This brochure will help you become familiar with dosing and administration for KADCYLA® (ado-trastuzumab emtansine) in the following treatment settings for HER2+ breast cancer:

- Early breast cancer
- Metastatic breast cancer

HER2=human epidermal growth factor receptor 2.

**Indications**

**Metastatic Breast Cancer (MBC)**

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

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

Select patients for therapy based on an FDA-approved companion diagnostic for KADCYLA.

**Early Breast Cancer (EBC)**

KADCYLA, as a single agent, is indicated for the adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment.

Select patients for therapy based on an FDA-approved companion diagnostic for KADCYLA.

**Important Safety Information**

**BOXED WARNINGS: HEPATOTOXICITY, CARDIAC TOXICITY, EMBRYO-FETAL TOXICITY**

- **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 during pregnancy can result in embryo-fetal harm. Advise patients of these risks and the need for effective contraception.

Please see Important Safety Information on pages 12-15, and accompanying Prescribing Information, including BOXED WARNINGS.
Dosing for **early breast cancer**

**Patients eligible for KADCYLA® (ado-trastuzumab emtansine)**

- Patients with HER2+ early breast cancer (EBC) who have residual invasive disease following neoadjuvant taxane and trastuzumab-based treatment

Select patients for therapy based on an FDA-approved companion diagnostic for KADCYLA.

**Recommended dosing**

Do not substitute trastuzumab for or with KADCYLA.

- 3.6 mg/kg given as an intravenous infusion every 3 weeks (21-day cycle) for a total of 14 cycles unless there is disease recurrence or unmanageable toxicity

For a total of

**14 CYCLES**

3.6 mg/kg every 3 weeks

**EBC dosing schedule**

- **Initial infusion:** 90 minutes + Observation for infusion-related reactions: ≥90 minutes
- If prior infusions were well tolerated, subsequent infusions: 30 minutes + Observation: ≥30 minutes
- **Treat for a total of 14 cycles** (every 3 weeks) unless there is disease recurrence or unmanageable toxicity

Closely monitor the infusion site for possible subcutaneous infiltration during drug administration.

Do not administer KADCYLA at doses greater than 3.6 mg/kg.

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Dosing for **metastatic breast cancer**

**Patients eligible for KADCYLA**

- Patients with HER2+ metastatic breast cancer (MBC) who were previously treated with 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 6 months of completing adjuvant therapy

Select patients for therapy based on an FDA-approved companion diagnostic for KADCYLA.

**Recommended dosing**

Do not substitute trastuzumab for or with KADCYLA.

- 3.6 mg/kg given as an intravenous infusion every 3 weeks (21-day cycle) until disease progression or unmanageable toxicity

3.6 mg/kg every 3 WEEKS

**MBC dosing schedule**

- **Initial infusion:** 90 minutes + Observation for infusion-related reactions: ≥90 minutes
- If prior infusions were well tolerated, subsequent infusions: 30 minutes + Observation: ≥30 minutes
- **Treat until disease progression or unmanageable toxicity**

Closely monitor the infusion site for possible subcutaneous infiltration during drug administration.

Do not administer KADCYLA at doses greater than 3.6 mg/kg.

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Please see Important Safety Information on pages 12-15, and accompanying Prescribing Information, including BOXED WARNINGS.
Additional dose considerations

Before administering KADCYLA® (ado-trastuzumab emtansine)

Assessment of HER2 protein overexpression and/or HER2 gene amplification should be performed using FDA-approved tests specific for breast cancers by laboratories with demonstrated proficiency.

Assess baseline characteristics
Some severe adverse reactions have been reported in clinical studies with KADCYLA. Before beginning treatment with KADCYLA, review guidelines below and the dosing modifications on pages 6-9.

