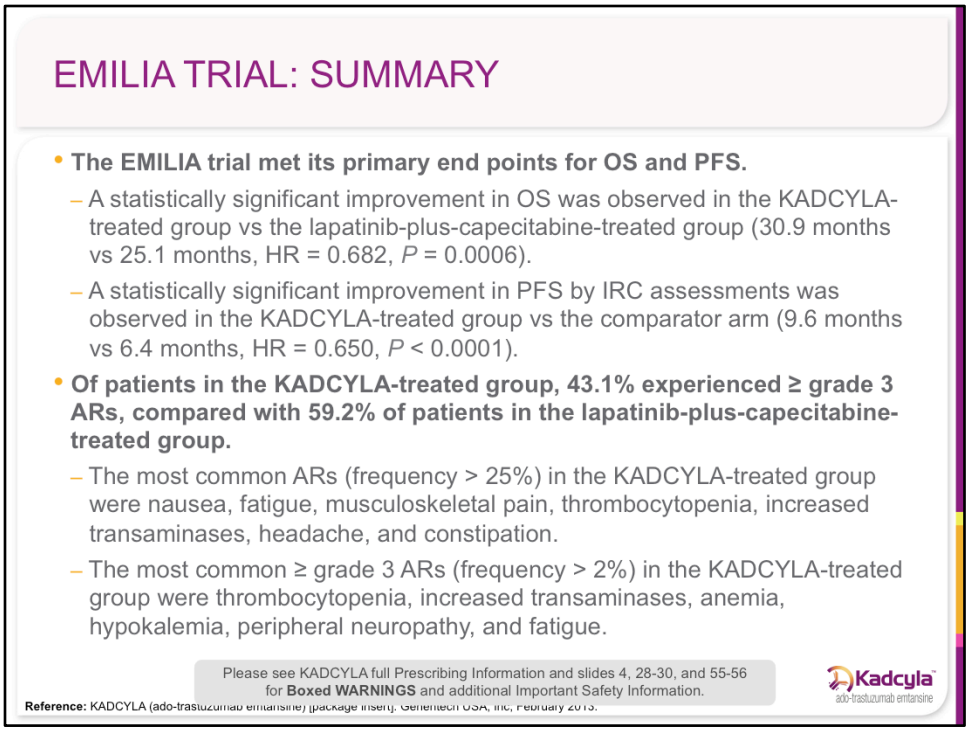
EMILIA Trial: KADCYLA Dose Reductions and Discontinuations

Review as stated.

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.



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EMILIA Trial: Summary

Review as stated.

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.

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KADCYLA: Dosage and Administration

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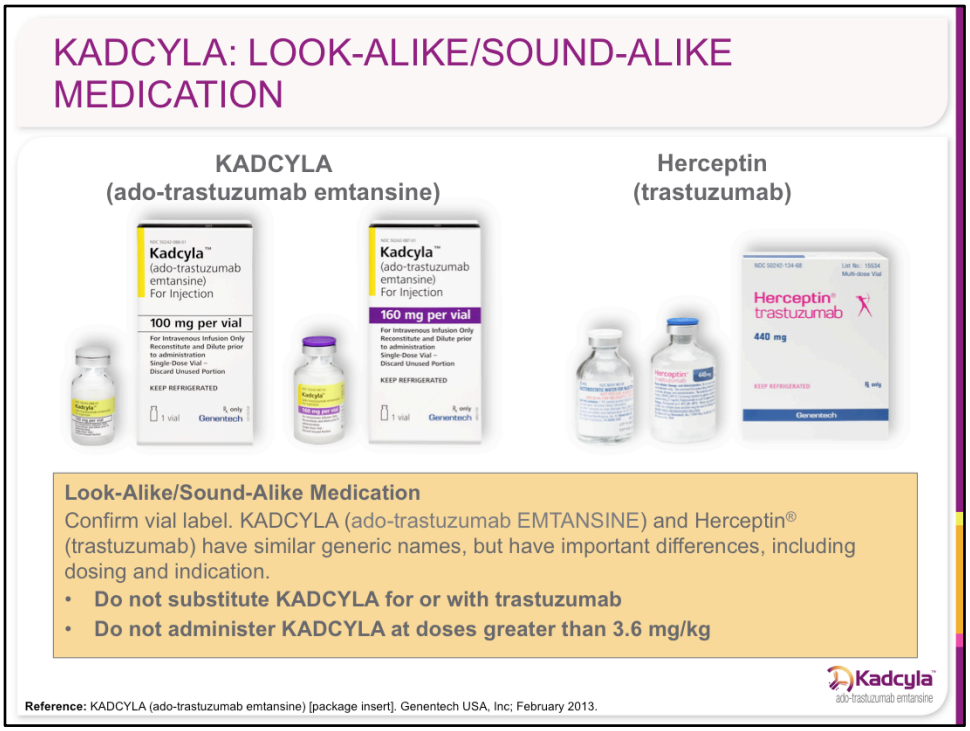

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KADCYLA: Look-Alike/Sound-Alike Medication

In order to prevent medication errors, it is important to check the vial labels to ensure that the drug being prepared and administered is KADCYLA (ado-trastuzumab emtansine) and not Herceptin (trastuzumab).

[[Click]] Look-Alike/Sound-Alike Medication

Confirm vial label. KADCYLA (ado-trastuzumab EMTANSINE) and Herceptin (trastuzumab) have similar generic names, but have important differences including dosing and indication.

- **Do not substitute KADCYLA for or with trastuzumab.**
- **Do not administer KADCYLA at doses greater than 3.6 mg/kg.**

There is no known antidote for overdose of KADCYLA. In clinical trials, overdose of KADCYLA has been reported at approximately 2 times the recommended dose, which resulted in grade 2 thrombocytopenia (resolved 4 days later) and 1 death. In the fatal case, the patient incorrectly received KADCYLA at 6 mg/kg and died approximately 3 weeks following the overdose; a cause of death and a causal relationship to KADCYLA were not established.

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.

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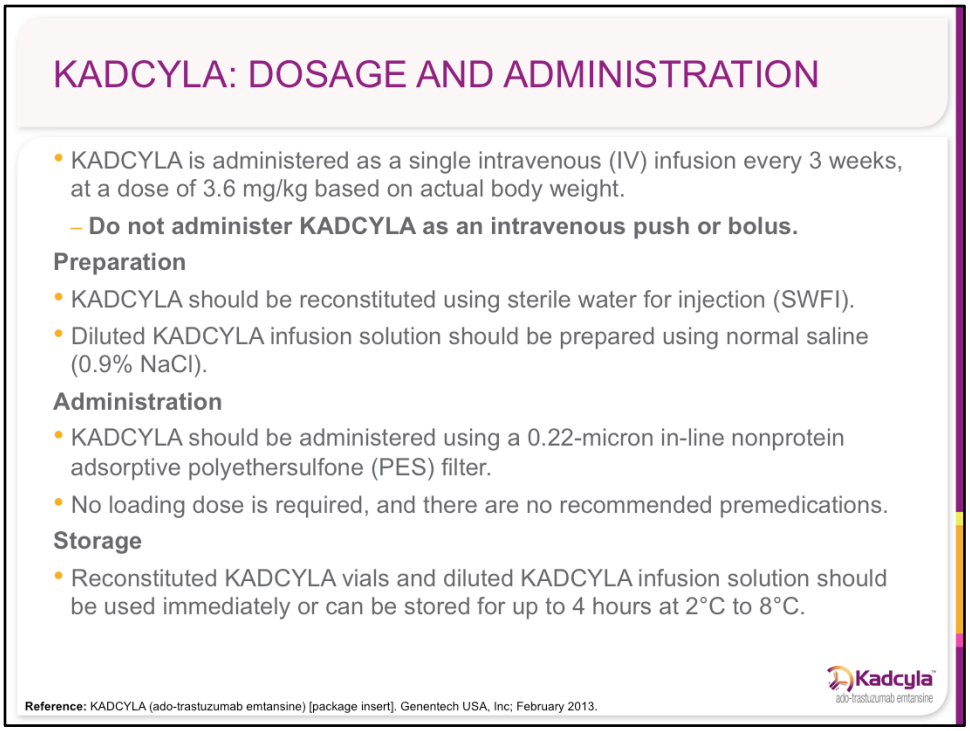

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KADCYLA: Dosage and Administration

- The recommended dose of KADCYLA is 3.6 mg/kg (based on actual body weight) given as an intravenous infusion every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.
    - **For intravenous infusion only. Do not administer as an intravenous push or bolus**.

