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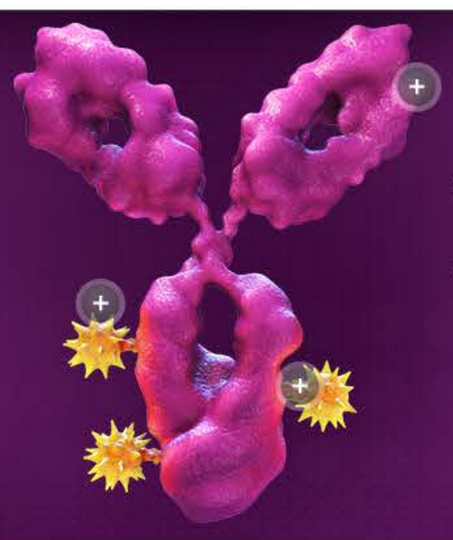

The first antibody-drug conjugate for the treatment of HER2-positive (HER2+) metastatic breast cancer (MBC)

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Indication

KADCYLA® (ado-trastuzumab emtansine), as a single agent, is indicated for the treatment of patients with HER2-positive (HER2+), metastatic breast cancer (MBC) 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

Important Safety Information

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**

Additional Important Safety Information

Left Ventricular Dysfunction (LVD)

- Patients treated with KADCYLA are at increased risk of developing LVD. In EMILIA, LVD occurred in 1.8% of patients in the KADCYLA-treated group and in 3.3% in the comparator group. Permanently discontinue KADCYLA if LVEF has not improved or has declined further

Pregnancy Registry

- Advise patients to contact their healthcare provider immediately if they suspect they may be pregnant. Encourage women who may be exposed to KADCYLA during pregnancy to enroll in the **MotHER Pregnancy Registry** by contacting 1-800-690-6720

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 IRRs and permanently discontinued in the event of a life-threatening IRR. Patients should be closely monitored for IRRs, especially during the first infusion

Hemorrhage

- Hemorrhagic events, sometimes fatal, have been reported in clinical trials. In EMILIA, the incidence of ≥ Grade 3 hemorrhage was 1.8% in the KADCYLA-treated group and 0.8% in the comparator group (overall incidence 32.2% and 16.4%, respectively)
- In some of the observed cases the patients were also receiving anticoagulation therapy or antiplatelet therapy, or had thrombocytopenia; in others, there were no known additional risk factors. Use caution with these agents and consider additional monitoring when concomitant use is medically necessary

Thrombocytopenia

- In EMILIA, the incidence of ≥ Grade 3 thrombocytopenia was 14.5% in the KADCYLA-treated group and 0.4% in the comparator group (overall incidence 31.2% and 3.3%, respectively)
- 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 (overall incidence 21.2% and 13.5%, respectively)
- 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. Specific treatment for KADCYLA extravasation is unknown

Nursing Mothers

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

Adverse Reactions

- The most common (frequency >25%) adverse drug reactions (ADR) across clinical trials with KADCYLA were nausea, fatigue, musculoskeletal pain, hemorrhage, thrombocytopenia, increased transaminases, headache, constipation, and epistaxis. In EMILIA, 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.

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

KADCYLA Access Solutions

Kadcyla® ado-trastuzumab emtansine for injection | Access Solutions®

KADCYLA Access Solutions helps to resolve access and reimbursement issues for individual patients every day. Our dedicated specialists help bring patient treatment and practice solutions together.

Our staff can:

- Help confirm **benefits and coverage** and resolve any related issues
- Refer underinsured patients for **co-pay assistance**
- **Provide free medicine to qualified uninsured patients** who meet specific financial and medical criteria through the Genentech® Access to Care Foundation (GATCF)
- **Individualize services** to meet your patients' specific needs

A permanent **J-code** is available for KADCYLA reimbursement. **Click here** for more information.

To speak live with one of our specialists, call 1 (888) 249-4918. You can also visit **Genentech-Access.com/KADCYLA** for more information.

Additional resources

- **Get KADCYLA Access Solutions information**
- **See the latest list of distributors**
- **Download the KADCYLA Material Safety Data Sheet**

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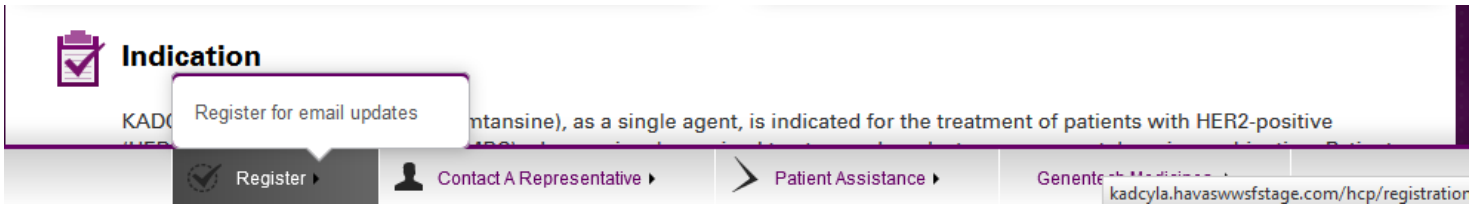
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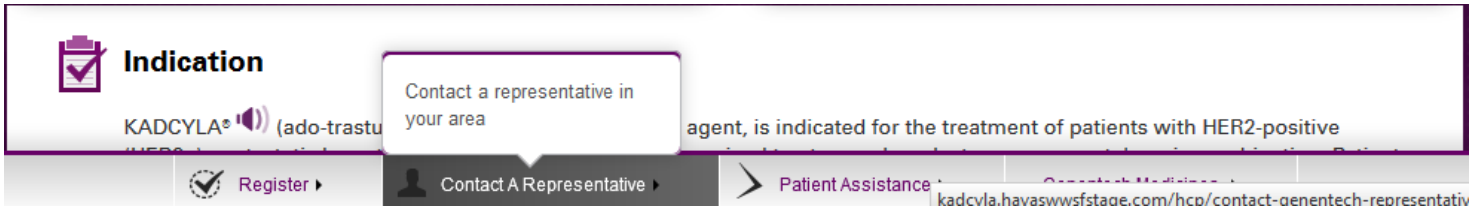
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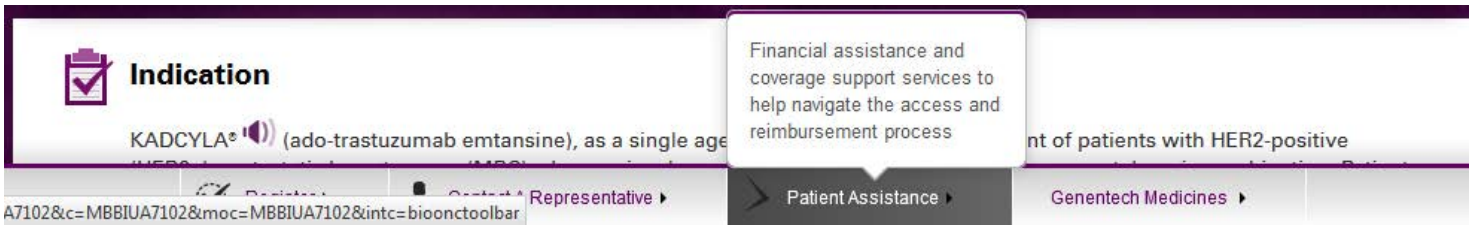
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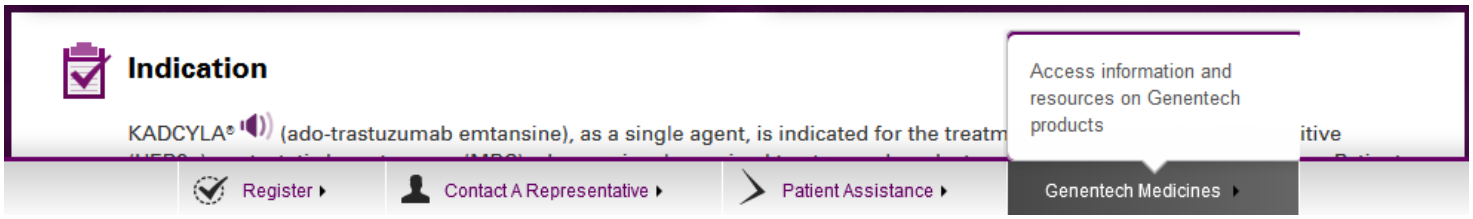
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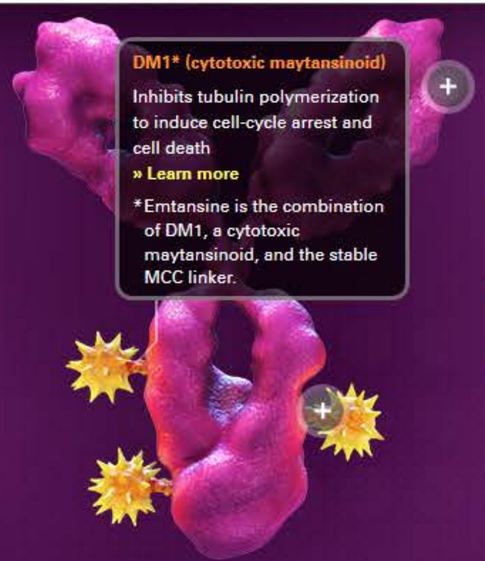

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MCC* (stable linker)
Stabilizes KADCYLA in circulation to release DM1 after entering the target cell
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*Emtansine is the combination of DM1, a cytotoxic maytansinoid, and the stable MCC linker.

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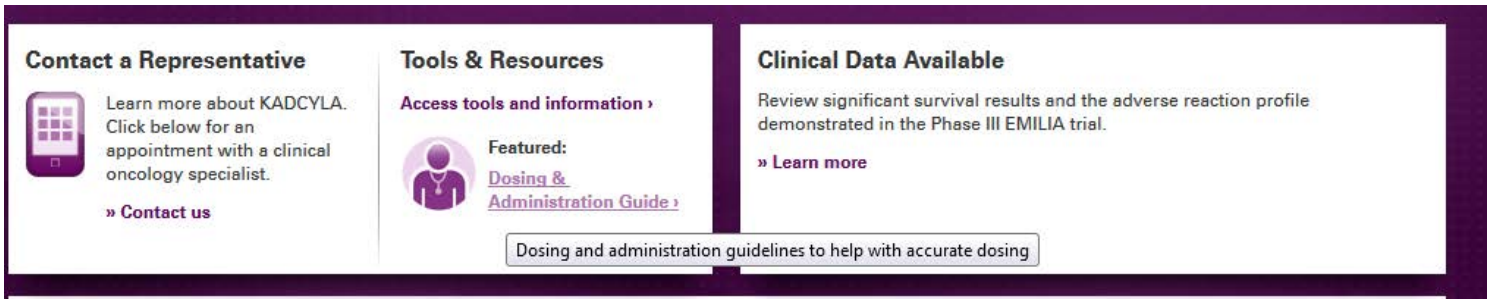
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- Develope nths of completing adjuvant therapy

Audio Glossary ×

KADCYLA (ado-trastuzumab emtansine)

Hear it pronounced

Important

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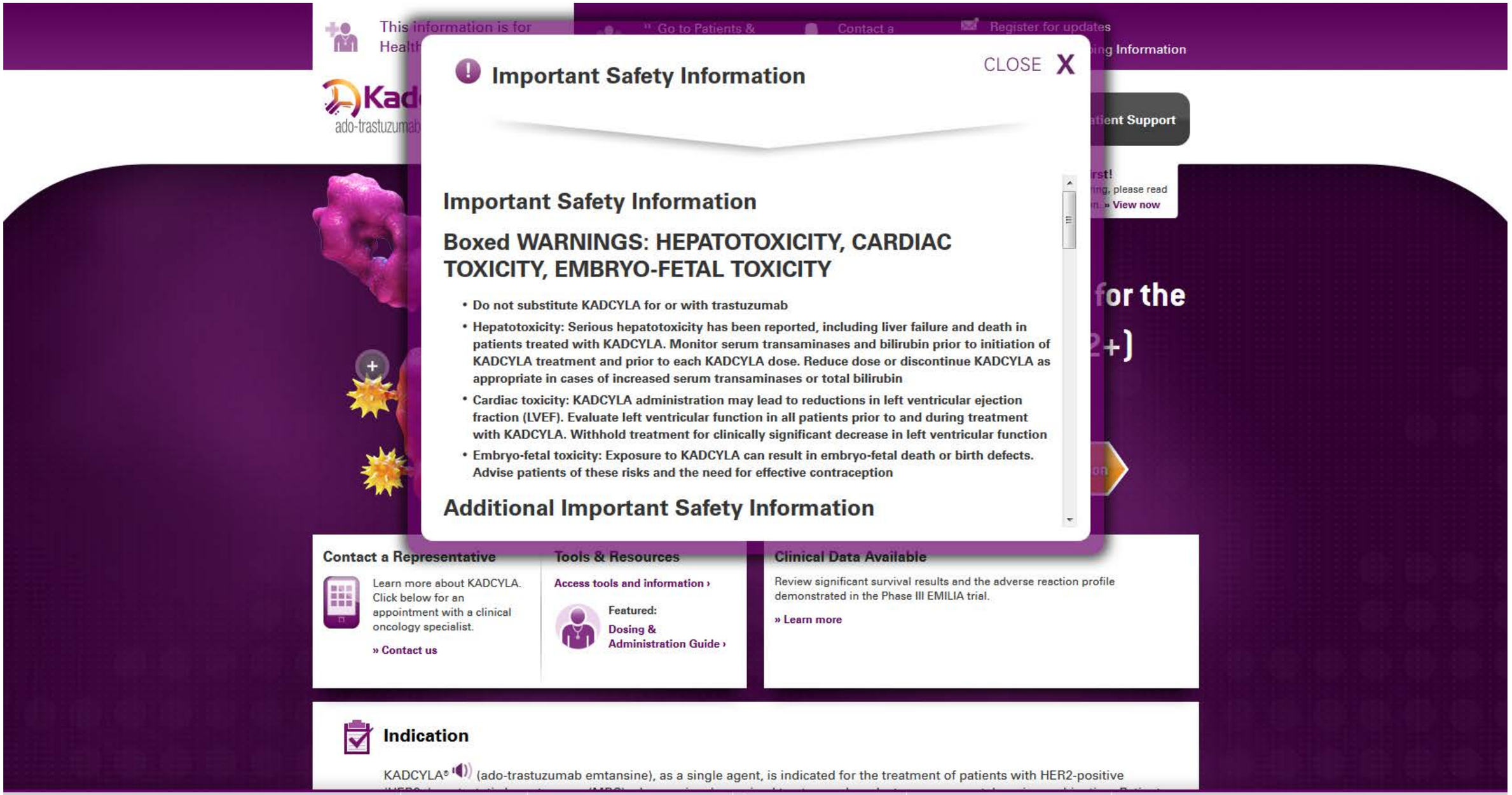
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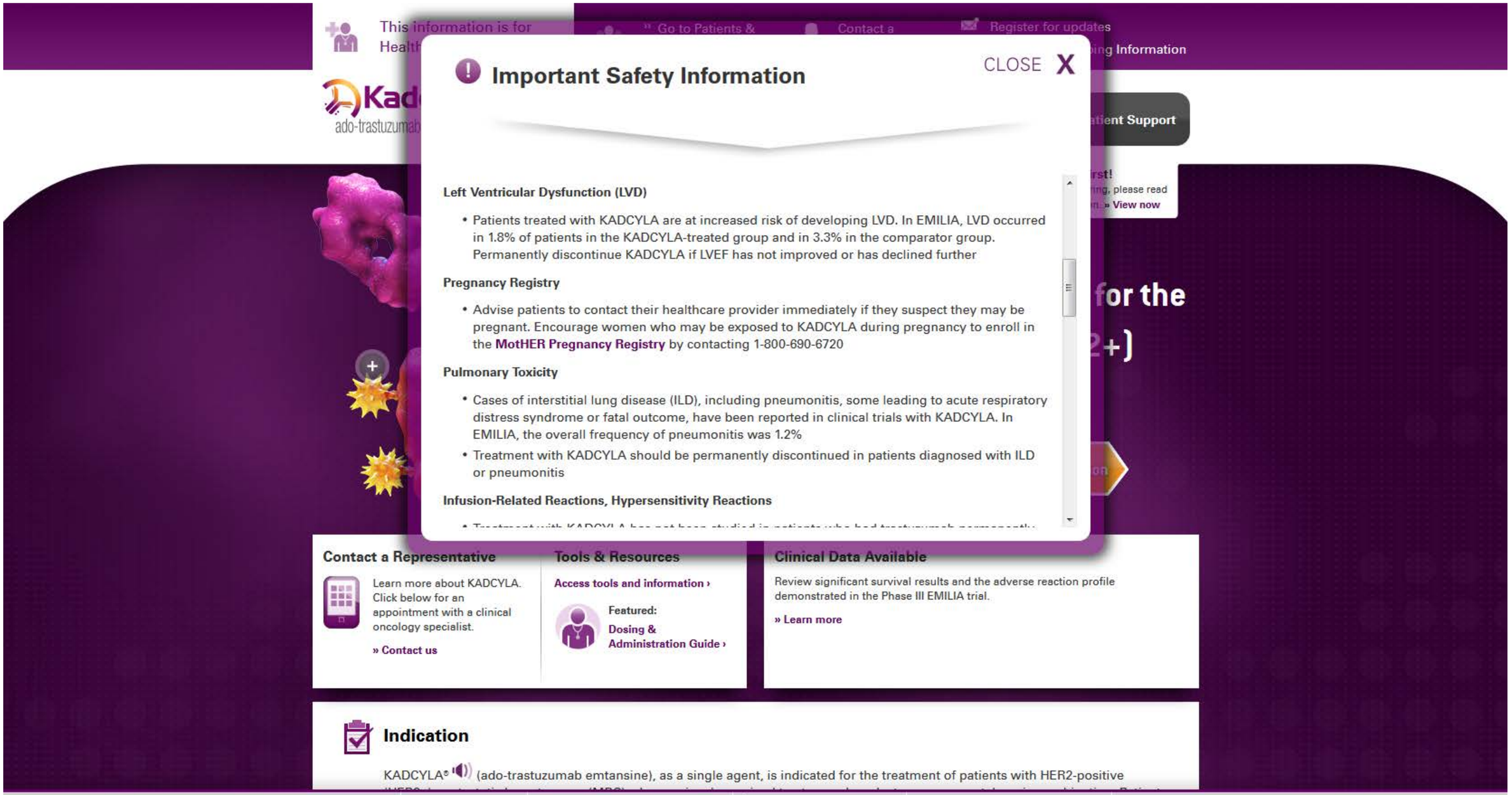
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Hemorrhage