Hepatotoxicity¹
- Assess baseline transaminases (aspartate transaminase, alanine transaminase) and total bilirubin prior to initiation of KADCYLA treatment
- Monitor liver function prior to each dose
- Reduce or discontinue dose as appropriate
- Permanently discontinue KADCYLA treatment in patients with serum transaminases >3 x ULN and concomitant total bilirubin >2 x ULN
- In cases of nodular regenerative hyperplasia, KADCYLA treatment must be permanently discontinued

Cardiotoxicity¹
- Assess baseline left ventricular ejection fraction (LVEF) prior to initiation of KADCYLA treatment
- Perform standard cardiac assessment at regular intervals (e.g. every 3 months) to ensure the LVEF is within the institution’s normal limits
- Withhold or discontinue dose as appropriate

Embryofetal toxicity¹
- Verify the pregnancy status of females of reproductive potential prior to initiation of KADCYLA treatment
- Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of KADCYLA

Thrombocytopenia¹
- Assess baseline platelet counts prior to initiation of KADCYLA treatment
- Monitor platelet count prior to each dose
- Modify, withhold, or discontinue dose as appropriate

During treatment

If a planned dose is delayed or missed¹:
- Administer as soon as possible; do not wait until the next planned cycle
- Adjust the schedule of administration to maintain a 3-week interval between doses
- Administer the infusion at the dose and rate the patient tolerated in the most recent infusion

If a patient develops an infusion-related reaction¹:
- Slow or interrupt the infusion rate of KADCYLA
- Permanently discontinue KADCYLA for life-threatening infusion-related reactions

Recommended dose reduction schedule for adverse reactions¹

<table>
<thead>
<tr>
<th>Dose</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.6 mg/kg</td>
<td>Starting dose</td>
</tr>
<tr>
<td>3 mg/kg</td>
<td>First dose reduction</td>
</tr>
<tr>
<td>2.4 mg/kg</td>
<td>Second dose reduction</td>
</tr>
<tr>
<td></td>
<td>Discontinue KADCYLA</td>
</tr>
</tbody>
</table>

Do not re-escalate the KADCYLA dose after a dose reduction is made.

Please see Important Safety Information on pages 12-15, and accompanying Prescribing Information, including BOXED WARNINGS.
Dose modifications for early breast cancer

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Severity</th>
<th>Treatment modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased Alanine Transaminase (ALT)</td>
<td>Grade 2-3 (&gt;3.0 to ≤20× ULN on day of scheduled treatment)</td>
<td>Do not administer KADCYLA until ALT recovers to Grade ≤1, and then reduce one dose level.</td>
</tr>
<tr>
<td></td>
<td>Grade 4 (&gt;20× ULN at any time)</td>
<td>Discontinue KADCYLA.</td>
</tr>
<tr>
<td>Increased Aspartate Transaminase (AST)</td>
<td>Grade 2 (&gt;3.0 to ≤5× ULN on day of scheduled treatment)</td>
<td>Do not administer KADCYLA until AST recovers to Grade ≤1, and then treat at the same dose level.</td>
</tr>
<tr>
<td></td>
<td>Grade 3 (&gt;5 to ≤20× ULN on day of scheduled treatment)</td>
<td>Do not administer KADCYLA until AST recovers to Grade ≤1, and then reduce one dose level.</td>
</tr>
<tr>
<td></td>
<td>Grade 4 (&gt;20× ULN at any time)</td>
<td>Discontinue KADCYLA.</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>TBILI &gt;1.0 to ≤2.0× the ULN on day of scheduled treatment</td>
<td>Do not administer KADCYLA until total bilirubin recovers to ≤1.0× ULN, and then reduce one dose level.</td>
</tr>
<tr>
<td></td>
<td>TBILI &gt;2× ULN at any time</td>
<td>Discontinue KADCYLA.</td>
</tr>
<tr>
<td>Nodular Regenerative Hyperplasia (NRH)</td>
<td>All Grades</td>
<td>Permanently discontinue KADCYLA.</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Grade 2-3 on day of scheduled treatment (25,000 to &lt;75,000/mm³)</td>
<td>Do not administer KADCYLA until platelet count recovers to Grade ≤1 (≥75,000/mm³), and then treat at the same dose level. If a patient requires 2 delays due to thrombocytopenia, consider reducing dose by one level.</td>
</tr>
<tr>
<td></td>
<td>Grade 4 at any time (&lt;25,000/mm³)</td>
<td>Do not administer KADCYLA until platelet count recovers to Grade ≤1 (≥75,000/mm³), and then reduce one dose level.</td>
</tr>
</tbody>
</table>