[[Click]] Preparation

- KADCYLA should be reconstituted using sterile water for injection (SWFI).
- Diluted KADCYLA infusion solution should be prepared using normal saline (0.9% sodium chloride).

[[Click]] Administration

- KADCYLA should be administered using a 0.22-micron in-line nonprotein adsorptive polyethersulfone (PES) filter.
- No loading dose is required, and there are no recommended premedications.

[[Click]] Storage

- Reconstituted KADCYLA vials and diluted KADCYLA infusion solution should be used immediately or can be stored for up to 4 hours at 2°C to 8°C. **Do not freeze.**

PRESENTER NOTE: <u>For Reactive Use Only</u>

For reactive response to customer question on spoilage: If the Genentech medicine prescribed for a labeled indication was spoiled and unable to be administered, the product might be eligible for replacement through the Genentech Spoilage Replacement Program. Please call Genentech Customer Operations at 1-800-551-2231 for more information.

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.

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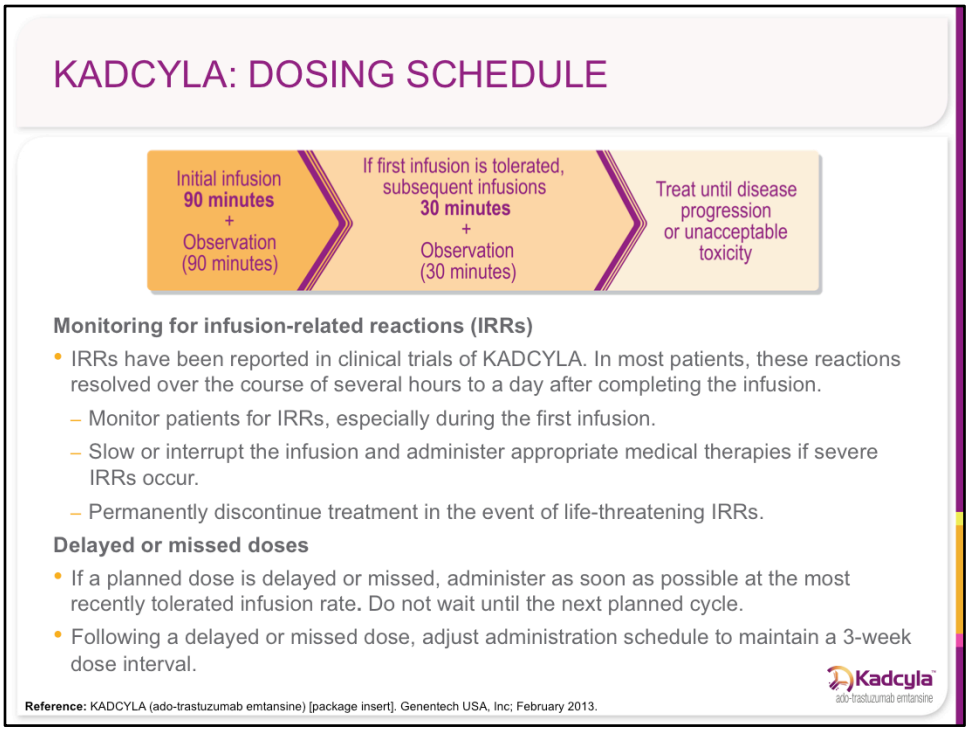

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KADCYLA: Dosing Schedule

First infusion: Administer infusion over 90 minutes. Patients should be observed during the first infusion and for at least 90 minutes following the initial dose for fever, chills, or other infusion-related reactions (IRRs). IRRs, characterized by one or more of the following symptoms—flushing, chills, pyrexia, dyspnea, hypotension, wheezing, bronchospasm, and tachycardia—have been reported in clinical trials with KADCYLA. In the EMILIA trial, the overall frequency of IRRs in patients treated with KADCYLA was 1.4%. In most patients, these reactions resolved over the course of several hours to a day after completing the infusion.

Slow or interrupt the infusion and administer appropriate medical therapies if severe IRRs occur.

- Permanently discontinue treatment in the event of life-threatening IRRs.

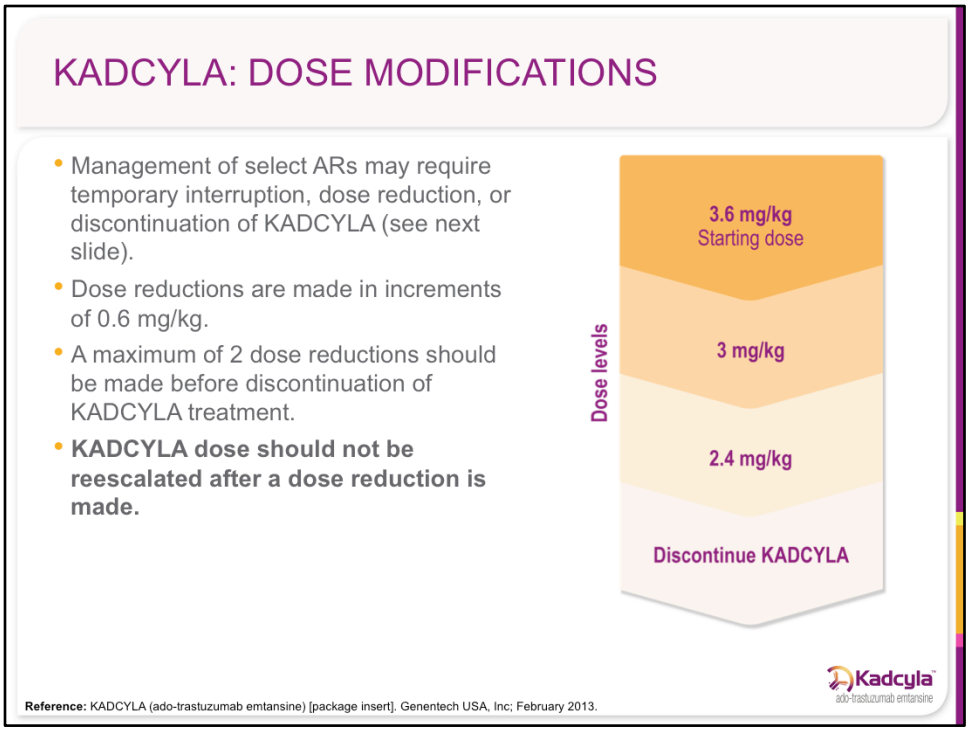
Subsequent infusions: Administer over 30 minutes if prior infusions were well tolerated. Patients should be observed during subsequent infusions and for at least 30 minutes after infusion.

***[[Click]]* Dose delay or missed dose**

- If a planned dose is delayed or missed, it should be administered as soon as possible; do not wait until the next planned cycle. The infusion may be administered at the dose and rate that the patient tolerated in the most recent infusion.
- The schedule of administration should be adjusted to maintain a 3-week interval between doses.

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.

49



[[Slide builds]]

KADCYLA: Dose Modifications

Management of select adverse reactions (ARs) may require temporary interruption, dose reduction, or discontinuation of KADCYLA. Please see the following slide for a list of the ARs.

[[Click]] Dose reductions are made in increments of 0.6 mg/kg.

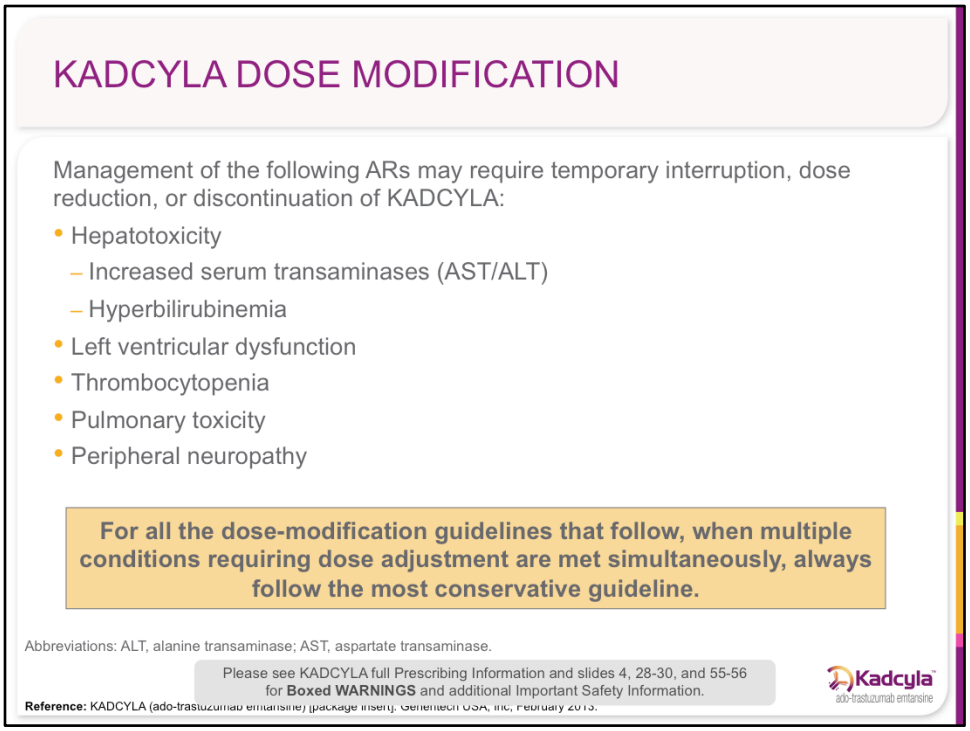
[[Click]] Two dose reductions are possible. If further dose reduction is required for patients receiving 2.4 mg/kg, discontinue KADCYLA.