- Hemorrhagic events, sometimes fatal, have been reported in clinical trials. In EMILIA, the incidence of ≥ Grade 3 hemorrhage was 1.8% in the KADCYLA-treated group and 0.8% in the comparator group (overall incidence 32.2% and 16.4%, respectively)
- In some of the observed cases the patients were also receiving anticoagulation therapy or antiplatelet therapy, or had thrombocytopenia; in others, there were no known additional risk factors. Use caution with these agents and consider additional monitoring when concomitant use is medically necessary

Thrombocytopenia

- In EMILIA, the incidence of ≥ Grade 3 thrombocytopenia was 14.5% in the KADCYLA-treated

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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 (overall incidence 21.2% and 13.5%, respectively)
- 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

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Extravasation

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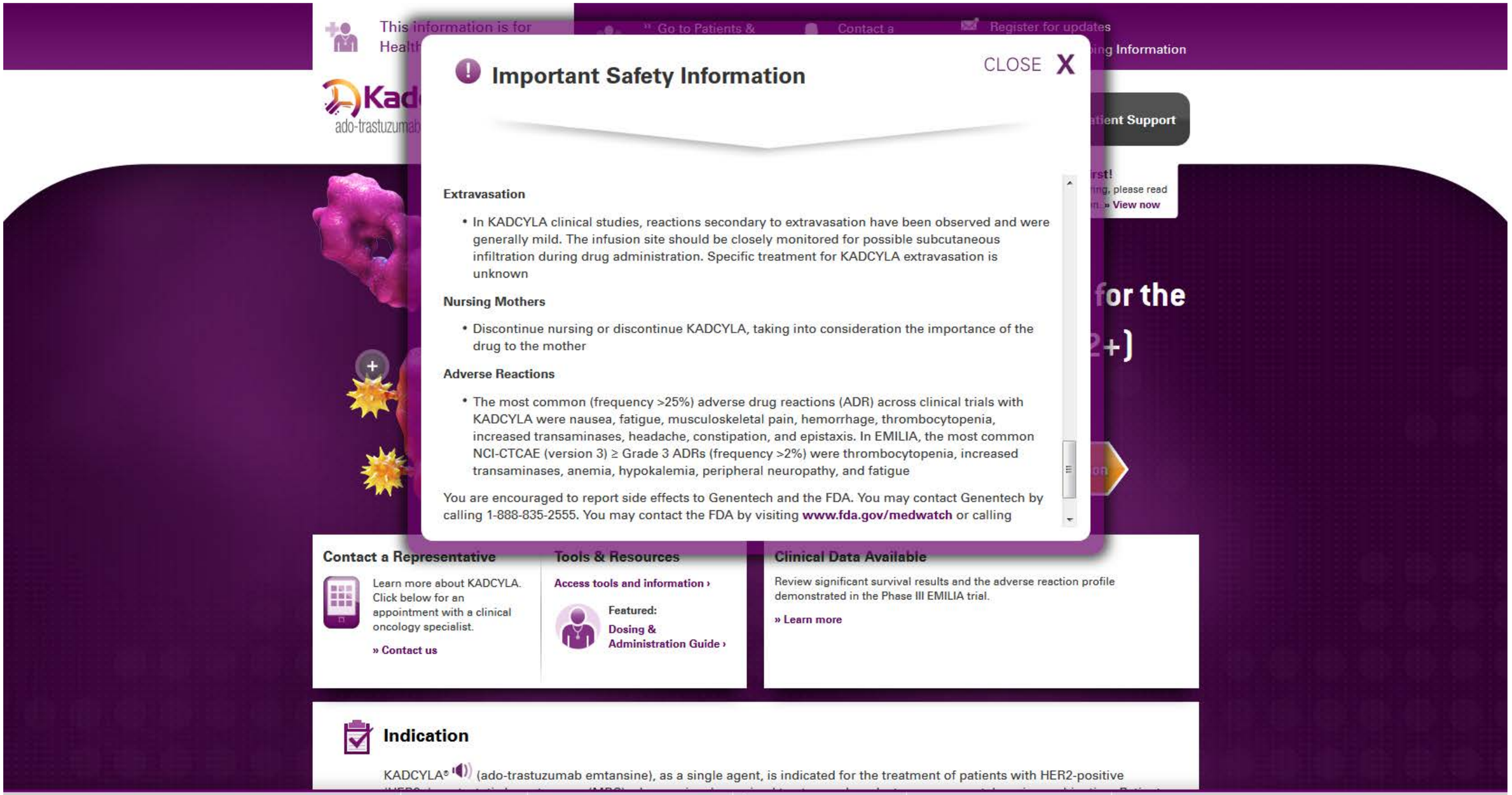
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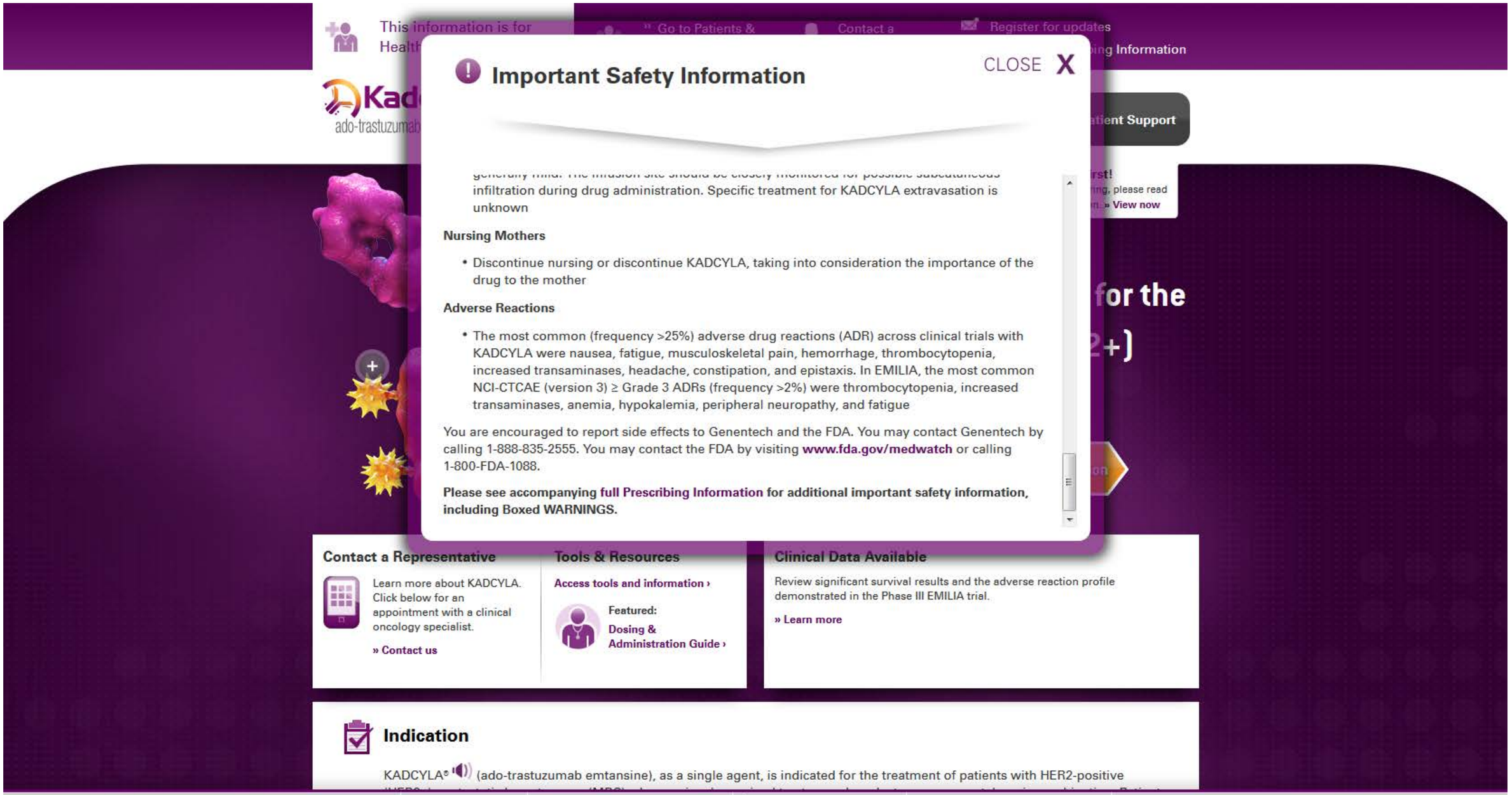
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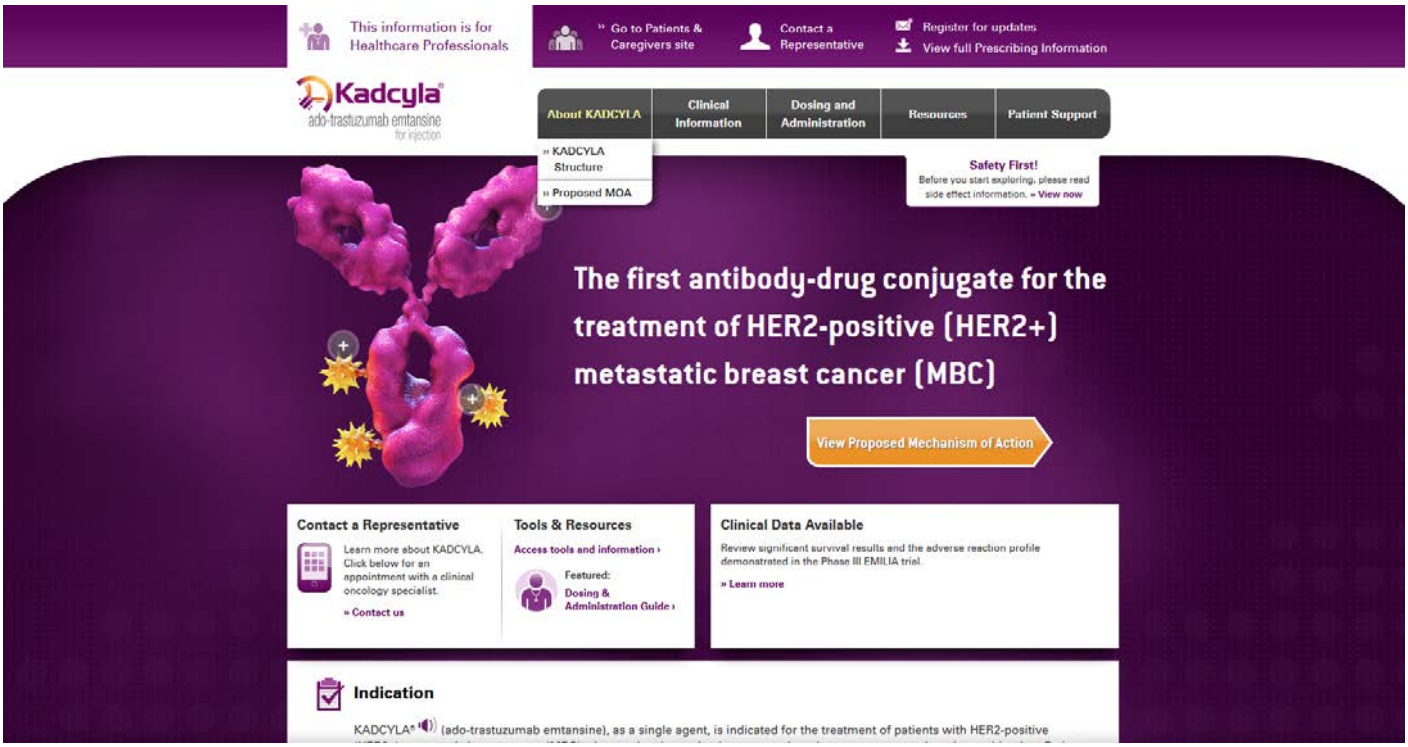
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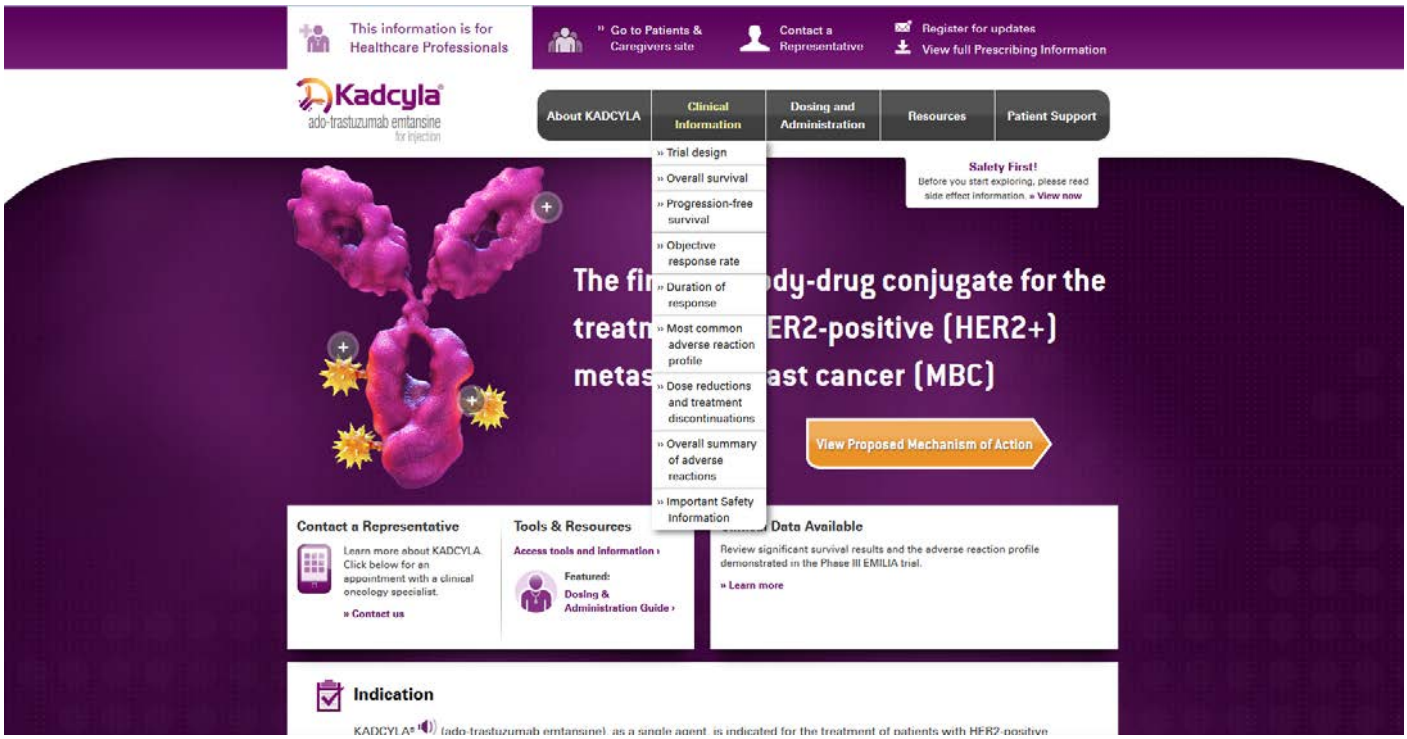
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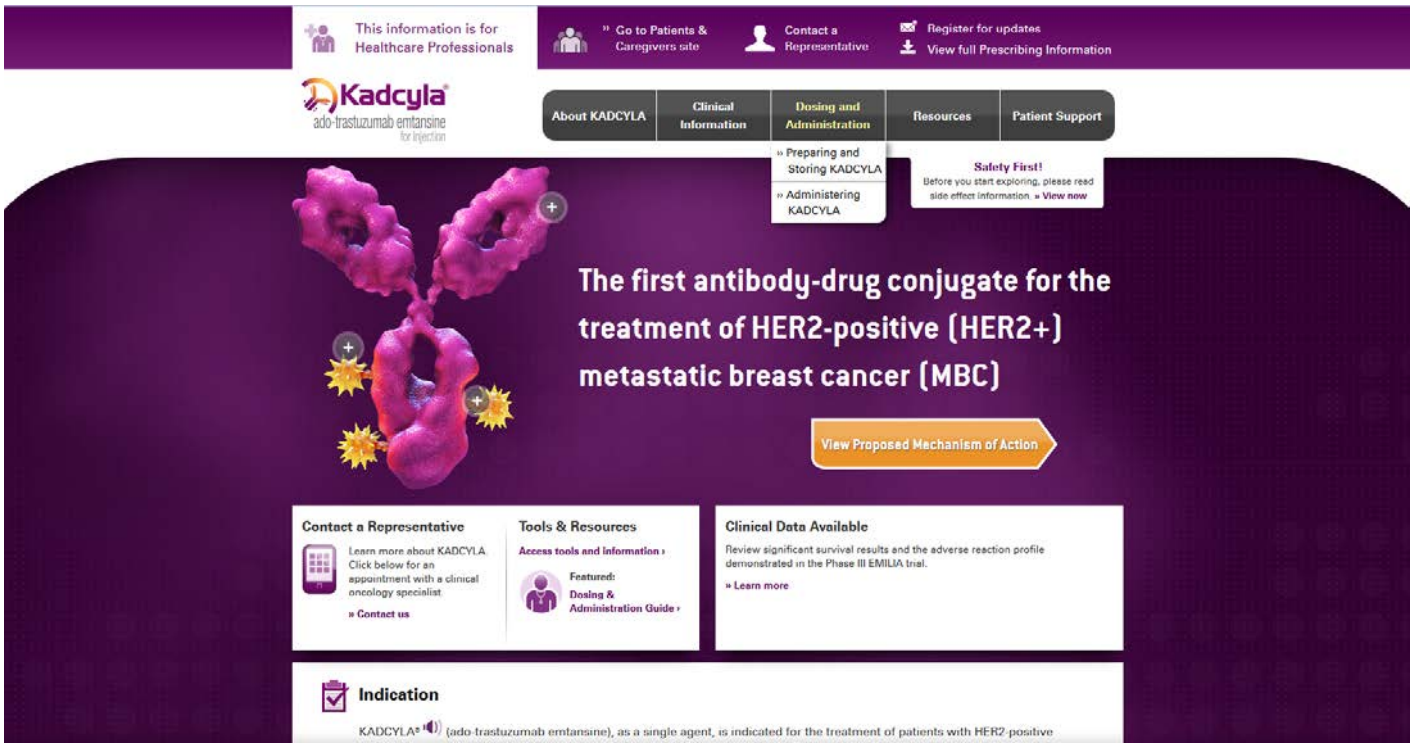
Indication
KADCYLA® (ado-trastuzumab emtansine), as a single agent, is indicated for the treatment of patients with HER2-positive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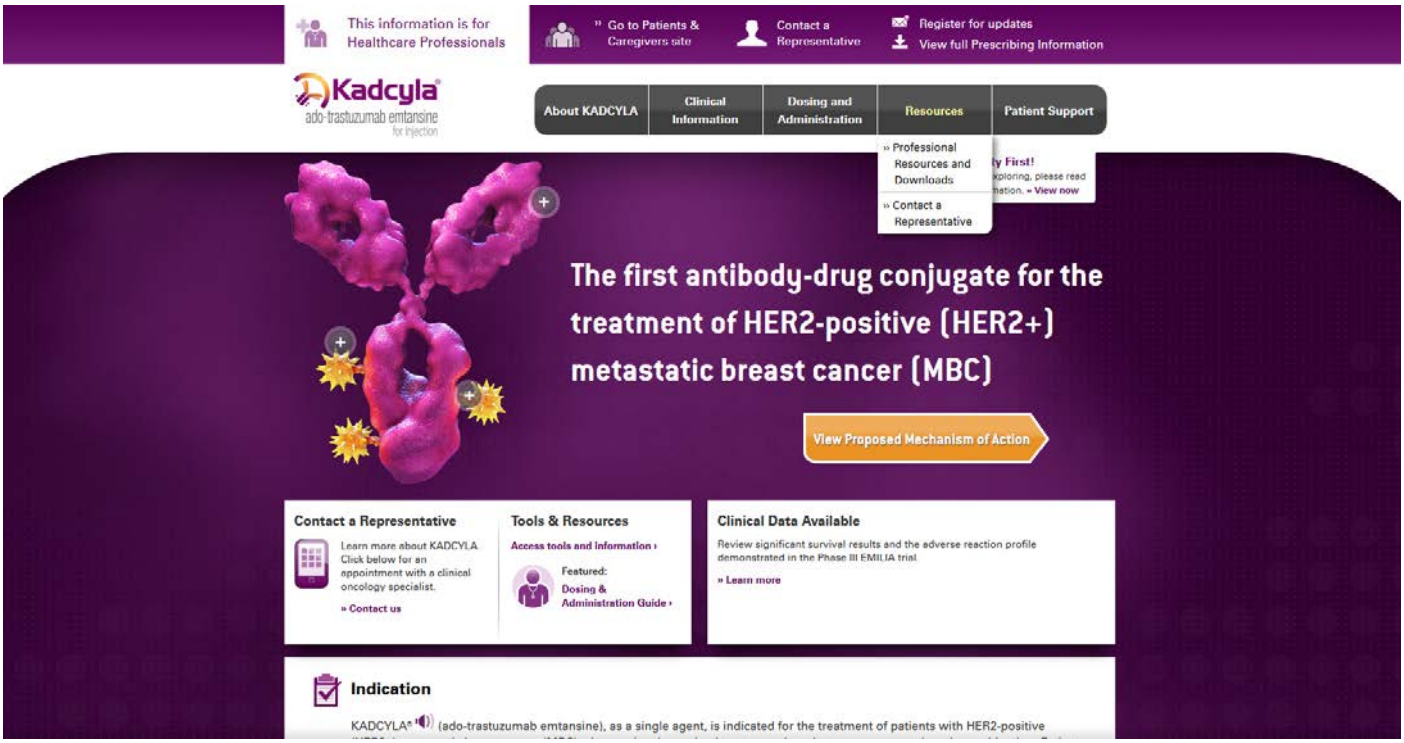
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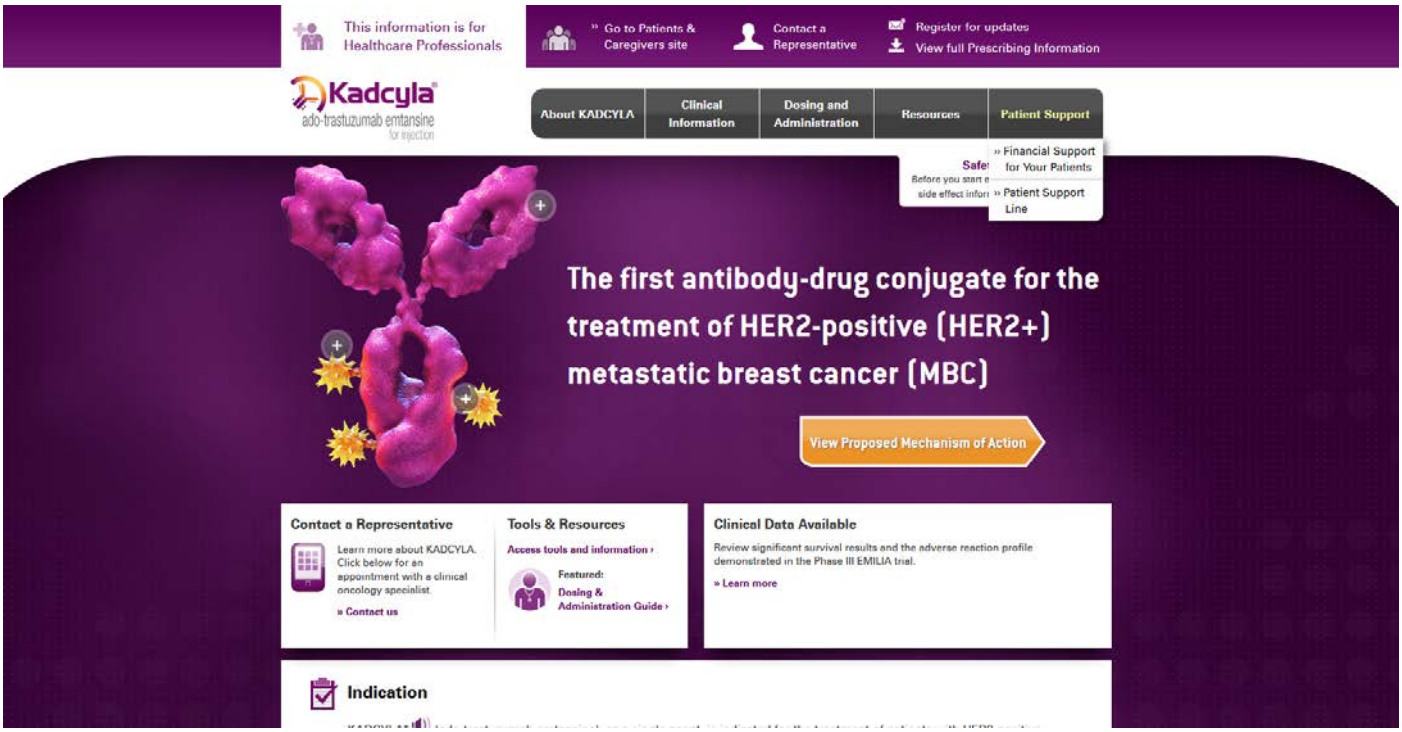
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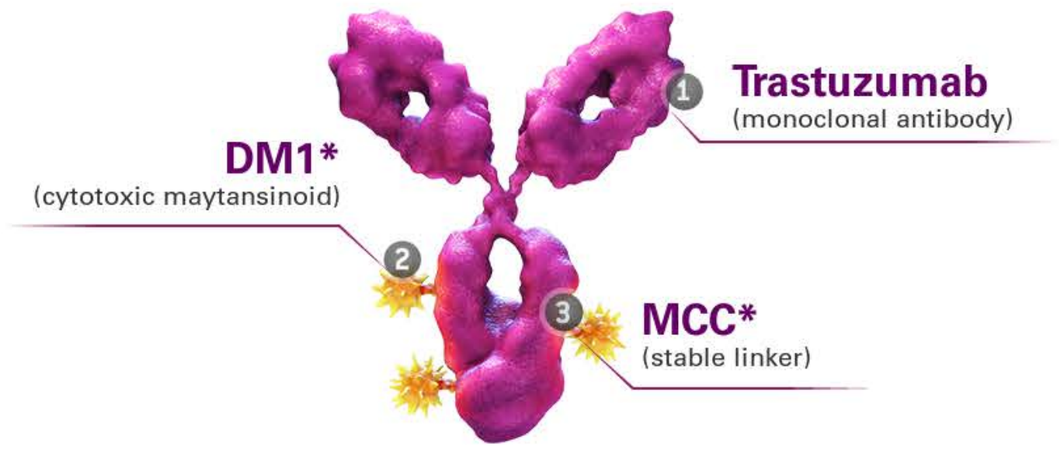
KADCYLA Structure | Proposed MOA