**Adverse reaction**

**Severity**

**Treatment modification**

Dose modifications for early breast cancer (cont’d)

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Severity</th>
<th>Treatment modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Ventricular Dysfunction</td>
<td>LVEF &lt;45%</td>
<td>Do not administer KADCYLA. Repeat LVEF assessment within 3 weeks. If LVEF &lt;45% is confirmed, discontinue KADCYLA.</td>
</tr>
<tr>
<td></td>
<td>LVEF 45% to &lt;50% and decrease is ≥10% points from baseline*</td>
<td>Do not administer KADCYLA. Repeat LVEF assessment within 3 weeks.</td>
</tr>
<tr>
<td></td>
<td>LVEF ≥50%</td>
<td>Continue treatment with KADCYLA.</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>Symptomatic CHF, Grade 3-4 LVSD or Grade 3-4 heart failure, or Grade 2 heart failure accompanied by LVEF &lt;45%</td>
<td>Discontinue KADCYLA.</td>
</tr>
<tr>
<td>Peripheral Neuropathy</td>
<td>Grade 3-4</td>
<td>Do not administer KADCYLA until resolution Grade ≤2.</td>
</tr>
<tr>
<td>Pulmonary Toxicity</td>
<td>Interstitial lung disease (ILD) or pneumonitis</td>
<td>Permanently discontinue KADCYLA.</td>
</tr>
<tr>
<td>Radiotherapy-Related Pneumonitis</td>
<td>Grade 2</td>
<td>Discontinue KADCYLA if not resolving with standard treatment.</td>
</tr>
<tr>
<td></td>
<td>Grade 3-4</td>
<td>Discontinue KADCYLA.</td>
</tr>
</tbody>
</table>

*Prior to starting KADCYLA treatment.

CHF = congestive heart failure; LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic dysfunction; TBILI = total bilirubin; ULN = upper limit of normal.
Dose modifications for metastatic breast cancer¹

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Severity</th>
<th>Treatment modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased Transaminase (AST/ALT)</td>
<td>Grade 2 (&gt;2.5 to ≤5x the ULN)</td>
<td>Treat at the same dose level.</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>Grade 3 (&gt;5 to ≤20x the ULN)</td>
<td>Do not administer KADCYLA until AST/ALT recovers to Grade ≤2, and then reduce one dose level.</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>Grade 4 (&gt;20x the ULN)</td>
<td>Discontinue KADCYLA.</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>Grade 2 (&gt;1.5 to ≤3x the ULN)</td>
<td>Do not administer KADCYLA until total bilirubin recovers to Grade ≤1, and then treat at the same dose level.</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>Grade 3 (&gt;3 to ≤10x the ULN)</td>
<td>Do not administer KADCYLA until total bilirubin recovers to Grade ≤1 and then reduce one dose level.</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>Grade 4 (&gt;10x the ULN)</td>
<td>Discontinue KADCYLA.</td>
</tr>
<tr>
<td>Drug Induced Liver Injury (DILI)</td>
<td>Serum transaminases &gt;3x ULN and concomitant total bilirubin &gt;2x ULN</td>
<td>Permanently discontinue KADCYLA in the absence of another likely cause for the elevation of liver enzymes and bilirubin, e.g. liver metastasis or concomitant medication.</td>
</tr>
<tr>
<td>Nodular Regenerative Hyperplasia (NRH)</td>
<td>All Grades</td>
<td>Permanently discontinue KADCYLA.</td>
</tr>
<tr>
<td>Nodular Regenerative Hyperplasia (NRH)</td>
<td>Grade 3 (25,000 to &lt;50,000/mm³)</td>
<td>Do not administer KADCYLA until platelet count recovers to Grade ≤1 (≥75,000/mm³), and then treat at the same dose level.</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Grade 4 (&lt;25,000/mm³)</td>
<td>Do not administer KADCYLA until platelet count recovers to Grade ≤1 (≥75,000/mm³), and then reduce one dose level.</td>
</tr>
</tbody>
</table>

Dose modifications for metastatic breast cancer¹ (cont’d)