[[Click]] **KADCYLA dose should not be reescalated after a dose reduction is made.**

The following slides will review situations in which dose adjustment or discontinuation may be required.

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.

50

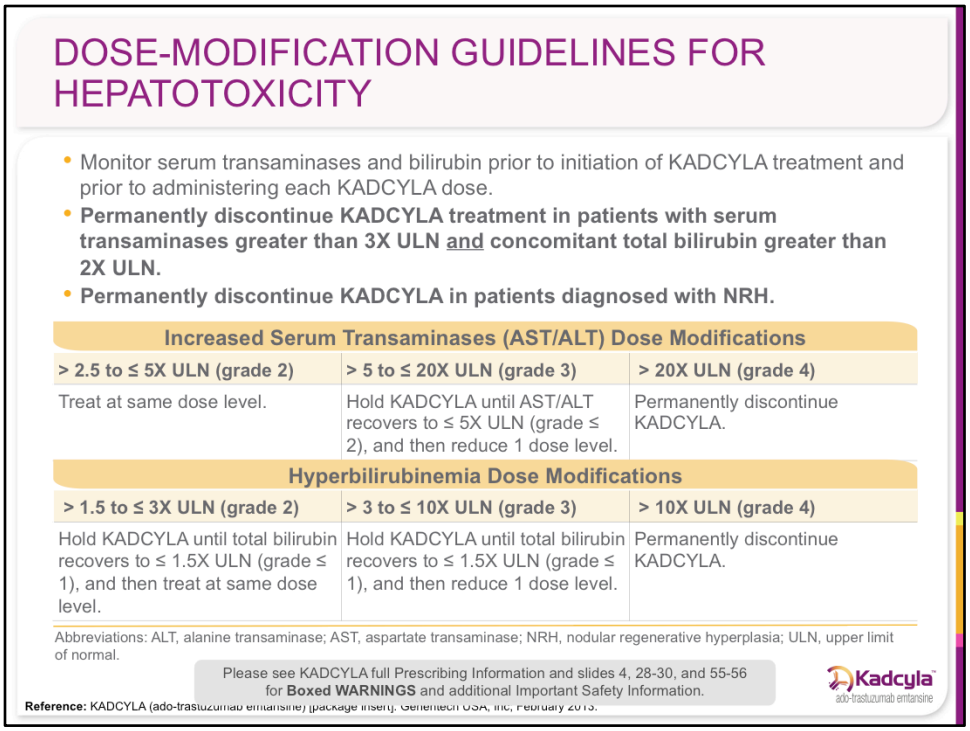


KADCYLA Dose Modification

Review as stated.

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.

51



DOSE-MODIFICATION GUIDELINES FOR HEPATOTOXICITY

- Monitor serum transaminases and bilirubin prior to initiation of KADCYLA treatment and prior to administering each KADCYLA dose.
- **Permanently discontinue KADCYLA treatment in patients with serum transaminases greater than 3X ULN and concomitant total bilirubin greater than 2X ULN.**
- **Permanently discontinue KADCYLA in patients diagnosed with NRH.**

Increased Serum Transaminases (AST/ALT) Dose Modifications		
> 2.5 to ≤ 5X ULN (grade 2)	**> 5 to ≤ 20X ULN (grade 3)**	**> 20X ULN (grade 4)**
Treat at same dose level.	Hold KADCYLA until AST/ALT recovers to ≤ 5X ULN (grade ≤ 2), and then reduce 1 dose level.	Permanently discontinue KADCYLA.
Hyperbilirubinemia Dose Modifications		
> 1.5 to ≤ 3X ULN (grade 2)	**> 3 to ≤ 10X ULN (grade 3)**	**> 10X ULN (grade 4)**
Hold KADCYLA until total bilirubin recovers to ≤ 1.5X ULN (grade ≤ 1), and then treat at same dose level.	Hold KADCYLA until total bilirubin recovers to ≤ 1.5X ULN (grade ≤ 1), and then reduce 1 dose level.	Permanently discontinue KADCYLA.

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; NRH, nodular regenerative hyperplasia; ULN, upper limit of normal.

Please see KADCYLA full Prescribing Information and slides 4, 28-30, and 55-56 for **Boxed WARNINGS** and additional Important Safety Information.

Kadcyla ado-trastuzumab emtansine

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. Genentech USA, Inc; February 2013.

KADCYLA: Dose-Modification Guidelines for Hepatotoxicity

Review as stated.

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.

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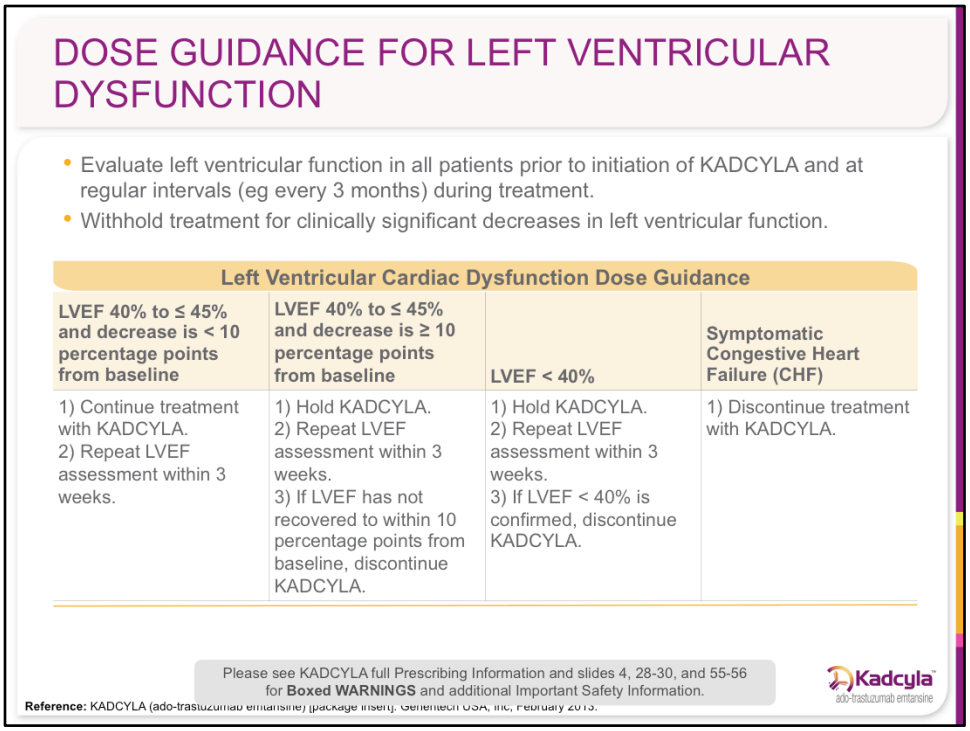

KADCYLA: Dose Guidance for Left Ventricular Dysfunction

Review as stated.

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.