The first HER2-targeted ADC

KADCYLA: A single agent with 3 components[1-3]



In preclinical studies

KADCYLA maintains the HER2 suppression and anticancer activities of trastuzumab[1]

- Suppresses downstream signaling pathways to inhibit tumor cell proliferation and survival[1,4]
- Triggers antibody-dependent cell-mediated cytotoxicity (ADCC)[1]
- Inhibits HER2 shedding[1]

KADCYLA delivers cytotoxic DM1 to target HER2-expressing cells

- Many normal cells express HER2[5]
  - Some cancer cells overexpress up to 200 times more HER2 than normal cells
- Provides cytotoxicity previously unavailable for clinical use[1,2]
  - DM1, a maytansinoid, is 20 to 200 times more potent than taxanes and vinca alkaloids[2]
- Stabilized in circulation by the MCC linker to release DM1 inside the target cell[1]

ADC=antibody-drug conjugate.

Next: See Proposed MOA

Indication

KADCYLA® (ado-trastuzumab emtansine), as a single agent, is indicated for the treatment of patients with HER2-positive (HER2+), metastatic breast cancer (MBC) 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

Important Safety Information

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**
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Additional Important Safety Information

Left Ventricular Dysfunction (LVD)

- Patients treated with KADCYLA are at increased risk of developing LVD. In EMILIA, LVD occurred in 1.8% of patients in the KADCYLA-treated group and in 3.3% in the comparator group. Permanently discontinue KADCYLA if LVEF has not improved or has declined further

Pregnancy Registry

- Advise patients to contact their healthcare provider immediately if they suspect they may be pregnant. Encourage women who may be exposed to KADCYLA during pregnancy to enroll in the **MotHER Pregnancy Registry** by contacting 1-800-690-6720

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 IRRs and permanently discontinued in the event of a life-threatening IRR. Patients should be closely monitored for IRRs, especially during the first infusion

Hemorrhage

- Hemorrhagic events, sometimes fatal, have been reported in clinical trials. In EMILIA, the incidence of ≥ Grade 3 hemorrhage was 1.8% in the KADCYLA-treated group and 0.8% in the comparator group (overall incidence 32.2% and 16.4%, respectively)
- In some of the observed cases the patients were also receiving anticoagulation therapy or antiplatelet therapy, or had thrombocytopenia; in others, there were no known additional risk factors. Use caution with these agents and consider additional monitoring when concomitant use is medically necessary

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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. Specific treatment for KADCYLA extravasation is unknown

Nursing Mothers

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

Adverse Reactions

- The most common (frequency >25%) adverse drug reactions (ADR) across clinical trials with KADCYLA were nausea, fatigue, musculoskeletal pain, hemorrhage, thrombocytopenia, increased transaminases, headache, constipation, and epistaxis. In EMILIA, the most common NCI-CTCAE (version 3) ≥ Grade 3 ADRs (frequency >2%) were thrombocytopenia, increased transaminases, anemia, hypokalemia, peripheral neuropathy, and fatigue

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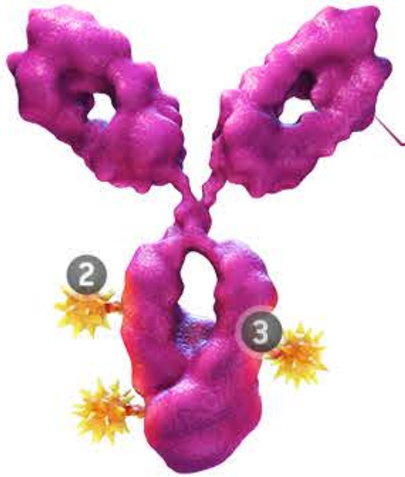
The first HER2-targeted ADC

KADCYLA: A single agent with 3 components[1-3]



Trastuzumab
(monoclonal antibody)

Binds to HER2 at subdomain IV to suppress downstream signaling

In preclinical studies

KADCYLA maintains the HER2 suppression and anticancer activities of trastuzumab[1]

KADCYLA delivers cytotoxic DM1 to target HER2-expressing cells

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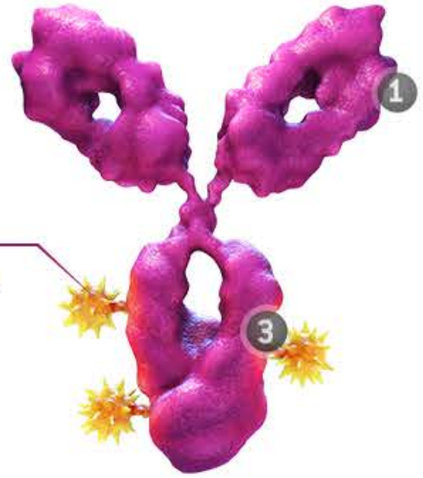
DM1*
(cytotoxic maytansinoid)

Inhibits tubulin polymerization to induce cell-cycle arrest and cell death

* Emtansine is the combination of DM1, a cytotoxic maytansinoid, and the stable MCC linker.



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MCC*
(stable linker)

Stabilizes KADCYLA in circulation to release DM1 after entering the target cell

* Emtansine is the combination of DM1, a cytotoxic maytansinoid, and the stable MCC linker.

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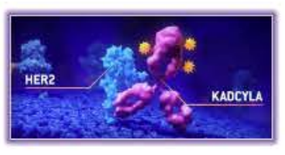

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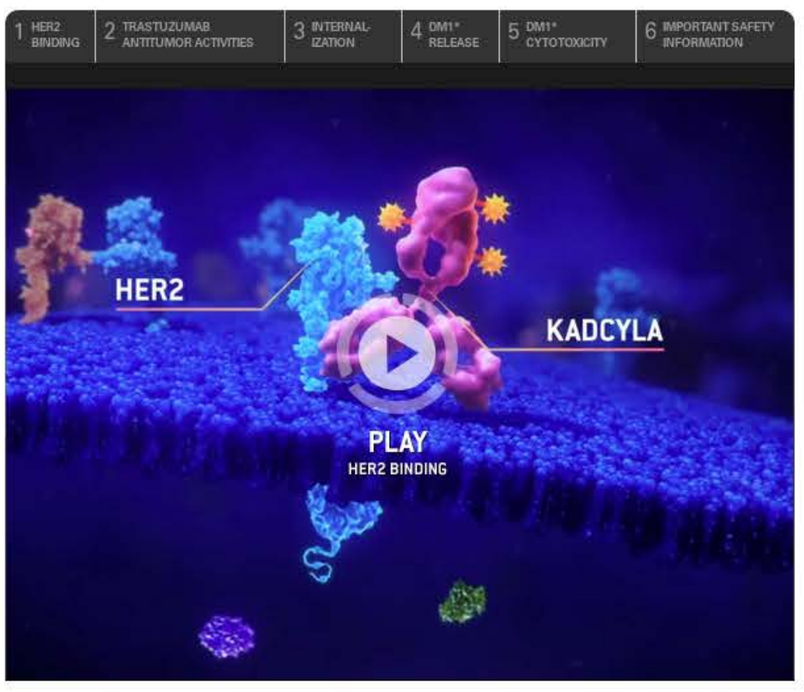

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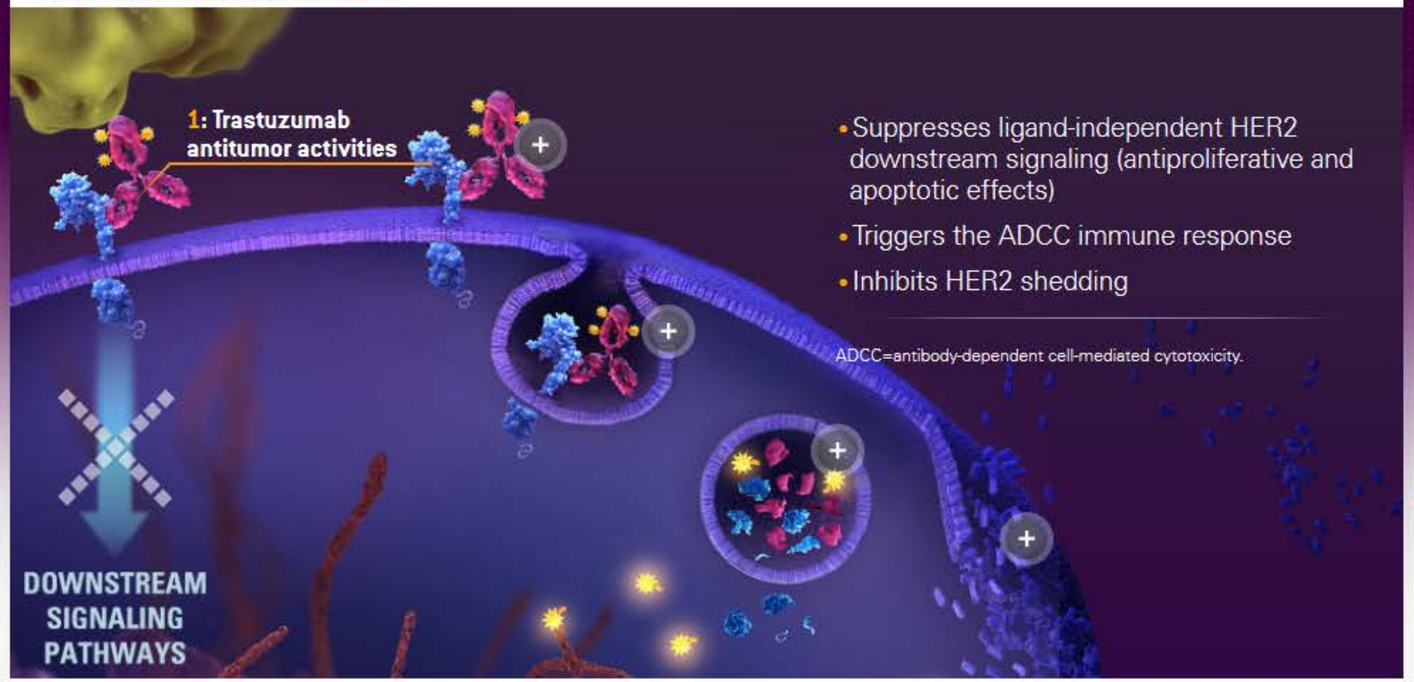