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Severity</th>
<th>Treatment modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Ventricular Dysfunction</td>
<td>Symptomatic CHF</td>
<td>Discontinue KADCYLA.</td>
</tr>
<tr>
<td>Left Ventricular Dysfunction</td>
<td>LVEF &lt;40%</td>
<td>Do not administer KADCYLA. Repeat LVEF assessment within 3 weeks.</td>
</tr>
<tr>
<td>Left Ventricular Dysfunction</td>
<td>LVEF 40% to ≤45% and decrease is ≥10% points from baseline</td>
<td>Do not administer KADCYLA. Repeat LVEF assessment within 3 weeks.</td>
</tr>
<tr>
<td>Left Ventricular Dysfunction</td>
<td>LVEF &gt;45%</td>
<td>Continue treatment with KADCYLA.</td>
</tr>
<tr>
<td>Pulmonary Toxicity</td>
<td>Interstitial lung disease (ILD) or pneumonitis</td>
<td>Permanently discontinue KADCYLA.</td>
</tr>
<tr>
<td>Peripheral Neuropathy</td>
<td>Grade 3-4</td>
<td>Do not administer KADCYLA until resolution Grade ≤2.</td>
</tr>
</tbody>
</table>

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

**Look-alike/sound-alike medication**
In order to prevent medication errors it is important to check the vial labels to ensure that the drug being prepared and administered is KADCYLA® (ado-trastuzumab emtansine) and not trastuzumab.

**Storage**
KADCYLA is supplied as lyophilized powder in single-dose vials.

**100 mg, single-dose vial**
NDC 50242-088-01

**160 mg, single-dose vial**
NDC 50242-087-01

Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F) until time of reconstitution. Do not freeze or shake.

**Preparation**

**Dose calculation**
1. Calculate dose (mg). Dosing for KADCYLA is weight based (3.6 mg/kg).

\[ \text{Patient Weight} \times 3.6 \text{ mg/kg} = \text{KADCYLA} \text{ mg} \]

**Reconstitution**
Prepare the solution for infusion, using aseptic technique. Appropriate procedures for the preparation of chemotherapeutic drugs should be used.

1. Using a sterile syringe, slowly inject 5 mL of Sterile Water for Injection into the 100 mg KADCYLA vial, or 8 mL of Sterile Water for Injection into the 160 mg KADCYLA vial to yield a solution containing 20 mg/mL. Swirl the vial gently until completely dissolved. Do not shake.

2. Inspect the reconstituted solution for particulates and discoloration. The reconstituted solution should be clear to slightly opalescent and free of visible particulates. The color of the reconstituted solution should be colorless to pale brown. Do not use if the reconstituted solution contains visible particulates or is cloudy or discolored.

3. The reconstituted product contains no preservative and is intended for single-dose only.

4. KADCYLA should be used immediately following reconstitution. If not used immediately, the reconstituted KADCYLA vials can be stored for up to 24 hours in a refrigerator at 2°C to 8°C (36°F to 46°F). Discard unused KADCYLA after 24 hours. **Do not freeze.**

**Dilution**
1. Calculate the volume of the 20 mg/mL reconstituted KADCYLA solution needed.

\[ \text{Patient dose based on weight} \text{ mg} + \text{Vial concentration} \text{ 20 mg/mL} = \text{KADCYLA mL} \]

2. Withdraw this amount from the vial and add it to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection. **Do not use dextrose (5%) solution.**

3. Gently invert the bag to mix the solution in order to avoid foaming. **Do not shake.**

4. The diluted KADCYLA infusion solution should be used immediately. If not used immediately, the solution may be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours prior to use. This storage time is additional to the time allowed for the reconstituted vials. **Do not freeze or shake.**

**Administration**
Administer KADCYLA as an intravenous infusion only with a 0.2 or 0.22 micron in-line polyethersulfone (PES) filter.

Do not administer as an intravenous push or bolus.

Do not mix KADCYLA, or administer as an infusion, with other drugs.
Indications & Important Safety Information

Indications

Metastatic Breast Cancer (MBC)
KADCYLA® (ado-trastuzumab emtansine), as a single agent, is indicated for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either:
- Received prior therapy for metastatic disease, or
- Developed disease recurrence during or within six months of completing adjuvant therapy.
Select patients for therapy based on an FDA-approved companion diagnostic for KADCYLA.