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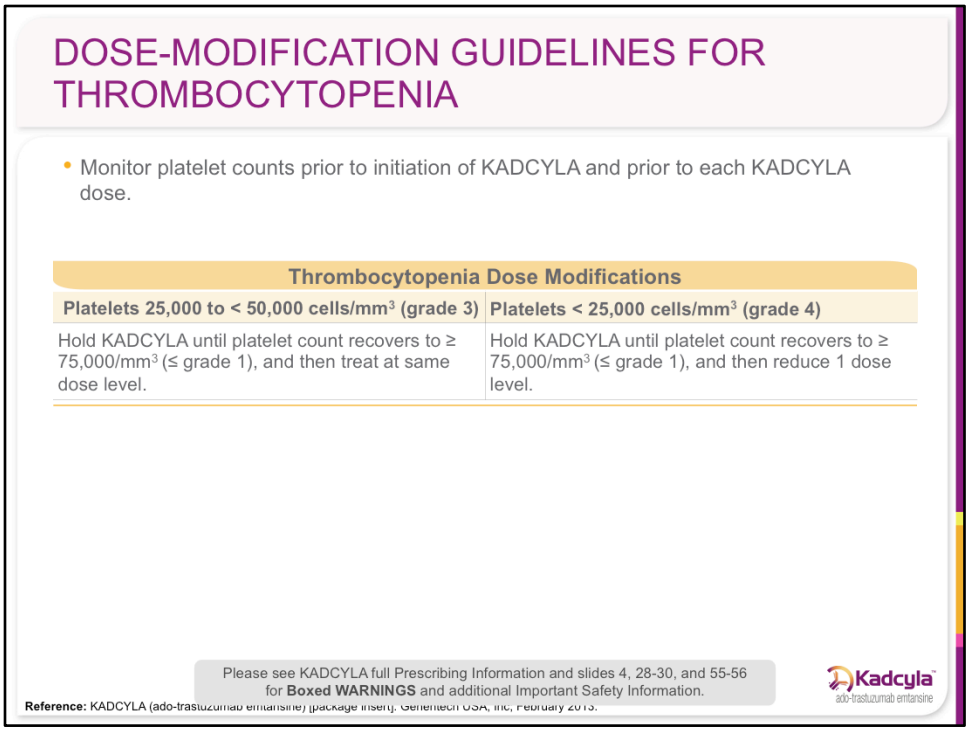

KADCYLA: Dose-Modification Guidelines for Thrombocytopenia

Review as stated.

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.

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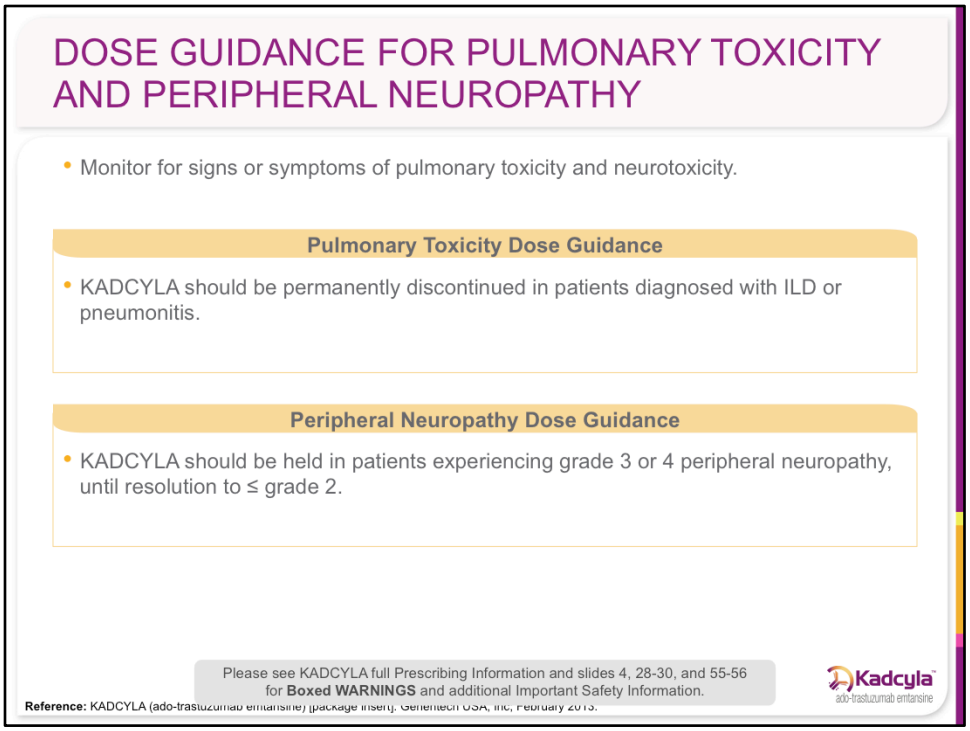
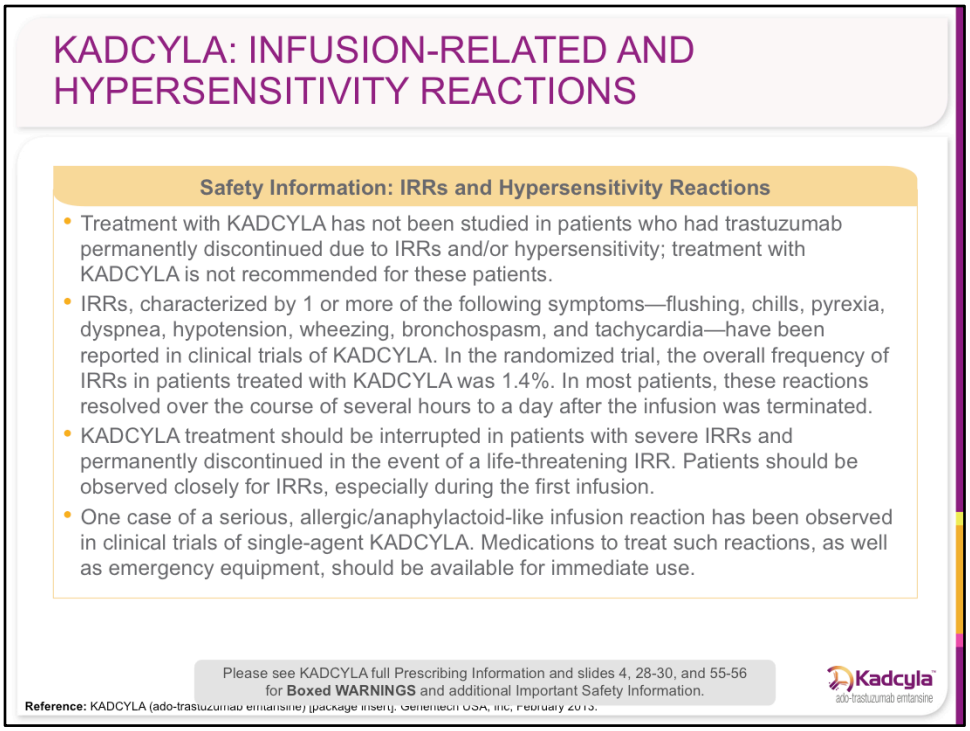


KADCYLA: Dose Guidance for Pulmonary Toxicity and Peripheral Neuropathy

Review as stated.

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.

55



KADCYLA: Infusion-Related and Hypersensitivity Reactions

Review as stated.

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.