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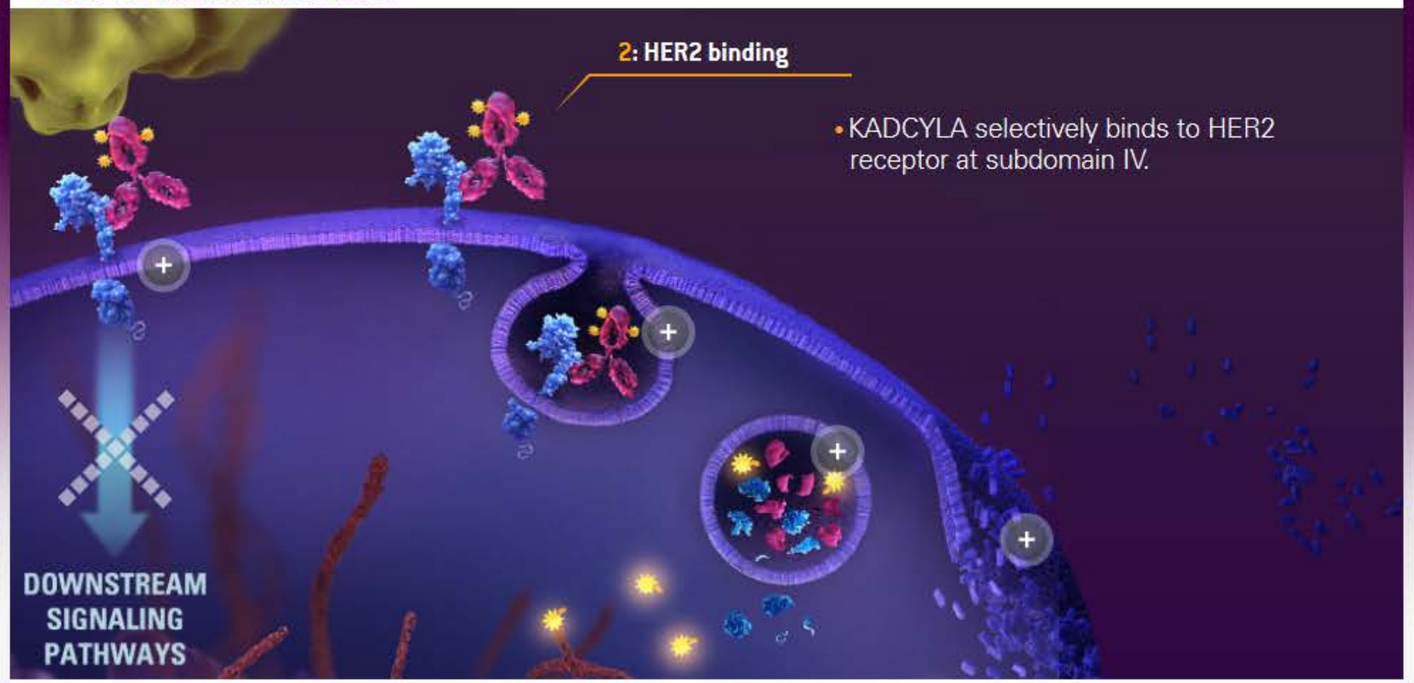

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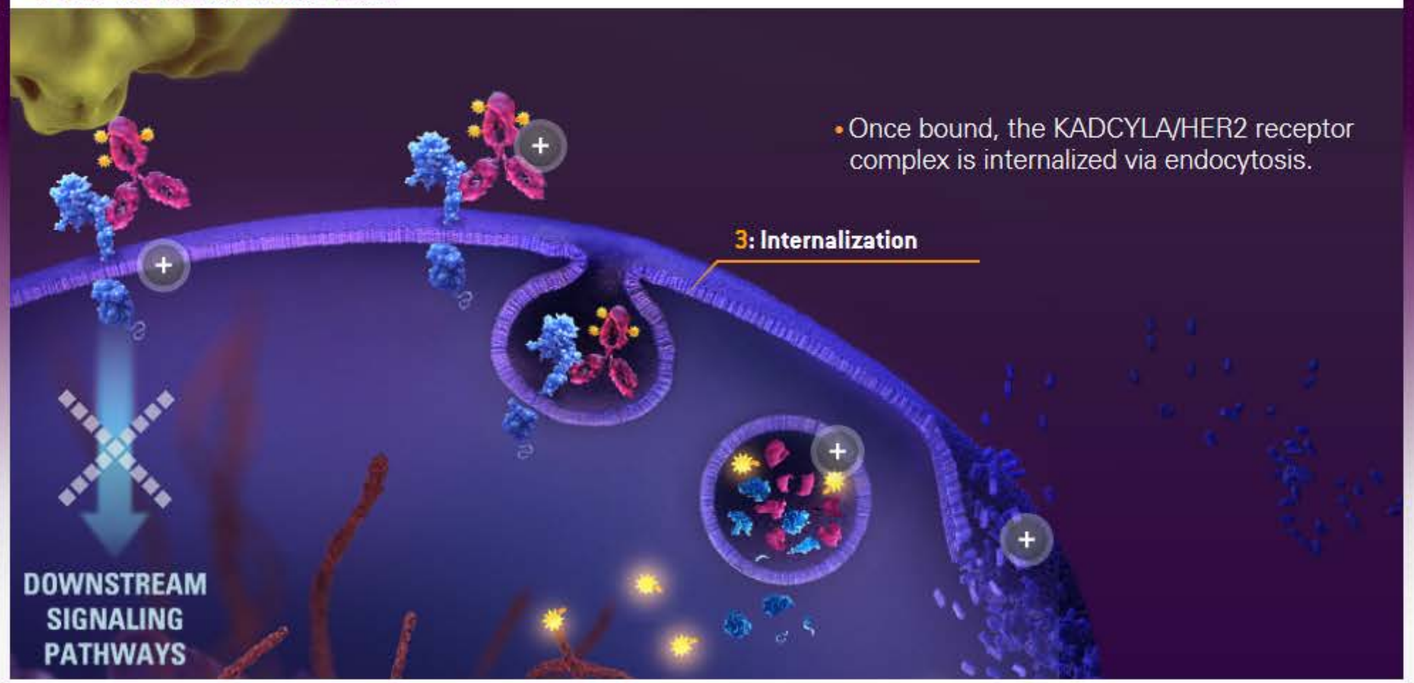

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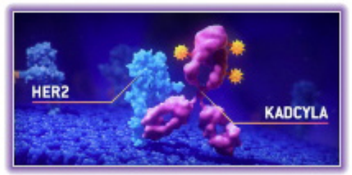

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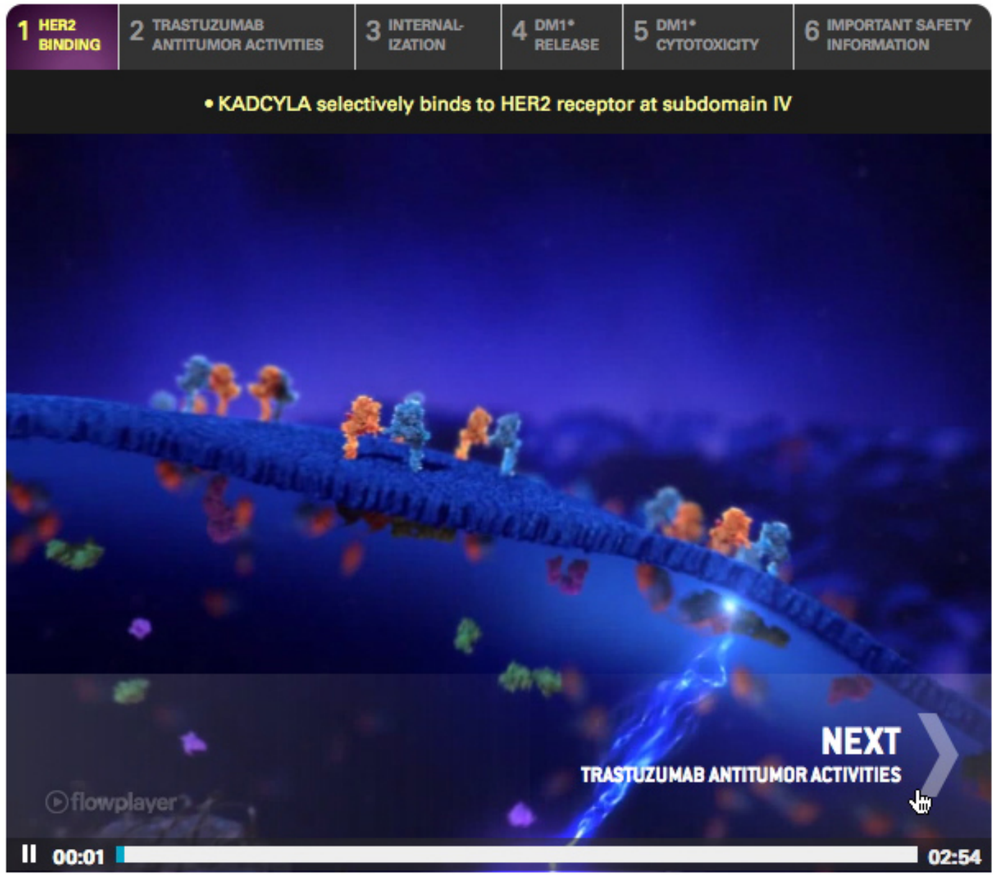

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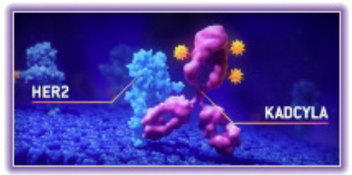

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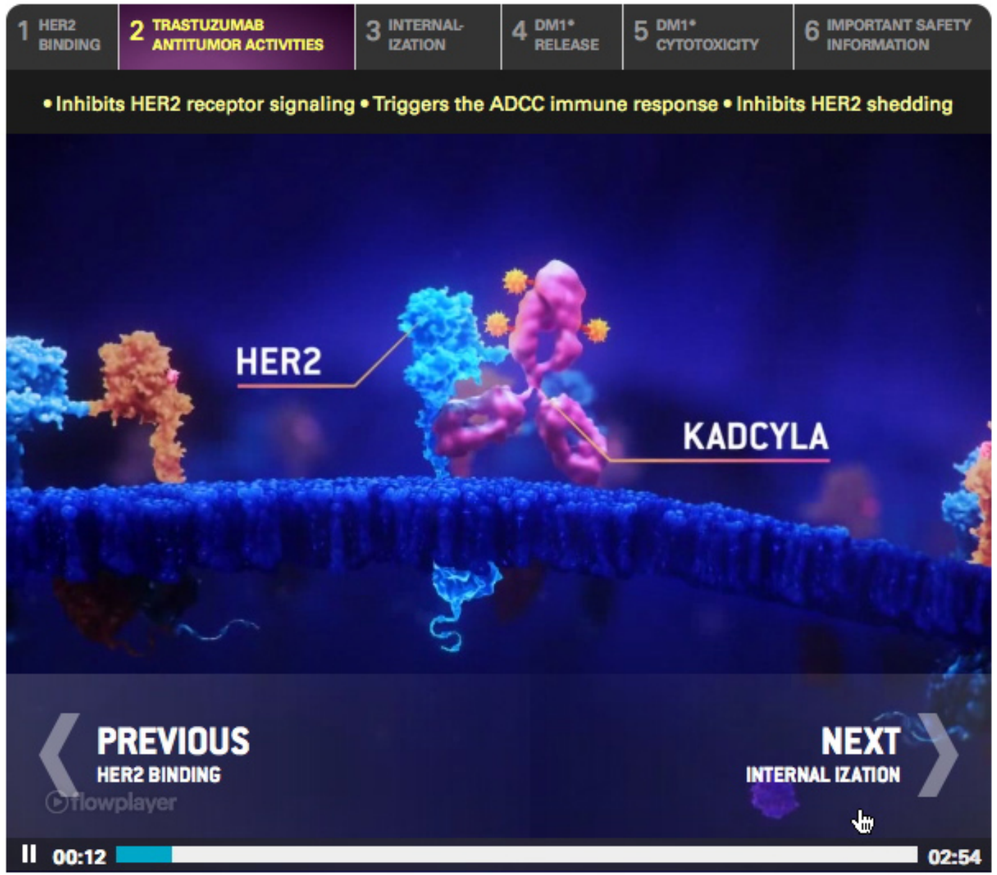

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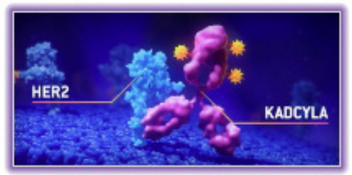

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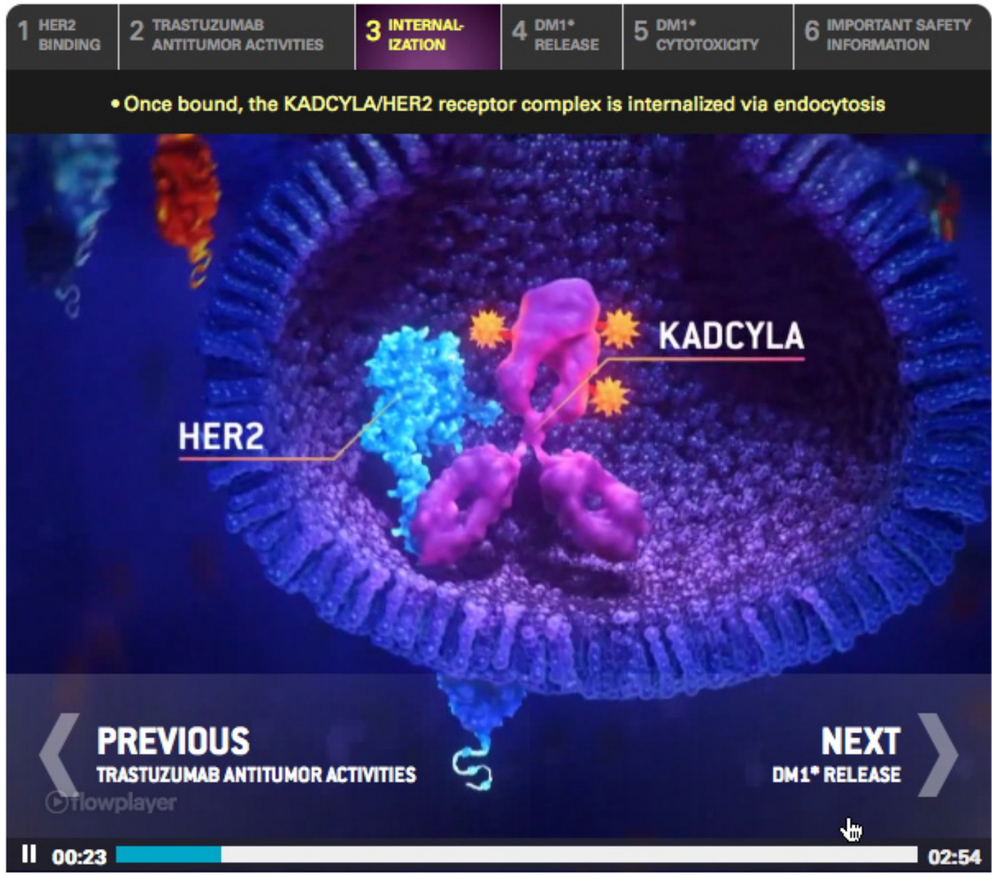

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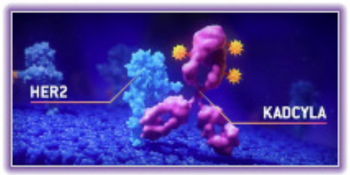

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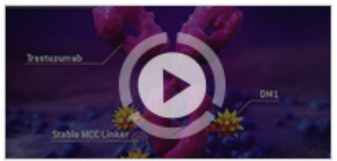

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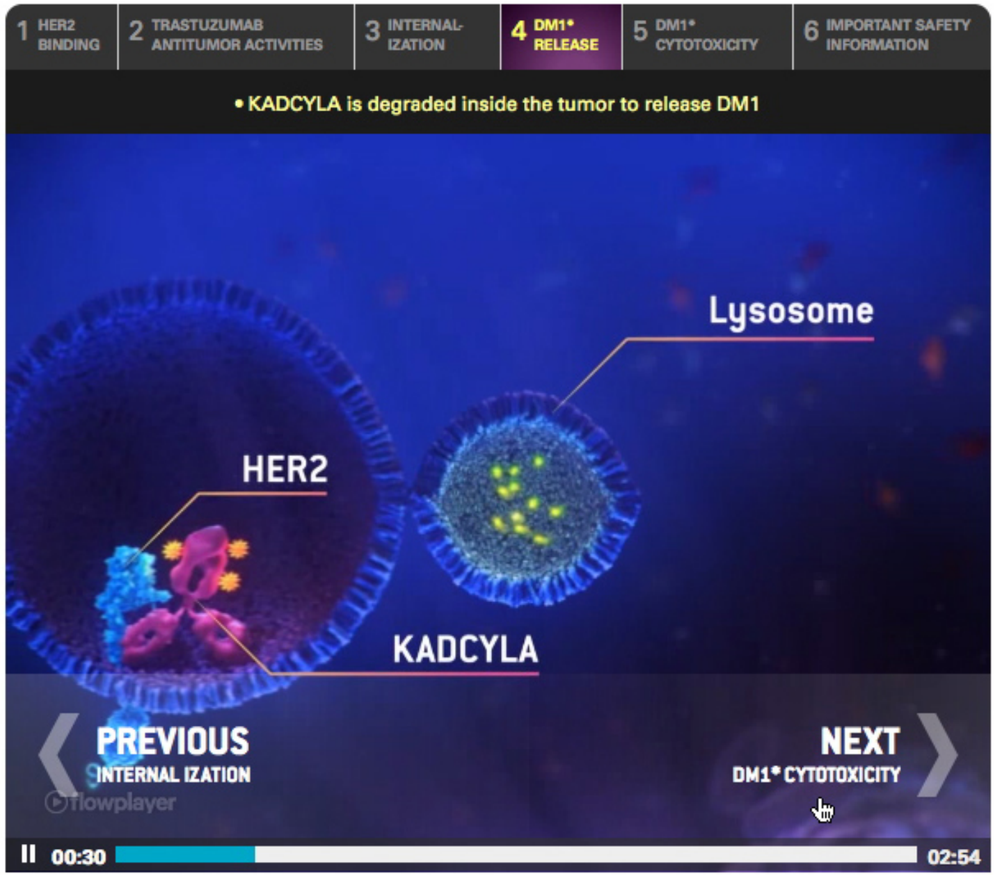

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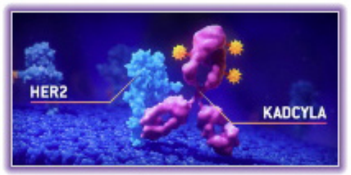

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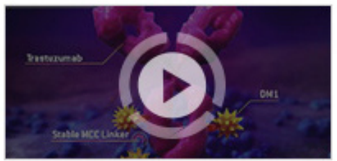