Early Breast Cancer (EBC)
KADCYLA, as a single agent, is indicated for the adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment.
Select patients for therapy based on an FDA-approved companion diagnostic for KADCYLA.

Important Safety Information

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

- 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 during pregnancy can result in embryo-fetal harm. Advise patients of these risks and the need for effective contraception.

Warnings and Precautions

Hepatotoxicity
- Hepatotoxicity, predominantly in the form of asymptomatic increases in the concentrations of serum transaminases, has been observed in KADCYLA clinical trials. Serious hepatotoxicity, including 3 fatal cases, has been observed in clinical trials with KADCYLA as single-agent. 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.

- Cases of nodular regenerative hyperplasia (NRH) of the liver, some fatal, have been observed in KADCYLA clinical trials. Permanently discontinue KADCYLA upon NRH diagnosis.

Left Ventricular Dysfunction (LVD)
- Patients treated with KADCYLA are at increased risk of developing LVD.
- In EMILIA for patients with metastatic breast cancer (MBC), LVD occurred in 1.8% of patients in the KADCYLA group and 3.3% of patients in the lapatinib + capecitabine group.
- In KATHERINE for patients with early breast cancer (EBC), LVD occurred in 0.4% of patients in the KADCYLA group and 0.6% of patients in the trastuzumab group.
- Assess LVEF prior to initiation of KADCYLA and at regular intervals during treatment. Permanently discontinue KADCYLA if LVEF has not improved or has declined further.

Embryo-Fetal Toxicity
- Verify the pregnancy status of females of reproductive potential prior to the initiation of KADCYLA.
- Advise pregnant women and females of reproductive potential that exposure to KADCYLA during pregnancy or within 7 months prior to conception can result in fetal harm.
- Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of KADCYLA.
- Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 4 months following the last dose of KADCYLA.
- If KADCYLA is administered during pregnancy, or if the patient becomes pregnant while receiving KADCYLA or within 7 months of the last dose of KADCYLA, immediately report exposure to Genentech at 1-888-835-2555.

Pulmonary Toxicity
- Cases of interstitial lung disease (ILD), including pneumonitis, some leading to acute respiratory distress syndrome or fatal outcome, have been reported in KADCYLA clinical trials.
- In EMILIA, the overall incidence of pneumonitis was 1.2%.
- In KATHERINE, pneumonitis was reported at an incidence of 1.1% (8 out of 740 patients treated with KADCYLA), with one case of Grade 3 pneumonitis. Radiation pneumonitis was reported at an incidence of 1.8% (11 out of 623 patients treated with adjuvant radiotherapy and KADCYLA), with 2 cases of Grade 3 radiation pneumonitis.

Please see Important Safety Information on pages 12-15, and accompanying Prescribing Information, including BOXED WARNINGS.
Important Safety Information (cont’d)

**Pulmonary Toxicity (cont’d)**

- Permanently discontinue treatment with Kadcyla in patients diagnosed with ILD or pneumonitis
- For patients with radiation pneumonitis in the adjuvant setting, Kadcyla should be permanently discontinued for Grade ≥ 3 or for Grade 2 not responding to standard treatment

**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 incidence of IRR in patients treated with Kadcyla was 1.4%
- In KATHERINE, the overall incidence of IRR in patients treated with Kadcyla was 1.6%
- 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 IRR and permanently discontinued in the event of a life-threatening IRR. Patients should be closely monitored for IRR, especially during the first infusion

**Hemorrhage**

- Hemorrhagic events, sometimes fatal, have been reported in Kadcyla clinical trials
- In EMILIA, the overall incidence of hemorrhage was 32% in the Kadcyla group and 16% in the lapatinib + capecitabine group (Grade ≥ 3 incidence was 1.8% and 0.8%, respectively)
- In KATHERINE, the overall incidence of hemorrhage was 29% in the Kadcyla group and 10% in the trastuzumab group (Grade ≥ 3 incidence was 0.4% and 0.3%, 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 overall incidence of thrombocytopenia was 31% in the Kadcyla group and 3.3% in the lapatinib + capecitabine group (Grade ≥ 3 incidence was 15% and 0.4%, respectively)
- In KATHERINE, the overall incidence of thrombocytopenia was 29% in the Kadcyla group and 2.4% in the trastuzumab group (Grade ≥ 3 incidence was 6% and 0.3%, respectively)
- In clinical trials of Kadcyla, the incidence and severity of thrombocytopenia were higher in Asian patients
- Monitor platelet counts prior to initiation of Kadcyla and prior to each dose. Institute dose modifications as appropriate