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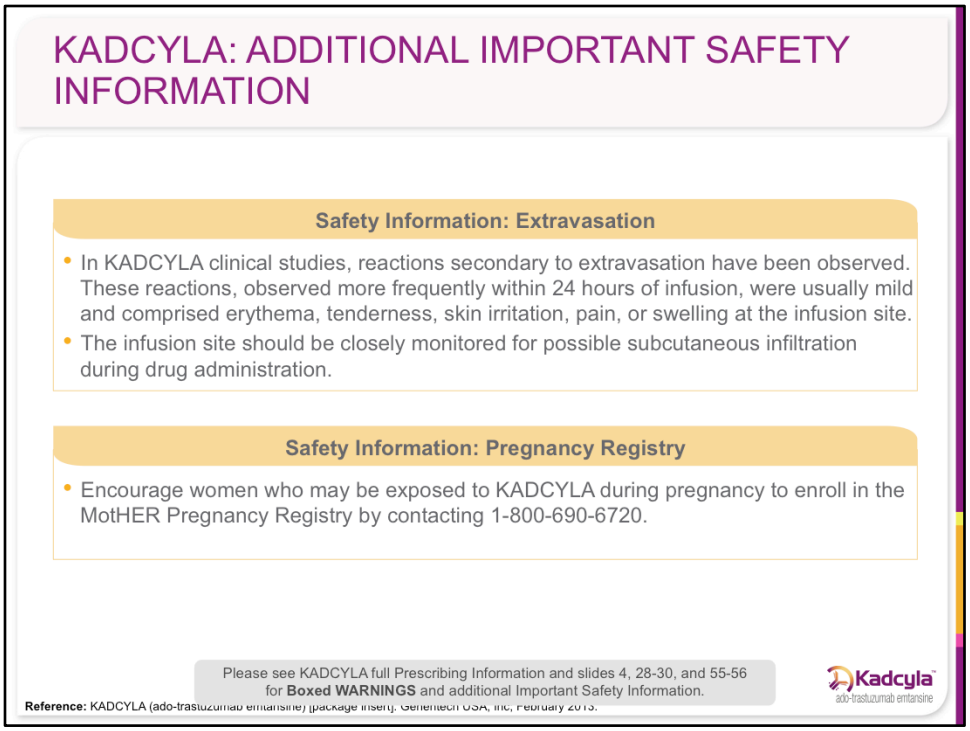
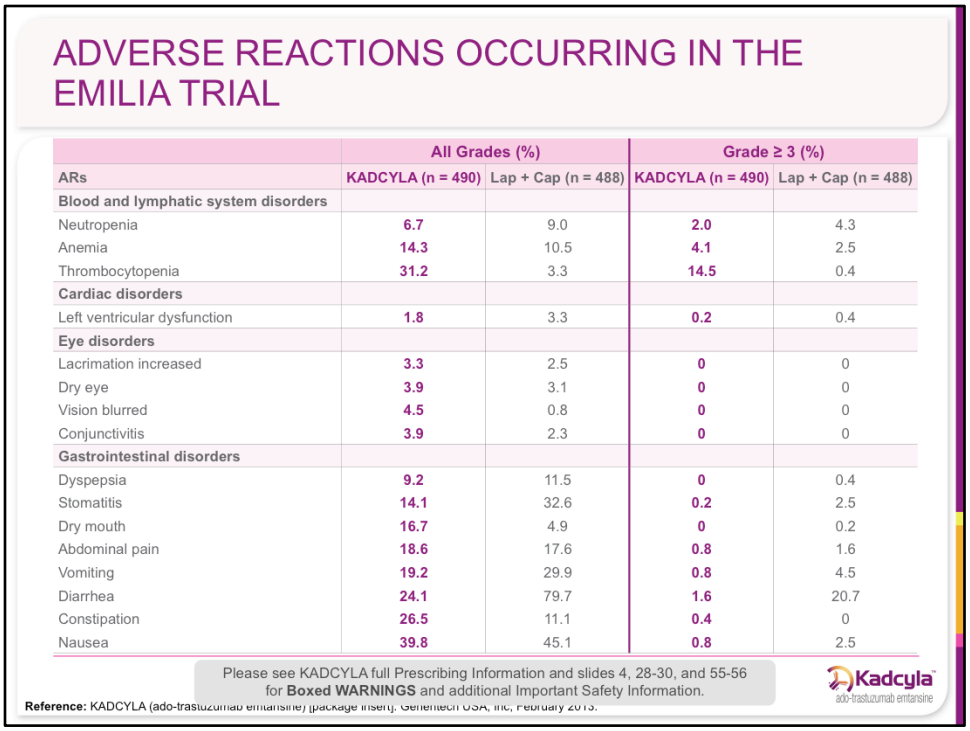


KADCYLA: Additional Important Safety Information

Review as stated.

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.

57



ADVERSE REACTIONS OCCURRING IN THE EMILIA TRIAL

	All Grades (%)		Grade ≥ 3 (%)	
ARs	KADCYLA (n = 490)	Lap + Cap (n = 488)	KADCYLA (n = 490)	Lap + Cap (n = 488)
Blood and lymphatic system disorders				
Neutropenia	6.7	9.0	2.0	4.3
Anemia	14.3	10.5	4.1	2.5
Thrombocytopenia	31.2	3.3	14.5	0.4
Cardiac disorders				
Left ventricular dysfunction	1.8	3.3	0.2	0.4
Eye disorders				
Lacrimation increased	3.3	2.5	0	0
Dry eye	3.9	3.1	0	0
Vision blurred	4.5	0.8	0	0
Conjunctivitis	3.9	2.3	0	0
Gastrointestinal disorders				
Dyspepsia	9.2	11.5	0	0.4
Stomatitis	14.1	32.6	0.2	2.5
Dry mouth	16.7	4.9	0	0.2
Abdominal pain	18.6	17.6	0.8	1.6
Vomiting	19.2	29.9	0.8	4.5
Diarrhea	24.1	79.7	1.6	20.7
Constipation	26.5	11.1	0.4	0
Nausea	39.8	45.1	0.8	2.5

Please see KADCYLA full Prescribing Information and slides 4, 28-30, and 55-56 for **Boxed WARNINGS** and additional Important Safety Information.

Kadcyla ado-trastuzumab emtansine

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. Genentech USA, Inc; February 2013.

Adverse Reactions Occurring in the EMILIA Trial

Review as stated.

The table on slides 36 through 38 lists all adverse reactions observed in the KADCYLA-treated arm of the EMILIA trial.

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.

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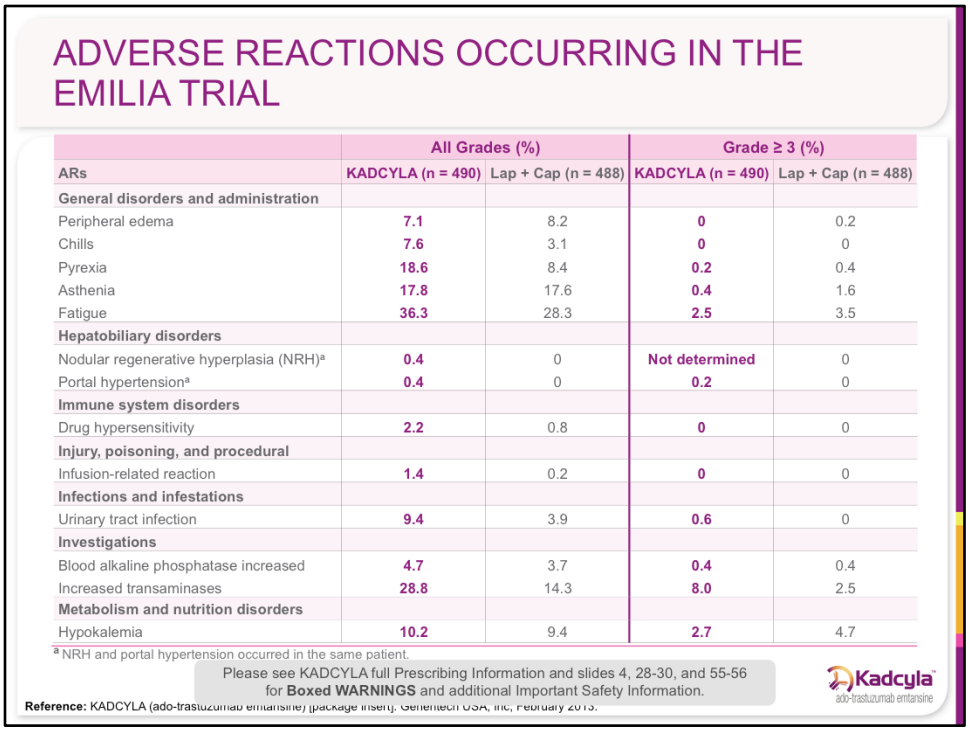

ADVERSE REACTIONS OCCURRING IN THE EMILIA TRIAL

	All Grades (%)		Grade ≥ 3 (%)	
ARs	**KADCYLA (n = 490)**	**Lap + Cap (n = 488)**	**KADCYLA (n = 490)**	**Lap + Cap (n = 488)**
General disorders and administration				
Peripheral edema	**7.1**	8.2	**0**	0.2
Chills	**7.6**	3.1	**0**	0
Pyrexia	**18.6**	8.4	**0.2**	0.4
Asthenia	**17.8**	17.6	**0.4**	1.6
Fatigue	**36.3**	28.3	**2.5**	3.5
Hepatobiliary disorders				
Nodular regenerative hyperplasia (NRH)[a]	**0.4**	0	**Not determined**	0
Portal hypertension[a]	**0.4**	0	**0.2**	0
Immune system disorders				
Drug hypersensitivity	**2.2**	0.8	**0**	0
Injury, poisoning, and procedural				
Infusion-related reaction	**1.4**	0.2	**0**	0
Infections and infestations				
Urinary tract infection	**9.4**	3.9	**0.6**	0
Investigations				
Blood alkaline phosphatase increased	**4.7**	3.7	**0.4**	0.4
Increased transaminases	**28.8**	14.3	**8.0**	2.5
Metabolism and nutrition disorders				
Hypokalemia	**10.2**	9.4	**2.7**	4.7

[a] NRH and portal hypertension occurred in the same patient.