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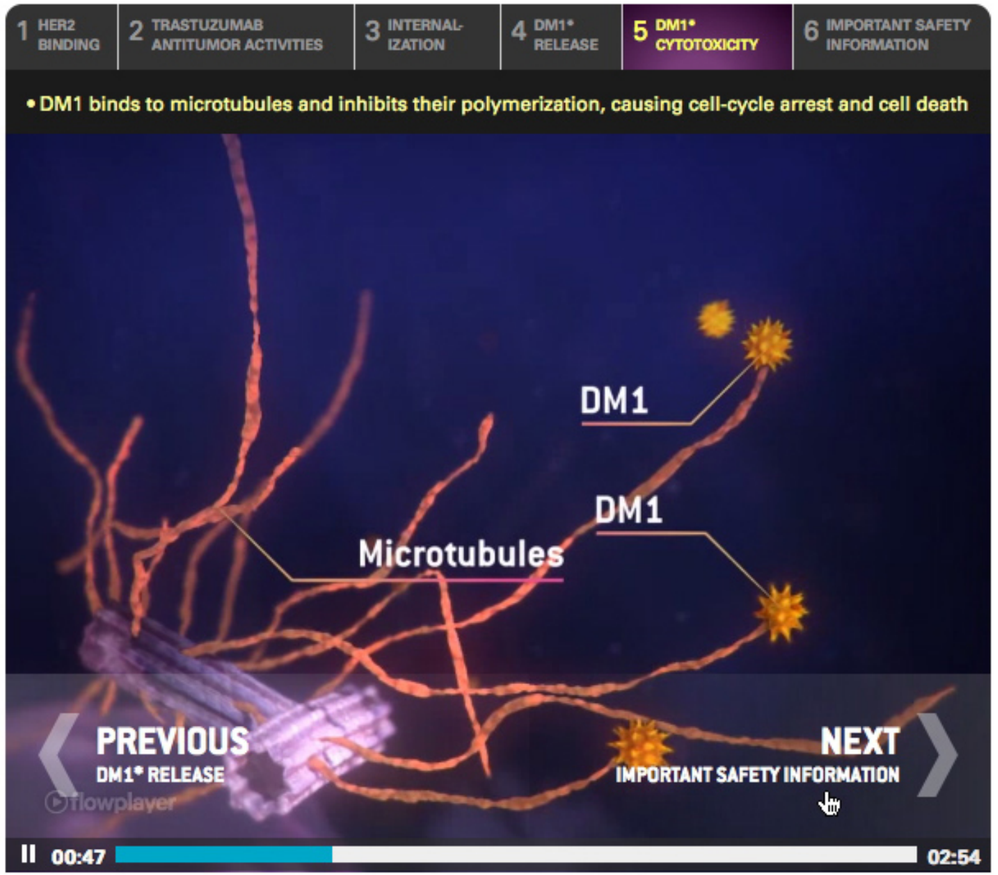

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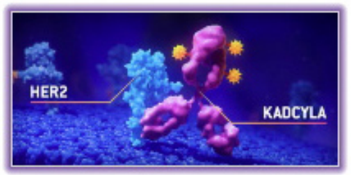

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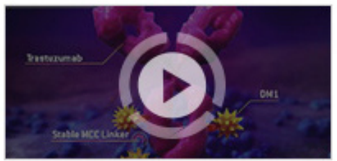

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1 HER2 BINDING | 2 TRASTUZUMAB ANTITUMOR ACTIVITIES | 3 INTERNAL-IZATION | 4 DM1* RELEASE | 5 DM1* CYTOTOXICITY | 6 IMPORTANT SAFETY INFORMATION

Indication

KADCYLA® (ado-trastuzumab emtansine), as a single agent, is indicated for the treatment of patients with HER2-positive (HER2+), metastatic breast cancer (MBC) 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

Important Safety Information

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**

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Next: See Clinical Information

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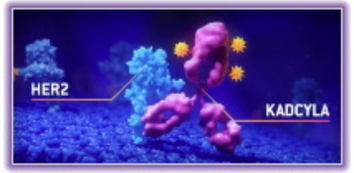

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Additional Important Safety Information

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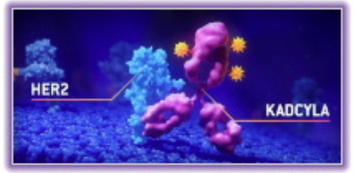

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Additional Important Safety Information

Left Ventricular Dysfunction (LVD)

- Patients treated with KADCYLA are at increased risk of developing LVD. In EMILIA, LVD occurred in 1.8% of patients in the KADCYLA-treated group and in 3.3% in the comparator group. Permanently discontinue KADCYLA if LVEF has not improved or has declined further

Pregnancy Registry

- Advise patients to contact their healthcare provider immediately if they suspect they may be pregnant. Encourage women who may be exposed to KADCYLA during pregnancy to enroll in the MotHER Pregnancy Registry by contacting 1-800-690-6720

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

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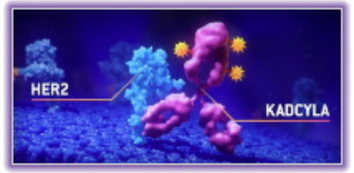

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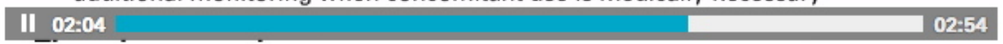
Infusion-Related Reactions, Hypersensitivity Reactions

- 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 IRRs and permanently discontinued in the event of a life-threatening IRR. Patients should be closely monitored for IRRs, especially during the first infusion

Hemorrhage

- Hemorrhagic events, sometimes fatal, have been reported in clinical trials. In EMILIA, the incidence of ≥ Grade 3 hemorrhage was 1.8% in the KADCYLA-treated group and 0.8% in the comparator group (overall incidence 32.2% and 16.4%, respectively)
- In some of the observed cases the patients were also receiving anticoagulation therapy or antiplatelet therapy, or had thrombocytopenia; in others, there were no known additional risk factors. Use caution with these agents and consider additional monitoring when concomitant use is medically necessary



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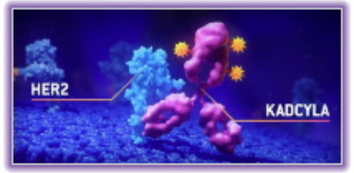

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- In some of the observed cases the patients were also receiving anticoagulation therapy or antiplatelet therapy, or had thrombocytopenia; in others, there were no known additional risk factors. Use caution with these agents and consider additional monitoring when concomitant use is medically necessary

Thrombocytopenia

- In EMILIA, the incidence of ≥ Grade 3 thrombocytopenia was 14.5% in the KADCYLA-treated group and 0.4% in the comparator group (overall incidence 31.2% and 3.3%, respectively)
- 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 (overall incidence 21.2% and 13.5%, respectively)
- 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

Next: See Clinical Information

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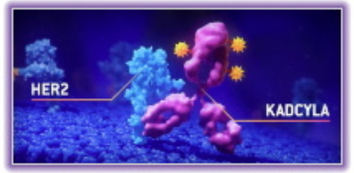

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- Monitor for signs or symptoms of neurotoxicity. KADCYLA should be temporarily discontinued in patients experiencing Grade 3 or 4 peripheral neuropathy until resolution to ≤ Grade 2

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. Specific treatment for KADCYLA extravasation is unknown

Nursing Mothers

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

Adverse Reactions

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Next: See Clinical Information

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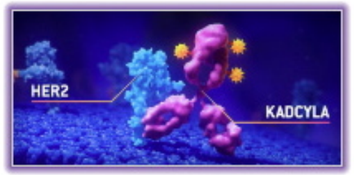

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- In KADCYLA clinical studies, reactions secondary to extravasation have been observed and were generally mild. The infusion site should be closely monitored for possible subcutaneous infiltration during drug administration. Specific treatment for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

Nursing Mothers

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

Adverse Reactions

- The most common (frequency >25%) adverse drug reactions (ADR) across clinical trials with KADCYLA were nausea, fatigue, musculoskeletal pain, hemorrhage, thrombocytopenia, increased transaminases, headache, constipation, and epistaxis. In EMILIA, 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.

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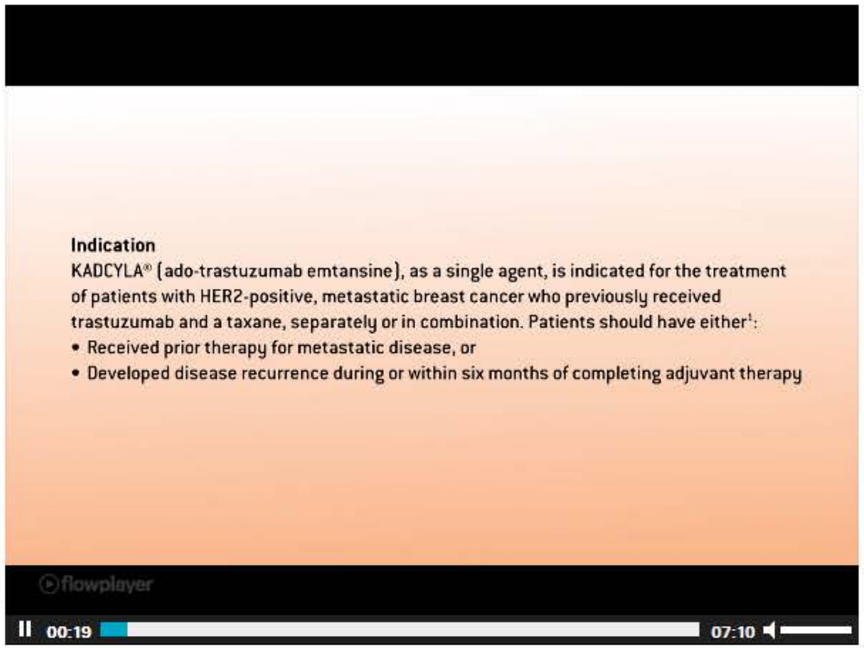

Next: See Clinical Information

Indication

KADCYLA® (ado-trastuzumab emtansine), as a single agent, is indicated for the treatment of patients with HER2-positive (HER2+), metastatic breast cancer (MBC) 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

Important Safety Information

Clinical Information

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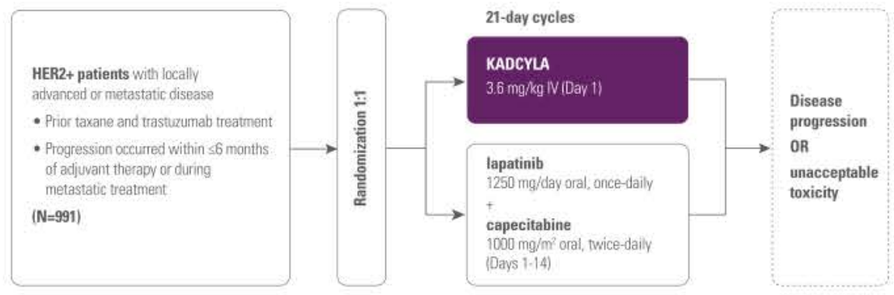
Demonstrated benefit in a well-designed clinical trial

Efficacy and safety were demonstrated in HER2-positive (HER2+) metastatic breast cancer (MBC) patients previously treated with trastuzumab and a taxane[1]

- The EMILIA trial was a large (N=991), Phase III, multi-institutional, randomized trial in patients with HER2+ unresectable locally advanced or MBC

EMILIA TRIAL DESIGN[1]



Trial endpoints

- **Primary endpoints:** Progression-free survival (PFS) by independent review committee (IRC), overall survival (OS), safety[2]
- **Key secondary endpoints:** PFS by investigator review, objective response rate (ORR), duration of response (DoR), and time to symptom progression (TTP)[1]

The *National Comprehensive Cancer Network Guidelines (NCCN Guidelines)®— Breast Cancer* recommend KADCYLA as a preferred agent for HER2+ recurrent or metastatic trastuzumab-exposed disease (Category 2A)[3]*

*Referenced with permission from NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines)®: Breast Cancer V.3.2014. © National Comprehensive Cancer Network, Inc. 2014. All rights reserved. To view the most recent and complete version of the guideline, go online to **nccn.org** . NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

Patient baseline characteristics were balanced between treatment arms

Most patients (88%) had received one or more lines of systemic therapy in the metastatic setting[1]

- 12% of patients received only neoadjuvant or adjuvant therapy and had disease relapse during or within 6 months of completing treatment

SELECTED BASELINE PATIENT CHARACTERISTICS[1,2,4]

	KADCYLA (n=495)	lapatinib + capecitabine (n=496)
Median age, years (range)	**53** (25-84)	53 (24-83)
Race, % (n)		
White	**72** (358)	75 (374)
Asian	**19** (94)	17 (86)
Black/African American	**6** (29)	4 (21)
Other	**1** (7)	2 (10)
Not available	**1** (7)	1 (5)
ECOG PS, % (n)		
0	**60** (299)	63 (312)
1	**39** (194)	36 (176)
Measurable disease by IRC, % (n)		
Yes	**80** (397)	78 (389)
Metastatic sites, % (n)		
<3	**61** (298)	62 (307)
≥3	**37** (189)	35 (175)
Unknown	**2** (8)	3 (14)
Hormonal status, % (n)		
ER+ and/or PR+	**57** (282)	53 (263)
ER- and PR-	**41** (202)	45 (224)
Unknown	**2** (11)	2 (9)
Prior treatment type, % (n)		
Chemotherapy (anthracycline)	**61** (303)	61 (302)
Chemotherapy (other)	**78** (385)	77 (382)
Hormonal therapy	**41** (205)	41 (204)
Trastuzumab	**100** (495)	100 (495)
Prior trastuzumab treatment, % (n)		
MBC (±EBC)	**100** (495)	100 (496)
EBC only	**16** (78)	16 (77)
Duration of prior trastuzumab treatment, % (n)		
<1 year	**42** (210)	43 (212)
≥1 year	**58** (285)	57 (284)

ECOG PS=Eastern Cooperative Oncology Group performance status; IRC=independent review committee; ER=estrogen receptor; PR=progesterone receptor; EBC=early breast cancer.

Next: See Clinical Efficacy Results

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Important Safety Information

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**

The following additional serious adverse reactions have been reported in clinical trials with KADCYLA:

- Interstitial lung disease (ILD), including pneumonitis, some leading to acute respiratory distress syndrome or fatality: KADCYLA should be permanently discontinued in patients diagnosed with ILD or pneumonitis
- Infusion-related reactions (IRR), hypersensitivity: KADCYLA treatment should be interrupted in patients with severe IRR and permanently discontinued in the event of a life-threatening IRR
- Thrombocytopenia: Monitor platelet counts prior to initiation of KADCYLA and prior to each dose. Institute dose modifications as appropriate
- Hemorrhage: Fatal cases of hemorrhage occurred in clinical trials among patients with no known identified risk factors, as well as among patients with thrombocytopenia and those receiving anticoagulation and antiplatelet therapy
- Peripheral neuropathy: KADCYLA should be temporarily discontinued in patients experiencing Grade 3 or 4 peripheral neuropathy until resolution to ≤ Grade 2
- Reactions secondary to extravasation: The infusion site should be closely monitored for possible subcutaneous infiltration during drug administration

Additional Important Safety Information:

- Detection of HER2 protein overexpression or gene amplification is necessary for selection of patients appropriate for KADCYLA therapy
- Nursing mothers: Discontinue nursing or discontinue KADCYLA, taking into consideration the importance of the drug to the mother
- The most common adverse drug reactions (frequency >25%) across clinical trials with KADCYLA were fatigue, nausea, musculoskeletal pain, hemorrhage, thrombocytopenia, headache, increased transaminases, constipation, and epistaxis

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.

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

References: 1. KADCYLA Prescribing Information. Genentech, Inc. July 2014. **2.** Verma S, Miles D, Gianni L, et al; EMILIA Study Group. Trastuzumab emtansine for HER2-positive advanced breast cancer [published correction appears in *N Engl J Med*. 2013;368:2442]. *N Engl J Med*. 2012;367:1783-1791 and Supplementary Appendix. **3.** National Comprehensive Cancer Network. *National Clinical Practice Guidelines in Oncology (NCCN Guidelines)® Breast Cancer*. Version 3.2014. **http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf**. Accessed July 24, 2014. **4.** Verma S, Miles D, Gianni L, et al. Updated overall survival results from EMILIA, a phase 3 study of trastuzumab emtansine (T-DM1) vs capecitabine and lapatinib in HER2-positive locally advanced or metastatic breast cancer. Presented at: European Society of Medical Oncology (ESMO) Congress; September 28-October 2, 2012; Vienna, Austria. **5.** Data on file. Genentech, Inc.

Clinical Information

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Interested in receiving a copy of the EMILIA study?

Talk to a representative about getting the EMILIA paper in *The New England Journal of Medicine*

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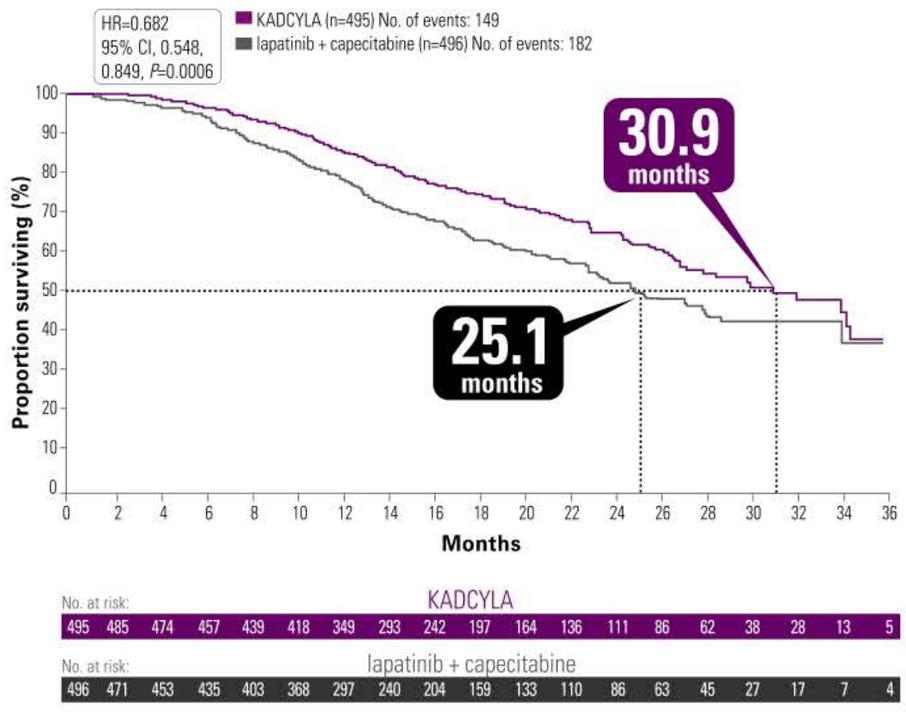
Results from the Phase III EMILIA trial: KADCYLA vs lapatinib + capecitabine

Proven survival benefit

KADCYLA extended median OS by nearly 6 months[1]

- 30.9 months with KADCYLA vs 25.1 months with lapatinib + capecitabine; *P*=0.0006

PRIMARY ENDPOINT: OVERALL SURVIVAL (OS)[1]



Select Important Safety Information:

Left Ventricular Dysfunction (LVD)

- Patients treated with KADCYLA are at increased risk of developing LVD. In the Phase III EMILIA trial, LVD occurred in 1.8% of patients in the KADCYLA group and in 3.3% in the lapatinib + capecitabine group. Assess LVEF prior to initiation of KADCYLA and at regular intervals during treatment. Permanently discontinue KADCYLA if significant decreases in LVEF have not improved or have declined further

Next: See Progression-Free Survival

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Additional Important Safety Information

Left Ventricular Dysfunction (LVD)

- Patients treated with KADCYLA are at increased risk of developing LVD. In EMILIA, LVD occurred in 1.8% of patients in the KADCYLA-treated group and in 3.3% in the comparator group. Permanently discontinue KADCYLA if LVEF has not improved or has declined further

Pregnancy Registry

- Advise patients to contact their healthcare provider immediately if they suspect they may be pregnant. Encourage women who may be exposed to KADCYLA during pregnancy to enroll in the **MotHER Pregnancy Registry** by contacting 1-800-690-6720

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 IRRs and permanently discontinued in the event of a life-threatening IRR. Patients should be closely monitored for IRRs, especially during the first infusion

Hemorrhage

- Hemorrhagic events, sometimes fatal, have been reported in clinical trials. In EMILIA, the incidence of ≥ Grade 3 hemorrhage was 1.8% in the KADCYLA-treated group and 0.8% in the comparator group (overall incidence 32.2% and 16.4%, respectively)
- In some of the observed cases the patients were also receiving anticoagulation therapy or antiplatelet therapy, or had thrombocytopenia; in others, there were no known additional risk factors. Use caution with these agents and consider additional monitoring when concomitant use is medically necessary

Thrombocytopenia

- In EMILIA, the incidence of ≥ Grade 3 thrombocytopenia was 14.5% in the KADCYLA-treated group and 0.4% in the comparator group (overall incidence 31.2% and 3.3%, respectively)
- 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 (overall incidence 21.2% and 13.5%, respectively)
- 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. Specific treatment for KADCYLA extravasation is unknown

Nursing Mothers

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

Adverse Reactions

- The most common (frequency >25%) adverse drug reactions (ADR) across clinical trials with KADCYLA were nausea, fatigue, musculoskeletal pain, hemorrhage, thrombocytopenia, increased transaminases, headache, constipation, and epistaxis. In EMILIA, the most common NCI-CTCAE (version 3) ≥ Grade 3 ADRs (frequency >2%) were thrombocytopenia, increased transaminases, anemia, hypokalemia, peripheral neuropathy, and fatigue

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

Reference: 1. KADCYLA Prescribing Information. Genentech, Inc. July 2014.