**Neurotoxicity**

- In EMILIA, the overall incidence of peripheral neuropathy was 21% in the Kadcyla group and 14% in the lapatinib + capecitabine group (Grade ≥ 3 incidence was 2.2% and 0.2%, respectively)
- In KATHERINE, the overall incidence of peripheral neuropathy was 32% in the Kadcyla group and 17% in the trastuzumab group (Grade ≥ 3 incidence was 1.6% and 0.1%, respectively)
- Monitor for signs or symptoms of neurotoxicity. Temporarily discontinue Kadcyla in patients experiencing Grade 3 or 4 peripheral neuropathy until resolution to ≤ Grade 2

**Extravasation**

- In Kadcyla clinical studies, reactions secondary to extravasation have been observed and were generally mild. Specific treatment for Kadcyla extravasation is unknown. Closely monitor the infusion site for possible subcutaneous infiltration during drug administration.

**Adverse Reactions**

**Metastatic Breast Cancer**

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

**Early Breast Cancer**

The most common adverse reactions seen with Kadcyla in the KATHERINE trial (frequency >25%) were fatigue, nausea, increased transaminases, musculoskeletal pain, hemorrhage, thrombocytopenia, headache, peripheral neuropathy, and arthralgia. The most common NCI–CTCAE (version 3) Grade ≥ 3 adverse reactions (frequency >2%) were thrombocytopenia and hypertension

**Use in Specific Populations**

**Lactation:** Advise women not to breastfeed during treatment and for 7 months following the last dose of Kadcyla

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 Important Safety Information on pages 12-15, and accompanying Prescribing Information, including BOXED WARNINGS.
Connecting patients to their Genentech medicine

- Genentech is here to help your patients get their Genentech medicine
- To learn more about Genentech Access Solutions programs and services, call (888) 249-4918 or visit genentech-access.com

Talk to eligible patients about enrolling today in Genentech’s BioOncology Co-pay Assistance Program

- Eligible patients with private insurance pay as little as $5 per valid prescription, subject to a maximum benefit of $25,000 for a 12-month period*
- To learn more about the BioOncology Co-pay Card or to get the full terms & conditions, call (888) 249-4918 or visit copayassistancenow.com

The BioOncology Co-Pay Assistance Program is valid ONLY for patients with commercial insurance who have a valid prescription for a Food and Drug Administration (FDA)-approved indication of a Genentech medication. Patients using Medicare, Medicaid, or any other federal or state government program to pay for their medications are not eligible.

Under the Program, the patient will pay a co-pay. After reaching the maximum Program benefit, the patient will be responsible for all out-of-pocket costs.

All participants are responsible for reporting the receipt of all Program benefits as required by any insurer or by law. No party may seek reimbursement for all or any part of the benefit received through this Program. This Program is void where prohibited by law. Genentech reserves the right to rescind, revoke, or amend the Program without notice at any time. Additional eligibility criteria apply. See full terms and conditions at copayassistancenow.com.

*For FDA-approved Genentech BioOncology therapies.
Indications

Metastatic Breast Cancer (MBC)

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

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

Select patients for therapy based on an FDA-approved companion diagnostic for KADCYLA.

Early Breast Cancer (EBC)

KADCYLA, as a single agent, is indicated for the adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment.

Select patients for therapy based on an FDA-approved companion diagnostic for KADCYLA.

Important Safety Information

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

- 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 during pregnancy can result in embryo-fetal harm. Advise patients of these risks and the need for effective contraception.

Please see Important Safety Information on pages 12-15, and accompanying Prescribing Information, including BOXED WARNINGS.