Please see KADCYLA full Prescribing Information and slides 4, 28-30, and 55-56 for **Boxed WARNINGS** and additional Important Safety Information.

Kadcyla ado-trastuzumab emtansine

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. Genentech USA, Inc; February 2013.

Adverse Reactions Occurring in the EMILIA Trial

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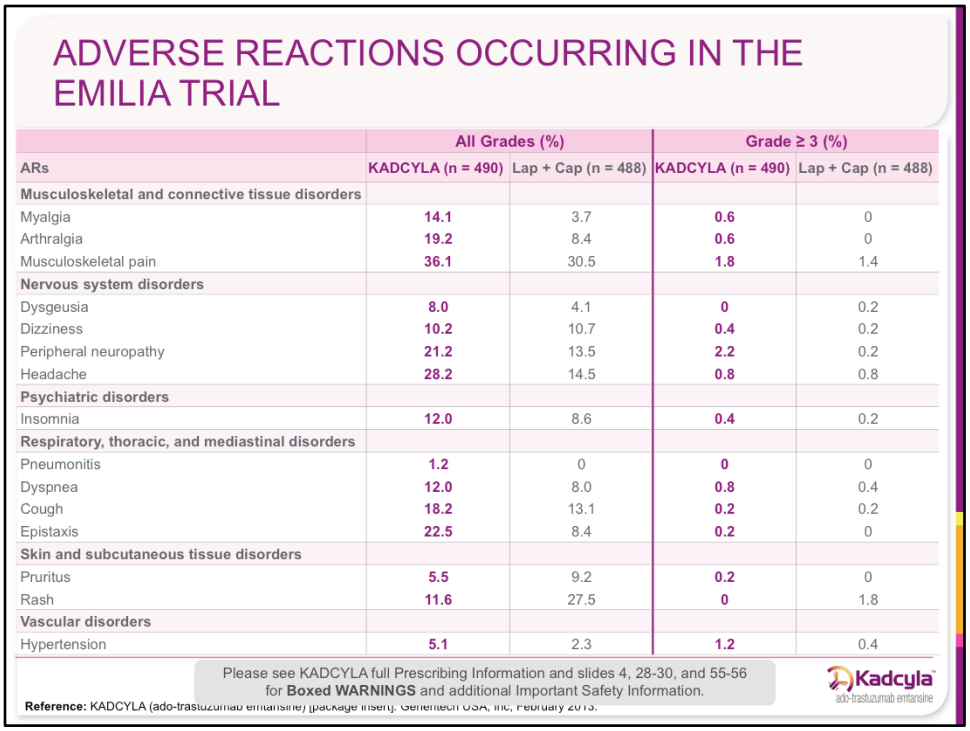
59



ADVERSE REACTIONS OCCURRING IN THE EMILIA TRIAL

	All Grades (%)		Grade ≥ 3 (%)	
ARs	**KADCYLA (n = 490)**	**Lap + Cap (n = 488)**	**KADCYLA (n = 490)**	**Lap + Cap (n = 488)**
Musculoskeletal and connective tissue disorders				
Myalgia	**14.1**	3.7	**0.6**	0
Arthralgia	**19.2**	8.4	**0.6**	0
Musculoskeletal pain	**36.1**	30.5	**1.8**	1.4
Nervous system disorders				
Dysgeusia	**8.0**	4.1	**0**	0.2
Dizziness	**10.2**	10.7	**0.4**	0.2
Peripheral neuropathy	**21.2**	13.5	**2.2**	0.2
Headache	**28.2**	14.5	**0.8**	0.8
Psychiatric disorders				
Insomnia	**12.0**	8.6	**0.4**	0.2
Respiratory, thoracic, and mediastinal disorders				
Pneumonitis	**1.2**	0	**0**	0
Dyspnea	**12.0**	8.0	**0.8**	0.4
Cough	**18.2**	13.1	**0.2**	0.2
Epistaxis	**22.5**	8.4	**0.2**	0
Skin and subcutaneous tissue disorders				
Pruritus	**5.5**	9.2	**0.2**	0
Rash	**11.6**	27.5	**0**	1.8
Vascular disorders				
Hypertension	**5.1**	2.3	**1.2**	0.4

Please see KADCYLA full Prescribing Information and slides 4, 28-30, and 55-56 for **Boxed WARNINGS** and additional Important Safety Information.

Kadcyla ado-trastuzumab emtansine

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. Genentech USA, Inc; February 2013.

Adverse Reactions Occurring in the EMILIA Trial

Review as stated.

The table on slides 36 through 38 lists all adverse reactions observed in the KADCYLA-treated arm of the EMILIA trial.

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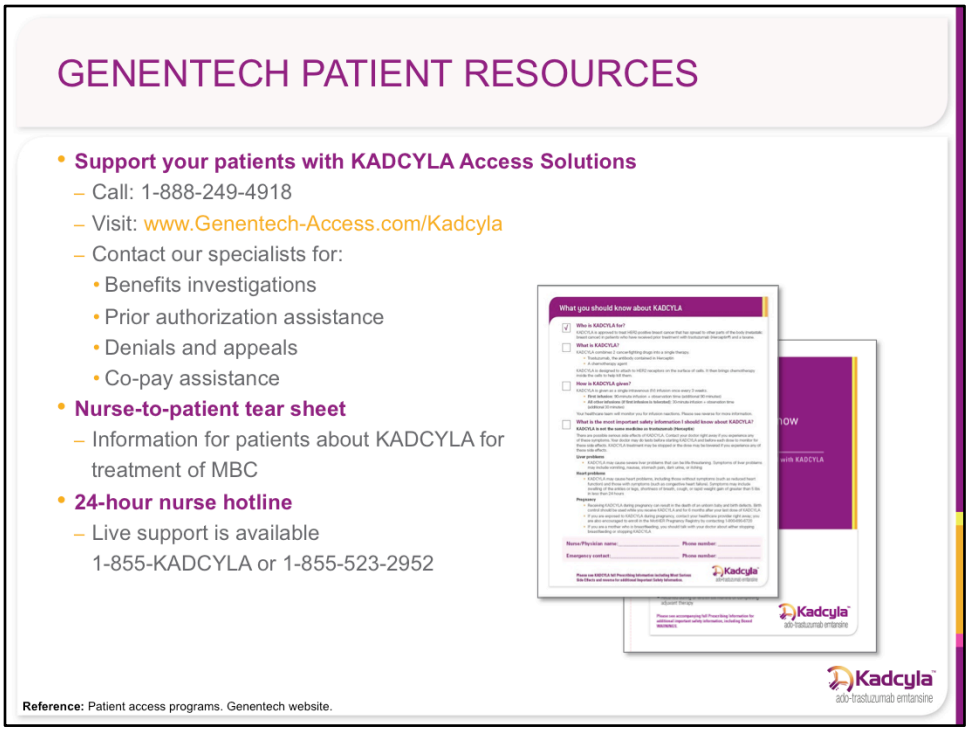

Genentech Patient Resources

Review as stated.

Reference: Patient access programs. Genentech website. http://www.genentech-access.com/patients. Accessed February 21, 2013.


THANK YOU & QUESTIONS

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OPTIONAL SLIDES

Kadcyla™
ado-trastuzumab emtansine

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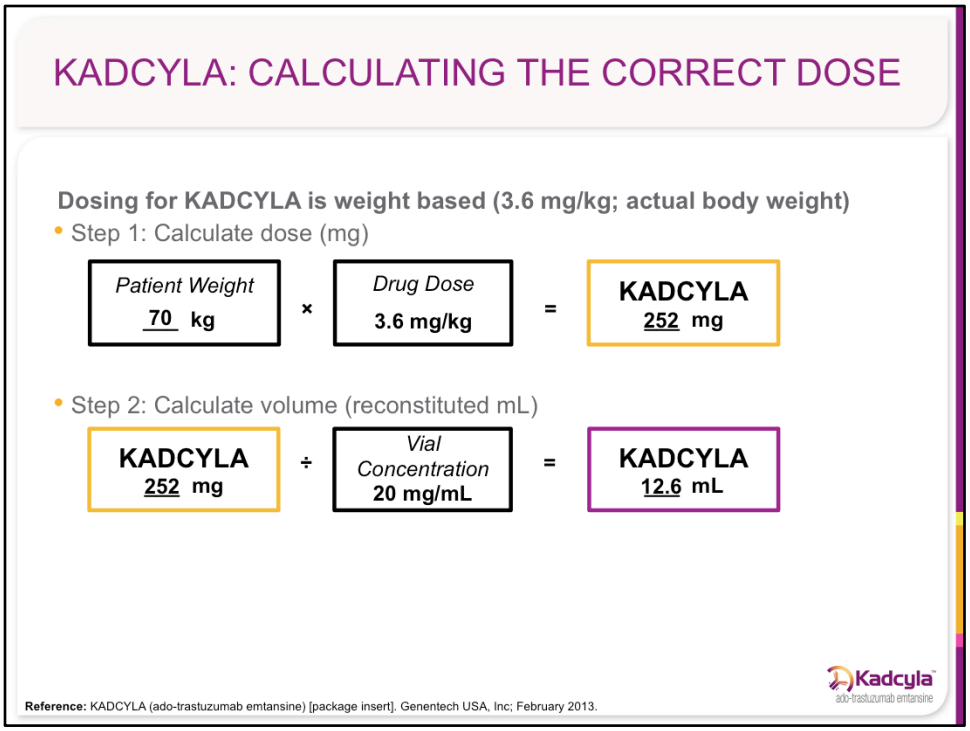

[[Slide builds]]

KADCYLA: Dose Calculation

Dosing for KADCYLA is based on actual patient body weight. The dose is 3.6 mg/kg.