Clinical Information

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Interested in receiving a copy of the EMILIA Study?

Talk to a representative about getting the EMILIA paper in *The New England Journal of Medicine*

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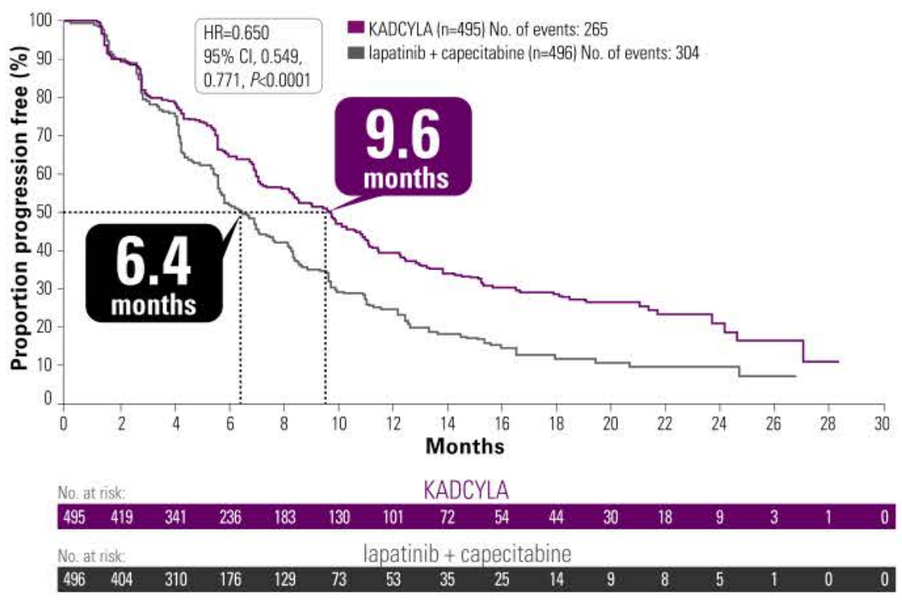
Results from the Phase III EMILIA trial: KADCYLA vs lapatinib + capecitabine

Significantly improved median PFS

50% improvement in median PFS by independent review[1]

- 9.6 months median PFS with KADCYLA vs 6.4 months with lapatinib + capecitabine; *P*<0.0001

PRIMARY ENDPOINT: PROGRESSION-FREE SURVIVAL (PFS)[1]



Select 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. Treatment with KADCYLA should be permanently discontinued in patients diagnosed with ILD or pneumonitis

Next: See Objective Response Rate

Indication

KADCYLA® (ado-trastuzumab emtansine), as a single agent, is indicated for the treatment of patients with HER2-positive (HER2+), metastatic breast cancer (MBC) 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

Important Safety Information

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**

Additional Important Safety Information

Left Ventricular Dysfunction (LVD)

- Patients treated with KADCYLA are at increased risk of developing LVD. In EMILIA, LVD occurred in 1.8% of patients in the KADCYLA-treated group and in 3.3% in the comparator group. Permanently discontinue KADCYLA if LVEF has not improved or has declined further

Pregnancy Registry

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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 IRRs and permanently discontinued in the event of a life-threatening IRR. Patients should be closely monitored for IRRs, especially during the first infusion

Hemorrhage

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- 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 (overall incidence 21.2% and 13.5%, respectively)
- 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. Specific treatment for KADCYLA extravasation is unknown

Nursing Mothers

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

Adverse Reactions

- The most common (frequency >25%) adverse drug reactions (ADR) across clinical trials with KADCYLA were nausea, fatigue, musculoskeletal pain, hemorrhage, thrombocytopenia, increased transaminases, headache, constipation, and epistaxis. In EMILIA, the most common NCI-CTCAE (version 3) ≥ Grade 3 ADRs (frequency >2%) were thrombocytopenia, increased transaminases, anemia, hypokalemia, peripheral neuropathy, and fatigue

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CONTACT A REPRESENTATIVE

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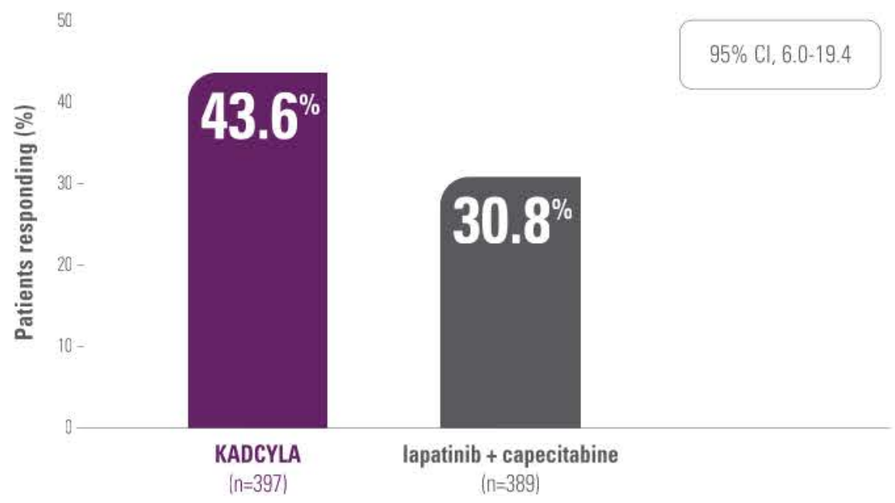
Results from the Phase III EMILIA trial: KADCYLA vs lapatinib + capecitabine

Achieved superior tumor response rates

KADCYLA was shown to shrink tumors in more patients[1,2]

- More patients had a complete response (1.0% vs 0.5%) or partial response (42.6% vs 30.3%) with KADCYLA than with lapatinib + capecitabine

OBJECTIVE RESPONSE RATE (ORR)[1]



ORR defined as the proportion of patients who achieved a complete response (disappearance of all target tumors) or a partial response (≥30% decrease in the sum of the longest diameters of target tumors) based on Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.0.[3-5]

Select Important Safety Information:

Infusion Related/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. KADCYLA treatment should be interrupted in patients with severe IRRs and permanently discontinued in the event of a life-threatening IRR

Hemorrhage

- Fatal cases have been observed in clinical trials. In some of the observed cases the patients were also receiving anticoagulation therapy or antiplatelet therapy, or had thrombocytopenia; in others, there were no known additional risk factors. Use caution with these agents and consider additional monitoring when concomitant use is medically necessary

Next: See Duration of Response

Indication

KADCYLA® (ado-trastuzumab emtansine), as a single agent, is indicated for the treatment of patients with HER2-positive (HER2+), metastatic breast cancer (MBC) who previously received trastuzumab and a taxane, separately or in combination. Patients should have either:

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Important Safety Information

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- **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**

Additional Important Safety Information

Left Ventricular Dysfunction (LVD)

- Patients treated with KADCYLA are at increased risk of developing LVD. In EMILIA, LVD occurred in 1.8% of patients in the KADCYLA-treated group and in 3.3% in the comparator group. Permanently discontinue KADCYLA if LVEF has not improved or has declined further

Pregnancy Registry

- Advise patients to contact their healthcare provider immediately if they suspect they may be pregnant. Encourage women who may be exposed to KADCYLA during pregnancy to enroll in the **MotHER Pregnancy Registry** by contacting 1-800-690-6720

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%
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Nursing Mothers

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

Adverse Reactions

- The most common (frequency >25%) adverse drug reactions (ADR) across clinical trials with KADCYLA were nausea, fatigue, musculoskeletal pain, hemorrhage, thrombocytopenia, increased transaminases, headache, constipation, and epistaxis. In EMILIA, the most common NCI-CTCAE (version 3) ≥ Grade 3 ADRs (frequency >2%) were thrombocytopenia, increased transaminases, anemia, hypokalemia, peripheral neuropathy, and fatigue

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Clinical Information

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CONTACT A REPRESENTATIVE

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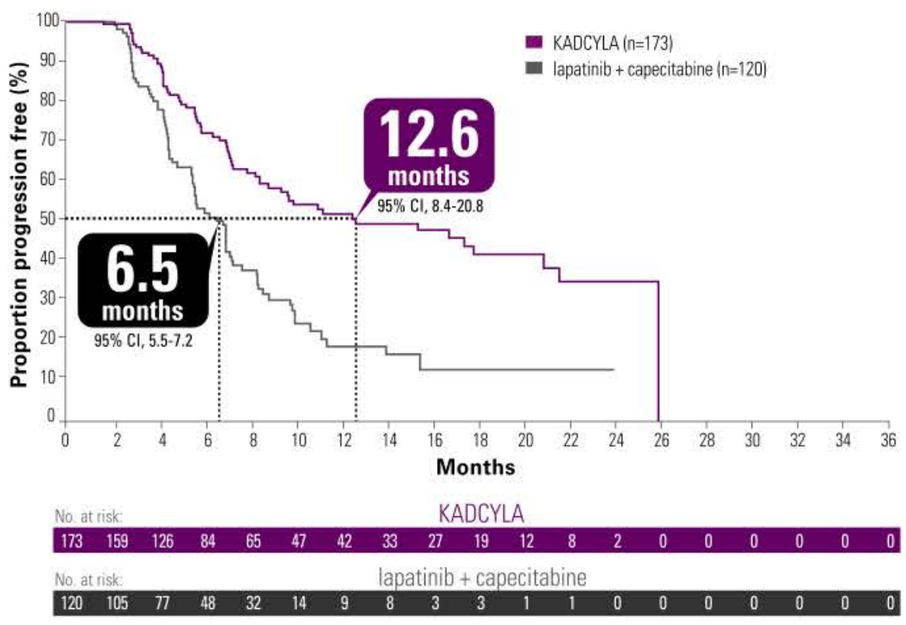
Results from the Phase III EMILIA trial: KADCYLA vs lapatinib + capecitabine

Sustained duration of response (DoR) beyond 1 year

Nearly doubled median DoR[1]

- 6.1 months improvement in median DoR was demonstrated (12.6 months vs 6.5 months with lapatinib + capecitabine)

DURATION OF RESPONSE (DoR)[2]



DoR defined as the time from initial documented tumor response (complete or partial) until documented disease progression. Only patients who achieved an initial response were evaluated for DoR.[3]

Select Important Safety Information:

Most Common Adverse Reactions

The most common ADRs seen with KADCYLA across clinical trials (frequency >25%) were:

Nausea
Musculoskeletal pain
Hemorrhage
Increased transaminases
Epistaxis
Constipation
Fatigue
Thrombocytopenia
Headache

Next: See Safety Information

Indication

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Clinical Information

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CONTACT A REPRESENTATIVE

Interested in a more detailed discussion of KADCYLA safety?

Review the KADCYLA safety profile with a KADCYLA representative

» Contact Us

Results from the Phase III EMILIA trial: KADCYLA vs lapatinib + capecitabine

Most common adverse reactions (ARs)

MOST COMMON ARs (>25%) ALL GRADES AND (>2%) GRADES ≥3[1]*

	KADCYLA (n=490)		lapatinib + capecitabine (n=488)	
ADVERSE REACTION*	**All Grades, %**	**Grades ≥3, %**	**All Grades, %**	**Grades ≥3, %**
Nausea	**39.8**	**0.8**	45.1	2.5
Fatigue	**36.3**	**2.5**	28.3	3.5
Musculoskeletal pain	**36.1**	**1.8**	30.5	1.4
Hemorrhage	**32.2**	**1.8**	16.4	0.8
Thrombocytopenia	**31.2**	**14.5**	3.3	0.4
Increased transaminases	**28.8**	**8.0**	14.3	2.5
Headache	**28.2**	**0.8**	14.5	0.8
Constipation	**26.5**	**0.4**	11.1	0.0
Diarrhea	**24.1**	**1.6**	79.7	20.7
Peripheral neuropathy	**21.2**	**2.2**	13.5	0.2
Vomiting	**19.2**	**0.8**	29.9	4.5
Anemia	**14.3**	**4.1**	10.5	2.5
Stomatitis	**14.1**	**0.2**	32.6	2.5
Rash	**11.6**	**0.0**	27.5	1.8
Hypokalemia	**10.2**	**2.7**	9.4	4.7
Neutropenia	**6.7**	**2.0**	9.0	4.3

*ARs categorized according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) (version 3).

Lower overall incidence of severe (Grades ≥3) ARs[1]

- Overall incidence of ARs Grades ≥3 was 43.1% vs 59.2% with lapatinib + capecitabine[1]
- Most common ARs (Grades ≥3) more frequently associated with KADCYLA than with lapatinib + capecitabine were thrombocytopenia, peripheral neuropathy, anemia, increased transaminases, musculoskeletal pain, hemorrhage, and constipation[1]
  - Incidence of alopecia was low (<5%) in both treatment arms[2]
- Diarrhea, hypokalemia, vomiting, neutropenia, fatigue, nausea, stomatitis, and rash (Grades ≥3) were the most common ARs more frequently associated with lapatinib + capecitabine than with KADCYLA[1]

>> See here for overall summary of adverse reactions from the EMILIA trial

Next: See Dose Reductions/Treatment Discontinuations

Indication

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- **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**

Additional Important Safety Information

Left Ventricular Dysfunction (LVD)

- Patients treated with KADCYLA are at increased risk of developing LVD. In EMILIA, LVD occurred in 1.8% of patients in the KADCYLA-treated group and in 3.3% in the comparator group. Permanently discontinue KADCYLA if LVEF has not improved or has declined further

Pregnancy Registry

- Advise patients to contact their healthcare provider immediately if they suspect they may be pregnant. Encourage women who may be exposed to KADCYLA during pregnancy to enroll in the **MotHER Pregnancy Registry** by contacting 1-800-690-6720

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 IRRs and permanently discontinued in the event of a life-threatening IRR. Patients should be closely monitored for IRRs, especially during the first infusion

Hemorrhage

- Hemorrhagic events, sometimes fatal, have been reported in clinical trials. In EMILIA, the incidence of ≥ Grade 3 hemorrhage was 1.8% in the KADCYLA-treated group and 0.8% in the comparator group (overall incidence 32.2% and 16.4%, respectively)
- In some of the observed cases the patients were also receiving anticoagulation therapy or antiplatelet therapy, or had thrombocytopenia; in others, there were no known additional risk factors. Use caution with these agents and consider additional monitoring when concomitant use is medically necessary

Thrombocytopenia

- In EMILIA, the incidence of ≥ Grade 3 thrombocytopenia was 14.5% in the KADCYLA-treated group and 0.4% in the comparator group (overall incidence 31.2% and 3.3%, respectively)
- 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 (overall incidence 21.2% and 13.5%, respectively)
- 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. Specific treatment for KADCYLA extravasation is unknown

Nursing Mothers

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

Adverse Reactions

- The most common (frequency >25%) adverse drug reactions (ADR) across clinical trials with KADCYLA were nausea, fatigue, musculoskeletal pain, hemorrhage, thrombocytopenia, increased transaminases, headache, constipation, and epistaxis. In EMILIA, 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.

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

References: 1. KADCYLA Prescribing Information. Genentech, Inc. July 2014. **2.** Data on file. Genentech, Inc.

Clinical Information

Safety First!
Before you start exploring, please read side effect information. » View now

CONTACT A REPRESENTATIVE

Interested in a more detailed discussion of KADCYLA safety?

Review the KADCYLA safety profile with a KADCYLA representative

» Contact Us

Results from the Phase III EMILIA trial: KADCYLA vs lapatinib + capecitabine

Fewer dose reductions and treatment discontinuations

NUMBER OF DOSE REDUCTIONS AND DISCONTINUATION RATES[1,2,3]

MANAGEMENT OUTCOMES	KADCYLA	lapatinib	capecitabine
Dose reductions	**16.3%**	27.3%	53.4%
Treatment discontinuations	**6.5%**	8.4%	10.5%
Dose delays	**23.7%**	36.9%	43.9%

- The most common ARs leading to dose reduction of KADCYLA (in ≥1% of patients) included thrombocytopenia, increased transaminases, and peripheral neuropathy[1]
- The most common ARs leading to discontinuation of KADCYLA were thrombocytopenia and increased AST[1]
- Incidence of dose delays was lower for KADCYLA (23.7%) compared with lapatinib (36.9%) or capecitabine (43.9%)[1,3]
  - ARs most frequently associated with a KADCYLA dose delay (in ≥1% of patients) were neutropenia, thrombocytopenia, leukopenia, fatigue, increased transaminases, and pyrexia[1]

Select Important Safety Information:

Thrombocytopenia

- Thrombocytopenia was reported in clinical trials of KADCYLA. The incidence and severity was higher in Asian patients. Monitor platelet counts prior to initiation of KADCYLA and prior to each dose. Institute dose modifications as appropriate

Hepatotoxicity

- Hepatotoxicity, predominantly in the form of asymptomatic increases in the concentrations of serum transaminases, has been observed in clinical trials with KADCYLA. Serious hepatobiliary disorders, including at least 2 fatal cases of severe drug-induced liver injury and associated hepatic encephalopathy, have also been reported in clinical trials with KADCYLA. Reduce dose or discontinue KADCYLA as appropriate in cases of increased serum transaminases or total bilirubin

Next: See Overall Summary of Adverse Reactions

Indication

KADCYLA® (ado-trastuzumab emtansine), as a single agent, is indicated for the treatment of patients with HER2-positive (HER2+), metastatic breast cancer (MBC) 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

Important Safety Information

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**

Additional Important Safety Information

Left Ventricular Dysfunction (LVD)

- Patients treated with KADCYLA are at increased risk of developing LVD. In EMILIA, LVD occurred in 1.8% of patients in the KADCYLA-treated group and in 3.3% in the comparator group. Permanently discontinue KADCYLA if LVEF has not improved or has declined further

Pregnancy Registry

- Advise patients to contact their healthcare provider immediately if they suspect they may be pregnant. Encourage women who may be exposed to KADCYLA during pregnancy to enroll in the **MotHER Pregnancy Registry** by contacting 1-800-690-6720

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

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- 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 IRRs and permanently discontinued in the event of a life-threatening IRR. Patients should be closely monitored for IRRs, especially during the first infusion

Hemorrhage

- Hemorrhagic events, sometimes fatal, have been reported in clinical trials. In EMILIA, the incidence of ≥ Grade 3 hemorrhage was 1.8% in the KADCYLA-treated group and 0.8% in the comparator group (overall incidence 32.2% and 16.4%, respectively)
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- 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. Specific treatment for KADCYLA extravasation is unknown

Nursing Mothers

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

Adverse Reactions

- The most common (frequency >25%) adverse drug reactions (ADR) across clinical trials with KADCYLA were nausea, fatigue, musculoskeletal pain, hemorrhage, thrombocytopenia, increased transaminases, headache, constipation, and epistaxis. In EMILIA, 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.

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

References: 1. KADCYLA Prescribing Information. Genentech, Inc. July 2014. **2.** Verma S, Miles D, Gianni L, et al; EMILIA Study Group. Trastuzumab emtansine for HER2-positive advanced breast cancer [published correction appears in *N Engl J Med.* 2013;368:2442]. *N Engl J Med.* 2012;367:1783-1791 and Supplementary Appendix. **3.** Center for Drug Evaluation and Research. Clinical review—BLA 125427: Kadcyla (ado-trastuzumab emtansine) for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Accessdata.fda.gov Web site. **http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/125427Orig1s000MedR.pdf**. Completed: January 25, 2013. Accessed July 24, 2014.

Clinical Information

Results from the Phase III EMILIA trial: KADCYLA vs lapatinib + capecitabine

Overall summary of adverse reactions

OVERALL SUMMARY OF ADVERSE REACTIONS (ARs)[1]

ADVERSE REACTION	KADCYLA (n=490)		lapatinib + capecitabine (n=488)	
	All Grades, %	Grades ≥3, %	All Grades, %	Grades ≥3, %
Blood and lymphatic system disorders				
Neutropenia	6.7	2.0	9.0	4.3
Anemia	14.3	4.1	10.5	2.5
Thrombocytopenia	31.2	14.5	3.3	0.4
Cardiac disorders				
Left ventricular dysfunction	1.8	0.2	3.3	0.4
Eye disorders				
Lacrimation increased	3.3	0.0	2.5	0.0
Dry eye	3.9	0.0	3.1	0.0
Vision blurred	4.5	0.0	0.8	0.0
Conjunctivitis	3.9	0.0	2.3	0.0
Gastrointestinal disorders				
Dyspepsia	9.2	0.0	11.5	0.4
Stomatitis	14.1	0.2	32.6	2.5
Dry mouth	16.7	0.0	4.9	0.2
Abdominal pain	18.6	0.8	17.6	1.6
Vomiting	19.2	0.8	29.9	4.5
Diarrhea	24.1	1.6	79.7	20.7
Constipation	26.5	0.4	11.1	0.0
Nausea	39.8	0.8	45.1	2.5
General disorders and administration				
Peripheral edema	7.1	0.0	8.2	0.2
Chills	7.6	0.0	3.1	0.0
Pyrexia	18.6	0.2	8.4	0.4
Asthenia	17.8	0.4	17.6	1.6
Fatigue	36.3	2.5	28.3	3.5
Hepatobiliary disorders				
Nodular regenerative hyperplasia*	0.4	ND	0.0	0.0
Portal hypertension*	0.4	0.2	0.0	0.0
Immune system disorders				
Drug hypersensitivity	2.2	0.0	0.8	0.0
Injury, poisoning, and procedural				
Infusion-related reaction	1.4	0.0	0.2	0.0
Infections and infestations				
Urinary tract infection	9.4	0.6	3.9	0.0
Investigations				
Blood alkaline phosphatase increased	4.7	0.4	3.7	0.4
Transaminases increased	28.8	8.0	14.3	2.5
Metabolism and nutrition disorders				
Hypokalemia	10.2	2.7	9.4	4.7
Musculoskeletal and connective tissue disorders				
Myalgia	14.1	0.6	3.7	0.0
Arthralgia	19.2	0.6	8.4	0.0
Musculoskeletal pain	36.1	1.8	30.5	1.4
Nervous system disorders				
Dysgeusia	8.0	0.0	4.1	0.2
Dizziness	10.2	0.4	10.7	0.2
Peripheral neuropathy	21.2	2.2	13.5	0.2
Headache	28.2	0.8	14.5	0.8
Psychiatric disorders				
Insomnia	12.0	0.4	8.6	0.2
Respiratory, thoracic, and mediastinal disorders				
Pneumonitis	1.2	0.0	0.0	0.0
Dyspnea	12.0	0.8	8.0	0.4
Cough	18.2	0.2	13.1	0.2
Epistaxis	22.5	0.2	8.4	0.0
Skin and subcutaneous tissue disorders				
Pruritus	5.5	0.2	9.2	0.0
Rash	11.6	0.0	27.5	1.8
Vascular disorders				
Hemorrhage	32.2	1.8	16.4	0.8
Hypertension	5.1	1.2	2.3	0.4

ND=not determined.

*Nodular regenerative hyperplasia and portal hypertension occurred in the same patient.

Next: See Dosing and Administration

Indication

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- Received prior therapy for metastatic disease, or
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Important Safety Information

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- **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**
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- **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**

Additional Important Safety Information

Left Ventricular Dysfunction (LVD)

- Patients treated with KADCYLA are at increased risk of developing LVD. In EMILIA, LVD occurred in 1.8% of patients in the KADCYLA-treated group and in 3.3% in the comparator group. Permanently discontinue KADCYLA if LVEF has not improved or has declined further

Pregnancy Registry

- Advise patients to contact their healthcare provider immediately if they suspect they may be pregnant. Encourage women who may be exposed to KADCYLA during pregnancy to enroll in the **MotHER Pregnancy Registry** by contacting 1-800-690-6720

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 IRRs and permanently discontinued in the event of a life-threatening IRR. Patients should be closely monitored for IRRs, especially during the first infusion

Hemorrhage

- Hemorrhagic events, sometimes fatal, have been reported in clinical trials. In EMILIA, the incidence of ≥ Grade 3 hemorrhage was 1.8% in the KADCYLA-treated group and 0.8% in the comparator group (overall incidence 32.2% and 16.4%, respectively)
- In some of the observed cases the patients were also receiving anticoagulation therapy or antiplatelet therapy, or had thrombocytopenia; in others, there were no known additional risk factors. Use caution with these agents and consider additional monitoring when concomitant use is medically necessary

Thrombocytopenia

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- 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 (overall incidence 21.2% and 13.5%, respectively)
- 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. Specific treatment for KADCYLA extravasation is unknown

Nursing Mothers

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

Adverse Reactions

- The most common (frequency >25%) adverse drug reactions (ADR) across clinical trials with KADCYLA were nausea, fatigue, musculoskeletal pain, hemorrhage, thrombocytopenia, increased transaminases, headache, constipation, and epistaxis. In EMILIA, 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.

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Reference: 1. KADCYLA Prescribing Information. Genentech, Inc. July 2014.

Dosing and Administration

Preparing and storing KADCYLA[1]

Calculating the correct dose

Dosing for KADCYLA is weight based (3.6 mg/kg; actual body weight).

1. **Calculate dose (mg)**

Patient Weight ____ kg × Drug Dose 3.6 mg/kg = KADCYLA ____ mg

2. **Calculate volume (reconstituted mL)**

KADCYLA ____ mg ÷ Vial Concentration 20 mg/mL = KADCYLA ____ mL

Example

For a patient who weighs 70 kg (154 lb)

Patient Weight 70 kg x Drug Dose 3.6 mg/kg = KADCYLA 252 mg

KADCYLA 252 mg ÷ Vial Concentration 20 mg/mL = KADCYLA 12.6 mL

Selecting the appropriate vial

KADCYLA is supplied as a sterile powder for concentrate and comes in 2 vial types. Vials will reconstitute to 20 mg/mL.

160 mg single-use vial yields 8 mL of reconstituted KADCYLA

100 mg single-use vial yields 5 mL of reconstituted KADCYLA

Look-Alike/Sound-Alike Medication[1]

Confirm vial label. KADCYLA (ado-trastuzumab EMTANSINE) and Herceptin® (trastuzumab) have similar generic names, but 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**

Instructions for reconstitution

Use aseptic technique for reconstitution and preparation of dosing solution.

- **Use appropriate procedures for the preparation of chemotherapeutic drugs**

1. To yield a single-use **reconstituted solution of 20 mg/mL** of KADCYLA for IV infusion, using a sterile syringe, slowly inject:
   - 8 mL of sterile water for injection (SWFI) into the 160 mg vial
   - 5 mL of SWFI into the 100 mg vial
2. Gently swirl the vial until solution is completely dissolved. **DO NOT FREEZE OR SHAKE.**
   - **Do not use if the reconstituted solution contains visible particulates or is cloudy or discolored**

Instructions for dilution

1. Add reconstituted KADCYLA solution to an infusion bag containing 250 mL of 0.9% sodium chloride injection.
   - **Do not use Dextrose (5%) solution to dilute KADCYLA**
2. Mix diluted solution by gentle inversion to avoid foaming. **DO NOT FREEZE OR SHAKE.**
3. Administer the infusion immediately after preparation, using a 0.22 micron in-line PES* filter.
   - **Do not mix or dilute KADCYLA with other drugs during preparation**

Storing KADCYLA

- Store vials in a refrigerator at 2°C-8°C (36°F-46°F) until time of use
- Reconstituted vials with SWFI and diluted KADCYLA infusion solution should be used immediately or may be stored in a refrigerator at 2°C-8°C (36°F-46°F) for up to 24 hours prior to use. **DO NOT FREEZE OR SHAKE**
  - Storage time for KADCYLA infusion solution is additional to the time allowed for the reconstituted vials
  - Discard any unused solution after 24 hours

*PES=polyethersulfone.

Next: Administering KADCYLA

Indication

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

Adverse Reactions

- The most common (frequency >25%) adverse drug reactions (ADR) across clinical trials with KADCYLA were nausea, fatigue, musculoskeletal pain, hemorrhage, thrombocytopenia, increased transaminases, headache, constipation, and epistaxis. In EMILIA, the most common NCI-CTCAE (version 3) ≥ Grade 3 ADRs (frequency >2%) were thrombocytopenia, increased transaminases, anemia, hypokalemia, peripheral neuropathy, and fatigue

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Dosing and Administration

Safety First!
Before you start exploring, please read side effect information. » View now

CONTACT A REPRESENTATIVE

Need printed information on dosing and administration for your office staff?

Get the Dosing and Administration Guide delivered by a KADCYLA representative

» Contact Us

Administering KADCYLA[1]

Single IV infusion every 3 weeks

- Administer at a dose of 3.6 mg/kg via IV infusion. **Do not administer KADCYLA as an intravenous push or bolus**
- An in-line PES* filter (0.22 micron) is required
- No loading dose
- No recommended premedications

*PES=polyethersulfone.

Dosing schedule for KADCYLA[1]

Initial infusion **90 minutes** + Observation (90 minutes) → If first infusion is tolerated, subsequent infusions **30 minutes** + Observation (30 minutes) → **Treat until disease progression or unacceptable toxicity**

Monitoring for infusion-related reactions (IRRs)

IRRs have been reported in clinical trials with KADCYLA. In most patients, these reactions resolved over the course of several hours to a day after completing the infusion.

- Monitor patients for IRRs, especially during the first infusion
- Slow or interrupt the infusion and administer appropriate medical therapies if severe IRRs occur
- Permanently discontinue treatment in the event of life-threatening infusion reactions

Dose modifications and reductions[1]

Severe adverse reactions have been reported in clinical studies with KADCYLA. Before beginning treatment with KADCYLA, review the Preadministration Guidelines and the Dose Modifications and Reductions Guidelines, which can be found in the **Dosing and Administration Guide**. For more information, download the accompanying full **Prescribing Information**.

- When multiple dose-modification events occur, always use the most conservative guideline

Hepatotoxicity
Increased serum transaminases (AST/ALT)
>2.5 to ≤5x ULN (Grade 2)
1) Treat at same dose level
>5 to ≤20x ULN (Grade 3)
1) Hold until recovery to ≤5x ULN 2) Then reduce one dose level
>20x ULN (Grade 4)
1) Permanently discontinue KADCYLA
Hyperbilirubinemia
>1.5 to ≤3x ULN (Grade 2)
1) Hold until total bilirubin level recovers to ≤1.5x ULN 2) Then treat at same dose level
>3 to ≤10x ULN (Grade 3)
1) Hold until total bilirubin level recovers to ≤1.5x ULN 2) Then reduce one dose level
>10x ULN (Grade 4)
1) Permanently discontinue KADCYLA
Permanently discontinue KADCYLA treatment in patients: • **with serum transaminases >3 x ULN and concomitant total bilirubin >2 x ULN, OR** • **diagnosed with nodular regenerative hyperplasia (NRH)**

Left ventricular cardiac dysfunction
LVEF 40% to ≤45% AND <10% point decline from baseline
1) Continue KADCYLA 2) Repeat LVEF assessment within 3 weeks
LVEF 40% to ≤45% AND ≥10% point decline from baseline
1) Do not administer KADCYLA 2) Repeat LVEF assessment within 3 weeks 3) If LVEF has not recovered to within 10% points of absolute baseline, discontinue KADCYLA
LVEF <40%
1) Do not administer KADCYLA 2) Repeat LVEF assessment within 3 weeks 3) If LVEF <40% is confirmed, discontinue KADCYLA
Symptomatic CHF
1) Discontinue KADCYLA

Thrombocytopenia
25,000 to <50,000 cells/mm³ (Grade 3)
1) Hold until recovered to ≥75,000 cells/mm³ 2) Then treat at same dose level
<25,000 cells/mm³ (Grade 4)
1) Hold until recovered to ≥75,000 cells/mm³ 2) Then reduce one dose level

AST=aspartate aminotransferase; ALT=alanine aminotransferase; ULN=upper limit of normal; LVEF=left ventricular ejection fraction; CHF=congestive heart failure.

- **Pulmonary Toxicity:** Permanently discontinue in patients diagnosed with interstitial lung disease (ILD) or pneumonitis
- **Peripheral Neuropathy:** Hold treatment in patients with severe to life-threatening peripheral neuropathy (Grades ≥3) until resolution to Grades ≤2

Dose reduction guidelines for KADCYLA[1]

- Dose reductions should be made in decrements of 0.6 mg/kg
- A maximum of 2 dose reductions should occur before discontinuation
- **KADCYLA dose should not be re-escalated after a dose reduction has been made**

Dose levels

3.6 mg/kg (Starting dose)
3 mg/kg
2.4 mg/kg
Discontinue KADCYLA

Missed doses[1]

If a planned dose is delayed or missed, administer as soon as possible at the most recently tolerated infusion rate. **Do not wait until the next planned cycle.**

Following a delayed or missed dose, adjust administration schedule to maintain a 3-week dosing interval.

Next: KADCYLA Professional Resources

Indication

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- Received prior therapy for metastatic disease, or
- Developed disease recurrence during or within six months of completing adjuvant therapy

Important Safety Information

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

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- **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**

Additional Important Safety Information

Left Ventricular Dysfunction (LVD)

- Patients treated with KADCYLA are at increased risk of developing LVD. In EMILIA, LVD occurred in 1.8% of patients in the KADCYLA-treated group and in 3.3% in the comparator group. Permanently discontinue KADCYLA if LVEF has not improved or has declined further

Pregnancy Registry

- Advise patients to contact their healthcare provider immediately if they suspect they may be pregnant. Encourage women who may be exposed to KADCYLA during pregnancy to enroll in the **MotHER Pregnancy Registry** by contacting 1-800-690-6720

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 IRRs and permanently discontinued in the event of a life-threatening IRR. Patients should be closely monitored for IRRs, especially during the first infusion

Hemorrhage

- Hemorrhagic events, sometimes fatal, have been reported in clinical trials. In EMILIA, the incidence of ≥ Grade 3 hemorrhage was 1.8% in the KADCYLA-treated group and 0.8% in the comparator group (overall incidence 32.2% and 16.4%, respectively)
- In some of the observed cases the patients were also receiving anticoagulation therapy or antiplatelet therapy, or had thrombocytopenia; in others, there were no known additional risk factors. Use caution with these agents and consider additional monitoring when concomitant use is medically necessary

Thrombocytopenia

- In EMILIA, the incidence of ≥ Grade 3 thrombocytopenia was 14.5% in the KADCYLA-treated group and 0.4% in the comparator group (overall incidence 31.2% and 3.3%, respectively)
- 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 (overall incidence 21.2% and 13.5%, respectively)
- 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. Specific treatment for KADCYLA extravasation is unknown

Nursing Mothers

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

Adverse Reactions

- The most common (frequency >25%) adverse drug reactions (ADR) across clinical trials with KADCYLA were nausea, fatigue, musculoskeletal pain, hemorrhage, thrombocytopenia, increased transaminases, headache, constipation, and epistaxis. In EMILIA, 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.

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

Reference: 1. KADCYLA Prescribing Information. Genentech, Inc., July 2014.

Resources

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Resources

Professional Resources and Downloads

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Professional Resources and Downloads

Within this section, healthcare providers can find important supplemental information to help in the treatment of patients with HER2-positive (HER2+) metastatic breast cancer (MBC).