[[Click]] First, calculate the mg of KADCYLA needed as shown.

[[Click]] Second, calculate the volume of reconstituted KADCYLA solution as shown.

[[Click]] For example, for a patient who weighs 70 kg (154 pounds), *[[Click]]* the correct dose of KADCYLA would be *[[Click]]* 252 mg, and *[[Click]]* the volume of reconstituted KADCYLA solution would be *[[Click]]* 12.6 mL.

Reference: KADCYLA [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.

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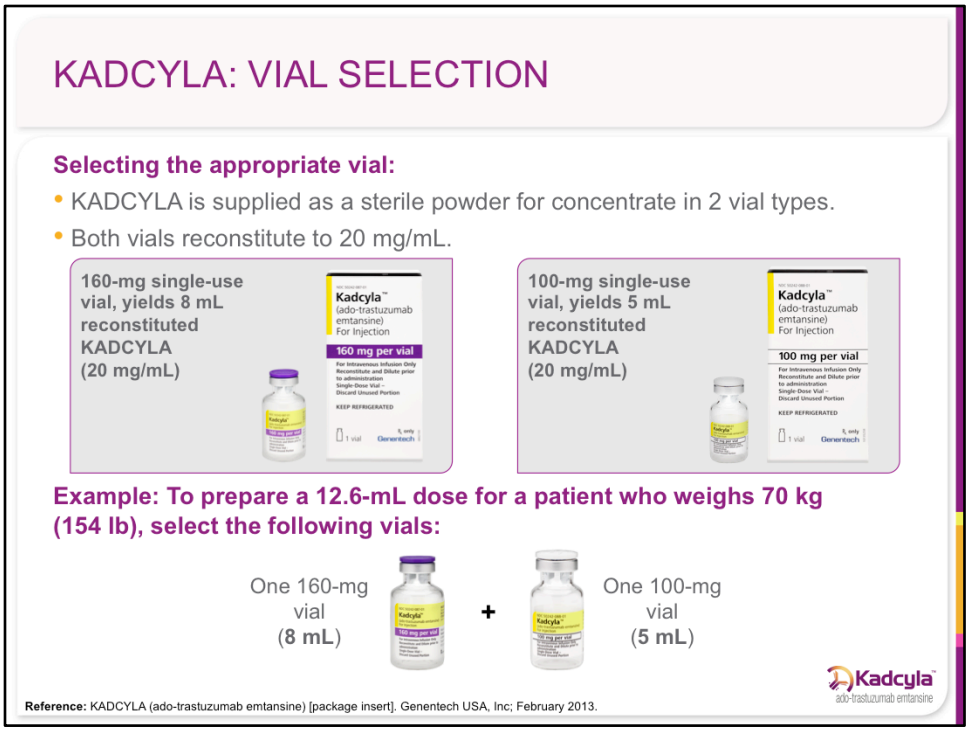

[[Slide builds]]

KADCYLA: Vial Selection

Review vial descriptions as stated.

[Click]] For the example of a 70-kg patient from the previous slide, one 160-mg vial plus one 100-mg vial would provide 13 mL of KADCYLA solution, enough to prepare the 12.6-mL dose.

This example demonstrates vial selection based on minimizing waste of KADCYLA solution. Actual vial selections may differ, depending on clinic or pharmacy standards in product stocking or other variables.

PRESENTER NOTE: <u>For Reactive Use Only</u>

For reactive response to customer questions on wastage: Wastage policies are payer-specific based on a patient's policy. You can contact the patient's payer directly for the most accurate information on reimbursement for wastage. I can also have a BioOncology Field Reimbursement Manager (BFRM) contact you should you have additional questions about billing and coding.

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.

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IPR2014-00676

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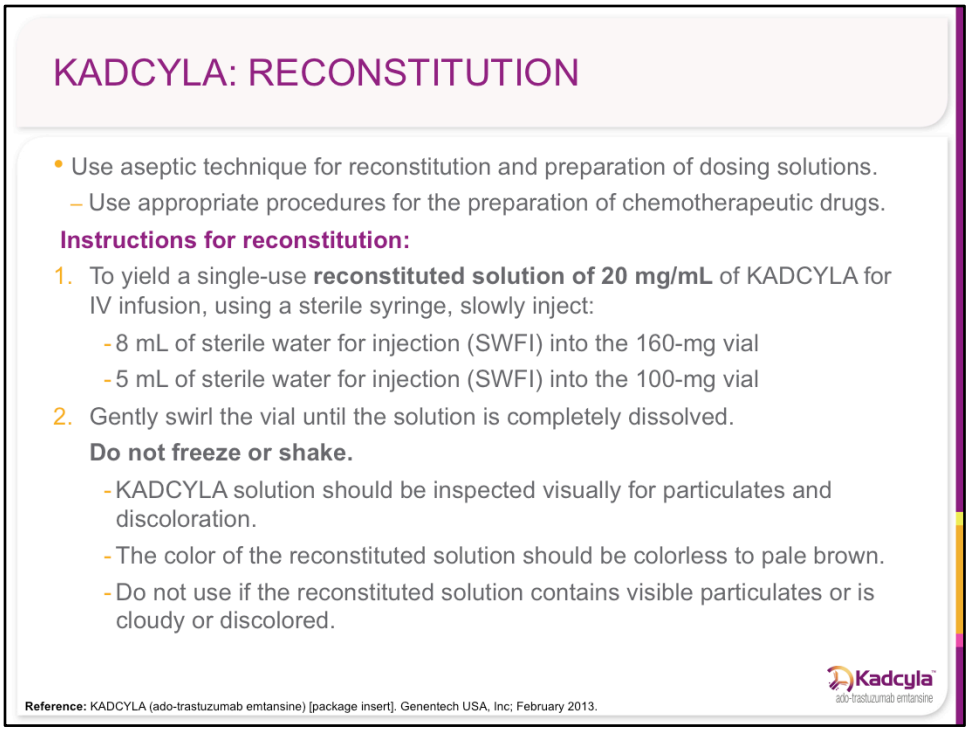

[[Slide builds]]

KADCYLA: Reconstitution

Review as stated.

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.

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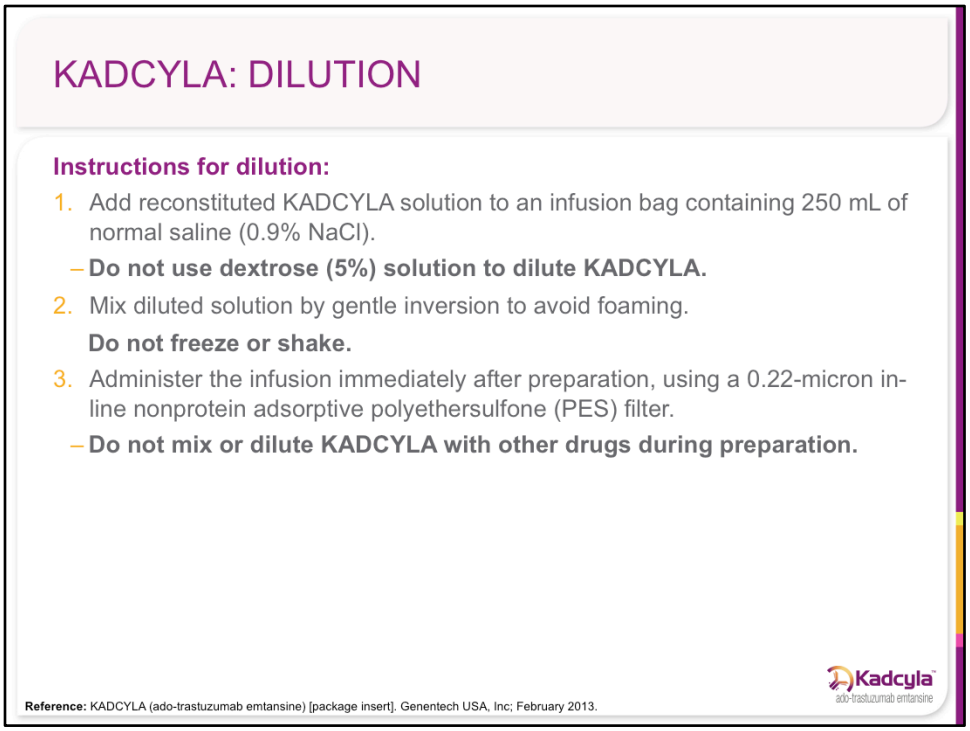

KADCYLA: Dilution

Calculate the volume of the 20-mg/mL reconstituted KADCYLA solution needed, withdraw this amount from the vial, and add it to an infusion bag containing 250 mL of normal saline (0.9% sodium chloride).