Clinical resources

Full Prescribing Information

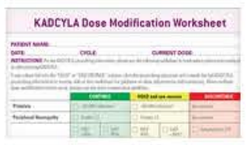
Full Prescribing Information for KADCYLA

» Download

Dosing and Administration Guide

Dosing and administration guidelines to help with accurate dosing

» Download



Dose Modification Worksheet

Quick reference sheet for modifying the dose of KADCYLA

» Download

Nurse-to-Patient Tear Sheet

A brief overview for patients, containing general information about KADCYLA

» Download

Non-clinical resources

Authorized Distributors of KADCYLA

» Leam more

Billing and Coding Information

Permanent **J-Code J9354**

» Leam more

KADCYLA Material Safety Data Sheet

» Download

Financial Resources

KADCYLA Access Solutions

Information for financial assistance to help support your patients

» KADCYLA Access Solutions

Indication

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Important Safety Information

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- **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**

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- Interstitial lung disease (ILD), including pneumonitis, some leading to acute respiratory distress syndrome or fatality: KADCYLA should be permanently discontinued in patients diagnosed with ILD or pneumonitis
- Infusion-related reactions (IRR), hypersensitivity: KADCYLA treatment should be interrupted in patients with severe IRR and permanently discontinued in the event of a life-threatening IRR
- Thrombocytopenia: Monitor platelet counts prior to initiation of KADCYLA and prior to each dose. Institute dose modifications as appropriate
- Hemorrhage: Fatal cases of hemorrhage occurred in clinical trials among patients with no known identified risk factors, as well as among patients with thrombocytopenia and those receiving anticoagulation and antiplatelet therapy
- Peripheral neuropathy: KADCYLA should be temporarily discontinued in patients experiencing Grade 3 or 4 peripheral neuropathy until resolution to ≤ Grade 2
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Your contact information will not be used for any other purpose than for the representative to respond to your information request.

Your Contact Information (*indicates a required field)

Provider Type*
Select

Specialty*
Select

First Name*

Last Name*

Email Address*

Confirm Email Address*

Zip Code*

Practice/Organization

Topic

- ☐ Clinical Data
- ☐ Nurse Support
- ☐ Reimbursement Support
- ☐ General KADCYLA

For your security, please enter the codes below:

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☐ **I would like to register for Genentech BioOncology updates**
By checking the box above, you agree to allow Genentech and its agents to collect the information provided and to be contacted by Genentech and its agents in the future regarding BioOncology products, and related disease education.

By submitting this form, you agree to allow Genentech and its agents to collect the information provided and to be contacted directly by a Genentech sales representative. Your information will not be used for any other purpose than for a representative to respond to your information request, or for us to send you other Genentech BioOncology updates if you have registered to receive them.

Genentech will not sell, rent, or otherwise distribute your name and any personally identifiable information outside of Genentech and its agents. Genentech will only use your information in accordance with its **Privacy Policy**.

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Specialty*
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Last Name*
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Email Address*
is missing and it is required

Confirm Email Address*
is missing and it is required

Zip Code*
is missing and it is required

Practice/Organization

Topic
- Clinical Data
- Nurse Support
- Reimbursement Support
- General KADCYLA

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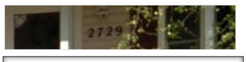

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Indication

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Provider Type*

Select

- Select
- Resident/Fellow
- Physician
- Nurse
- Pharmacist
- Nurse Practitioner
- Clinical Coordinator (Nurse)
- Clinical Nurse Specialist
- Physician Assistant
- Other

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Select

- Select
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- Radiation Oncology
- Surgical Oncology

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Thank you

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Your request has been submitted. One of our Genentech sales representatives will contact you directly within 2 business days.

Indication

KADCYLA® (ado-trastuzumab emtansine), as a single agent, is indicated for the treatment of patients with HER2-positive

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Patient Support

Financial Support for Your Patients

› Patient Support Line

KADCYLA Access Solutions

KADCYLA Access Solutions helps to resolve access and reimbursement issues for individual patients every day. Our dedicated specialists help bring patient treatment and practice solutions together.

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BioOncology Co-pay Card

Genentech offers the Genentech BioOncology Co-pay Card to help qualified patients with the out-of-pocket costs associated with their KADCYLA prescription.

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Genentech Access to Care Foundation (GATCF)

GATCF was established to help patients with unmet medical needs who are uninsured or rendered uninsured by payer denial and who meet specific financial and medical criteria to receive proper medical treatment.

»Leam more

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Patient Support

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Patient Support

› Financial Support for Your Patients

Patient Support Line

KADCYLA Patient Support Line

Expert information any time your patients need it

When your patients have important questions about KADCYLA treatment, you want them to get information you can trust. With the KADCYLA Support Line, registered oncology nurses are always available to answer their questions and provide information about KADCYLA.

We're here to help 24 hours a day—call the support line any time. Our nurses will be able to answer questions from patients about:

- How KADCYLA is designed to work
- The potential benefits of KADCYLA
- Side effects of KADCYLA
- What to expect from KADCYLA treatment
- Finding reimbursement help for KADCYLA

Every nurse on our team:

- Specializes in oncology
- Has about 20 years of experience
- Is knowledgeable about KADCYLA treatment

Genentech will not provide medical advice regarding your patient's medical condition.

FOR 24-HOUR SUPPORT, CALL 1-855-KADCYLA (1-855-523-2952)

Indication

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- **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**

The following additional serious adverse reactions have been reported in clinical trials with KADCYLA:

- Interstitial lung disease (ILD), including pneumonitis, some leading to acute respiratory distress syndrome or fatality: KADCYLA should be permanently discontinued in patients diagnosed with ILD or pneumonitis
- Infusion-related reactions (IRR), hypersensitivity: KADCYLA treatment should be interrupted in patients with severe IRR and permanently discontinued in the event of a life-threatening IRR
- Thrombocytopenia: Monitor platelet counts prior to initiation of KADCYLA and prior to each dose. Institute dose modifications as appropriate
- Hemorrhage: Fatal cases of hemorrhage occurred in clinical trials among patients with no known identified risk factors, as well as among patients with thrombocytopenia and those receiving anticoagulation and antiplatelet therapy
- Peripheral neuropathy: KADCYLA should be temporarily discontinued in patients experiencing Grade 3 or 4 peripheral neuropathy until resolution to ≤ Grade 2
- Reactions secondary to extravasation: The infusion site should be closely monitored for possible subcutaneous infiltration during drug administration

Additional Important Safety Information:

- Detection of HER2 protein overexpression or gene amplification is necessary for selection of patients appropriate for KADCYLA therapy
- Nursing mothers: Discontinue nursing or discontinue KADCYLA, taking into consideration the importance of the drug to the mother
- The most common adverse drug reactions (frequency >25%) across clinical trials with KADCYLA were fatigue, nausea, musculoskeletal pain, hemorrhage, thrombocytopenia, headache, increased transaminases, constipation, and epistaxis

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.

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

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By registering at this site, you certify that you are a healthcare professional licensed in the United States or its territories and are indicating that you wish to receive information about KADCYLA (ado-trastuzumab emtansine), other Genentech BioOncology products, and related disease education. Genentech's intent is to only provide information to healthcare professionals licensed in the United States or its territories who would likely be treating patients within the FDA-approved indications for this product.

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Important Safety Information

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

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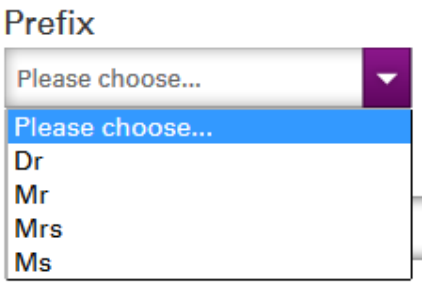
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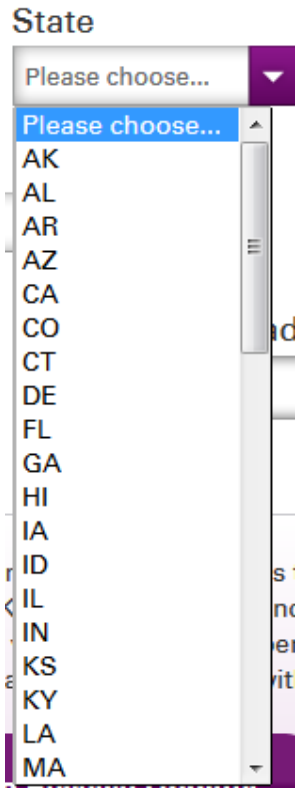
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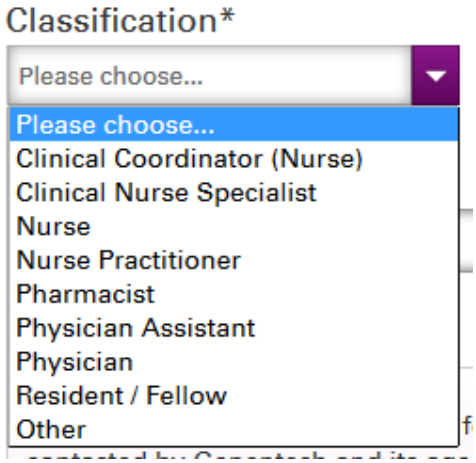
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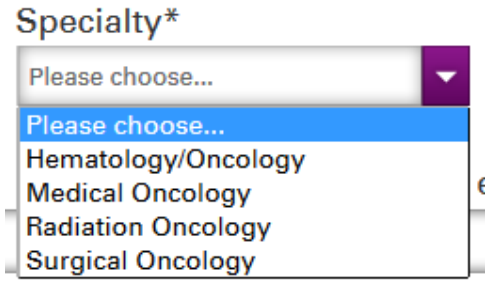
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Important Safety Information

Indication

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- Received prior therapy for metastatic disease, or
- Developed disease recurrence during or within six months of completing adjuvant therapy

Important Safety Information
Warnings and Precautions

Hepatotoxicity (Boxed WARNING)

Hepatotoxicity, predominantly in the form of asymptomatic increases in the concentrations of serum transaminases, has been observed in clinical trials with KADCYLA.

Serious hepatobiliary disorders, including at least 2 fatal cases of severe drug-induced liver injury and associated hepatic encephalopathy, have been reported in clinical trials with KADCYLA. Some of the observed cases may have been confounded by comorbidities and concomitant medications with known hepatotoxic potential.

Monitor serum transaminases and bilirubin prior to initiation of KADCYLA treatment and prior to each KADCYLA dose. Patients with known active hepatitis B virus or hepatitis C virus were excluded from EMILIA. Reduce dose or discontinue KADCYLA as appropriate in cases of increased serum transaminases and/or total bilirubin. Permanently discontinue KADCYLA treatment in patients with serum transaminases > 3X ULN and concomitant total bilirubin > 2X ULN.

In clinical trials of KADCYLA, cases of nodular regenerative hyperplasia (NRH) of the liver have been identified from liver biopsies (3 cases out of 884 treated patients, 1 of which was fatal). NRH should be considered in all patients with clinical symptoms of portal hypertension and/or cirrhosis-like pattern seen on the computed tomography scan of the liver but with normal transaminases and no manifestations of cirrhosis. Diagnosis can be confirmed only by histopathology. Upon diagnosis, KADCYLA treatment must be permanently discontinued.

Left Ventricular Dysfunction (Boxed WARNING)

Patients treated with KADCYLA are at increased risk of developing left ventricular dysfunction. A decrease of LVEF to <40% has been observed in patients treated with KADCYLA. In EMILIA, left ventricular dysfunction occurred in 1.8% of patients in the KADCYLA-treated group and 3.3% of patients in the comparator group.

Assess LVEF prior to initiation of KADCYLA and at regular intervals (eg every 3 months) during treatment. Treatment with KADCYLA has not been studied in patients with LVEF <50% prior to treatment. If, at routine monitoring, LVEF is <40%, or is 40% to 45% with a 10% or greater absolute decrease below the pretreatment value, withhold KADCYLA and repeat LVEF assessment within approximately 3 weeks. Permanently discontinue KADCYLA if the LVEF has not improved or has declined further.

Embryo-Fetal Toxicity (Boxed WARNING)

Pregnancy Category D: KADCYLA can cause fetal harm or death when administered to a pregnant woman. There are no adequate and well-controlled studies of KADCYLA in pregnant women and no reproductive and developmental toxicology studies have been conducted with ado-trastuzumab emtansine. Nevertheless, treatment with trastuzumab, the antibody component of KADCYLA, during pregnancy in the postmarketing setting has resulted in oligohydramnios, some associated with fatal pulmonary hypoplasia, skeletal abnormalities and neonatal death. DM1, the cytotoxic component, can be expected to cause embryo-fetal toxicity.

If KADCYLA is used during pregnancy, or if the patient becomes pregnant while receiving KADCYLA, apprise the patient of the potential hazard to the fetus.

Verify pregnancy status prior to the initiation of KADCYLA. Advise patients of the risks of embryo-fetal death and birth defects and the need for contraception during and for 6 months following treatment. Advise patients to contact their healthcare provider immediately if they suspect they may be pregnant.

If KADCYLA is administered during pregnancy or if a patient becomes pregnant while receiving KADCYLA, immediately report exposure to the Genentech Adverse Event Line at 1-888-835-2555. Encourage women who may be exposed during pregnancy to enroll in the **MotHER Pregnancy Registry** by contacting 1-800-690-6720.

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. Signs and symptoms include dyspnea, cough, fatigue, and pulmonary infiltrates. In EMILIA, the overall frequency of pneumonitis was 1.2%.

Treatment with KADCYLA should be permanently discontinued in patients diagnosed with ILD or pneumonitis.

Patients with dyspnea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of pulmonary events.

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; treatment with KADCYLA is not recommended for these patients.

Infusion-related reactions, characterized by one or more of the following symptoms—flushing, chills, pyrexia, dyspnea, hypotension, wheezing, bronchospasm, and tachycardia—have been reported in clinical trials of KADCYLA. In the randomized 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 the infusion was terminated.

KADCYLA treatment should be interrupted in patients with severe IRRs and permanently discontinued in the event of a life-threatening IRR. Patients should be observed closely for IRRs especially during the first infusion.

One case of a serious, allergic/anaphylactoid-like infusion reaction has been observed in clinical trials of single-agent KADCYLA. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use.

Hemorrhage

Cases of hemorrhagic events, including central nervous system, respiratory, and gastrointestinal hemorrhage, have been reported in clinical trials with KADCYLA. Some of these bleeding events resulted in fatal outcomes. In EMILIA the incidence of ≥ Grade 3 hemorrhage was 1.8% in the KADCYLA-treated group and 0.8% in the comparator group.

Although in some of the observed cases the patients were also receiving anticoagulation therapy or antiplatelet therapy, or had thrombocytopenia, in others there were no known additional risk factors. Anticoagulation therapy and antiplatelet agents may increase the risk of bleeding. Use caution with these agents and consider additional monitoring when concomitant use is medically necessary.

Thrombocytopenia

Thrombocytopenia was reported in clinical trials of KADCYLA. The majority of these patients had Grade 1 or 2 events (< LLN to ≥50,000/mm^3) with the nadir occurring by day 8 and generally improving to Grade 0 or 1 (≥75,000/mm^3) by the next scheduled dose. In clinical trials of KADCYLA, the incidence and severity of thrombocytopenia were higher in Asian patients.

In EMILIA, the incidence of ≥ Grade 3 thrombocytopenia was 14.5% in the KADCYLA-treated group and 0.4% in the comparator group. In Asian patients, the incidence of ≥ Grade 3 thrombocytopenia was 45.1% in the KADCYLA group and 1.3% in the comparator group.

Monitor platelet counts prior to initiation of KADCYLA and prior to each KADCYLA dose. KADCYLA has not been studied in patients with platelet counts ≤100,000/mm^3 prior to initiation of treatment. In the event of decreased platelet count to Grade 3 or greater (<50,000/mm^3), do not administer KADCYLA until platelet counts recover to Grade 1 (≥75,000/mm^3). Patients with thrombocytopenia (≤100,000/mm^3) prior to initiation of KADCYLA and patients on anticoagulant treatment should be closely monitored during treatment with KADCYLA.

Neurotoxicity

Peripheral neuropathy, mainly as Grade 1 and predominantly sensory, was reported in clinical trials of KADCYLA. In EMILIA, the incidence of ≥ Grade 3 peripheral neuropathy was 2.2% in the KADCYLA-treated group and 0.2% in the comparator group.

KADCYLA should be temporarily discontinued in patients experiencing Grade 3 or 4 peripheral neuropathy until resolution to ≤ Grade 2. Patients should be clinically monitored on an ongoing basis for signs/symptoms of neurotoxicity.

HER2 Testing

Detection of HER2 protein overexpression or gene amplification is necessary for selection of patients appropriate for KADCYLA therapy because these are the only patients studied for whom benefit has been shown. Assessment of HER2 status should be done using an FDA-approved test performed by laboratories with demonstrated proficiency.

In the randomized study, patients with breast cancer were required to have evidence of HER2 overexpression defined as 3+ IHC and/or FISH amplification ratio ≥2.0 assessed by a validated test.

Extravasation

In KADCYLA clinical studies, reactions secondary to extravasation have been observed. These reactions, observed more frequently within 24 hours of infusion, were usually mild and comprised of erythema, tenderness, skin irritation, pain, or swelling at the infusion site. The infusion site should be closely monitored for possible subcutaneous infiltration during drug administration. Specific treatment for KADCYLA extravasation is unknown.

Use in Specific Populations

Nursing Mothers

It is not known whether KADCYLA specifically is excreted in human milk, but IgG is known to be excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or discontinue KADCYLA, taking into account the importance of the drug to the mother.

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- The most common adverse drug reactions (frequency >25%) across clinical trials with KADCYLA were fatigue, nausea, musculoskeletal pain, hemorrhage, thrombocytopenia, headache, increased transaminases, constipation, and epistaxis

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.

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

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Indication

KADCYLA® (ado-trastuzumab emtansine), as a single agent, is indicated for the treatment of patients with HER2-positive (HER2+), metastatic breast cancer (MBC) 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

Important Safety Information

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**

The following additional serious adverse reactions have been reported in clinical trials with KADCYLA:

- Interstitial lung disease (ILD), including pneumonitis, some leading to acute respiratory distress syndrome or fatality: KADCYLA should be permanently discontinued in patients diagnosed with ILD or pneumonitis
- Infusion-related reactions (IRR), hypersensitivity: KADCYLA treatment should be interrupted in patients with severe IRR and permanently discontinued in the event of a life-threatening IRR
- Thrombocytopenia: Monitor platelet counts prior to initiation of KADCYLA and prior to each dose. Institute dose modifications as appropriate
- Hemorrhage: Fatal cases of hemorrhage occurred in clinical trials among patients with no known identified risk factors, as well as among patients with thrombocytopenia and those receiving anticoagulation and antiplatelet therapy
- Peripheral neuropathy: KADCYLA should be temporarily discontinued in patients experiencing Grade 3 or 4 peripheral neuropathy until resolution to ≤ Grade 2
- Reactions secondary to extravasation: The infusion site should be closely monitored for possible subcutaneous infiltration during drug administration

Additional Important Safety Information:

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