- **Do not use dextrose (5%) solution to dilute KADCYLA.**

Mix the diluted solution by gentle inversion to avoid foaming. **Do not freeze or shake.**

Administer the infusion immediately after preparation.

- Use a 0.22-micron in-line nonprotein adsorptive PES filter.
- **Do not mix or dilute KADCYLA with other drugs during preparation.**

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.

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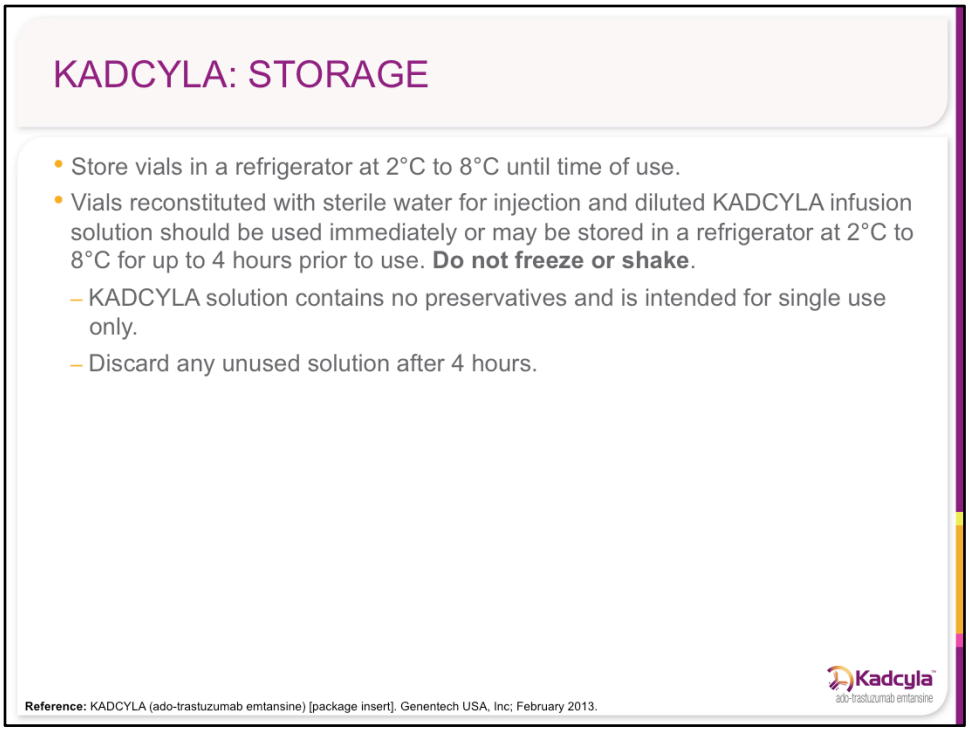
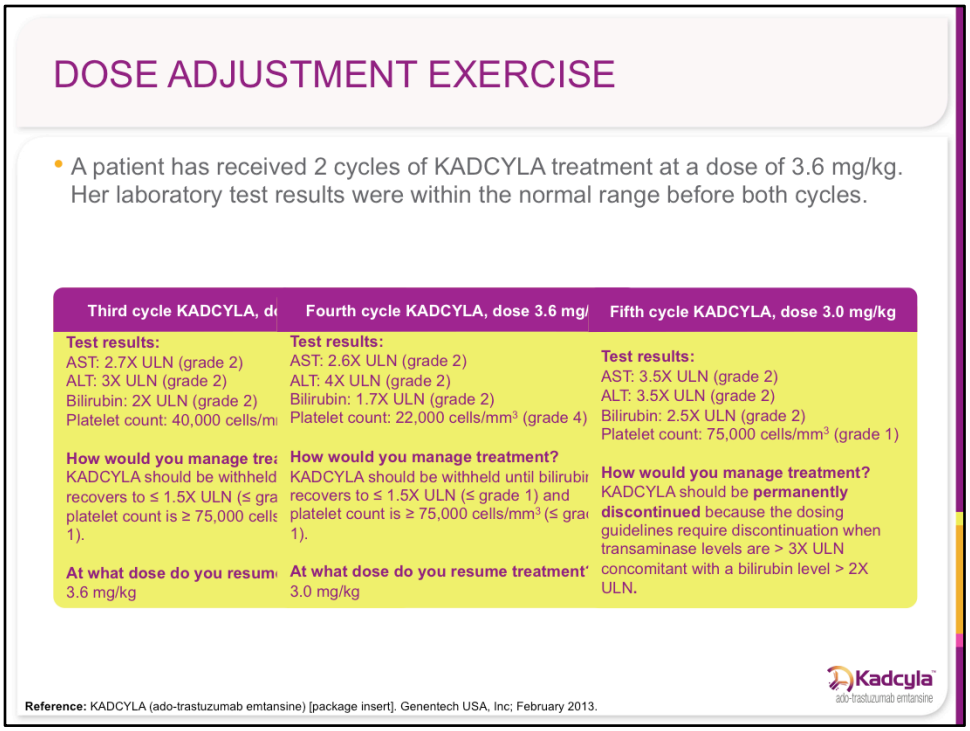


KADCYLA: Storage

Review as stated.

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.



[[Slide builds]]
KADCYLA: Dose Adjustment Exercise
Your patient was started on KADCYLA at 3.6 mg/kg. She tolerated her first 2 cycles of therapy well; her platelet counts were within normal limits prior to both treatments. Your patient is coming in for her third cycle of KADCYLA. You review her labs, and her bilirubin level is now 2X the upper limit of normal (ULN) (grade 2) and her platelet count is 40,000 (grade 3). Similar lab values to those of this patient were observed in the KADCYLA-treated group in the EMILIA trial; 17% of patients experienced elevated bilirubin levels of any grade, and 14% of patients experienced decreased platelet counts of grade 3. The patient is asymptomatic. How do you manage her treatment that day?
[[Click]] Hold treatment until bilirubin recovers to grade less than or equal to 1 and platelet count recovers to grade less than or equal to 1.
[[Click]] At which dose do you resume treatment?
[[Click]] 3.6 mg/kg.

[[Click]] Prior to the patient's fourth cycle of KADCYLA, you review her labs and find her bilirubin level is 1.7X the ULN (grade 2) and her platelet count is 22,000 (grade 4). In the EMILIA trial, 3% of patients in the KADCYLA-treated group experienced decreased platelet counts of grade 4 as observed in this patient. The patient is asymptomatic. How do you manage her treatment that day?
[[Click]] Hold treatment until bilirubin recovers to grade less than or equal to 1 and platelet count recovers to grade less than or equal to 1.
[[Click]] At what dose do you resume treatment?
[[Click]] Reduce one dose level to 3.0 mg/kg since her platelet count is recovering from grade 4.

[[Click]] Prior to the patient's fifth cycle of KADCYLA, her alanine transaminase (ALT) and aspartate transaminase (AST) levels are 3.5X the ULN (grade 2) and her bilirubin level is 2.5X the ULN (grade 2). How do you manage her treatment that day?
[[Click]] Permanently discontinue therapy because her transaminase levels are greater than 3X the ULN concomitant with a bilirubin level greater than 2X the ULN.

Reference: KADCYLA (ado-trastuzumab emtansine) [package insert]. South San Francisco, CA: Genentech USA, Inc; February 2013.