KADCYLA dosing and administration guide

The first antibody-drug conjugate (ADC) approved for HER2-positive (HER2+) metastatic breast cancer (MBC)

**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

Please see pages 2-3 for additional Important Safety Information and accompanying full Prescribing Information, including Boxed WARNINGS.
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.

Embryo-Fetal Toxicity

• Verify the pregnancy status of women 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.
• If KADCYLA is administered during pregnancy or if a patient becomes pregnant while receiving KADCYLA or within 7 months following the last dose of KADCYLA, immediately report exposure to the Genentech Adverse Event Line 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 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 pneumonitis 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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Important Safety Information

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 severe adverse reactions Grades ≥3 (frequency >2%) were thrombocytopenia, increased transaminases, anemia, hypokalemia, peripheral neuropathy, and fatigue according to NCI-CTCAE (version 3)

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.

20 mg/mL INJECTION FOR INTRA VENOUS USE
KADCYLA dosing and administration guide

The first antibody-drug conjugate (ADC) approved for HER2-positive (HER2+) metastatic breast cancer (MBC)

Indication

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

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• 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

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Preparing and storing KADCYLA

Calculation the correct dose

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

1. Calculate dose (mg)

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

2. Calculate volume (reconstituted mL)

\[
\frac{\text{KADCYLA (mg)}}{20 \text{ mg/mL}} = \text{KADCYLA (mL)}
\]

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

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

Please see pages 2-3 for additional Important Safety Information and accompanying full Prescribing Information, including Boxed WARNINGS.
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 0.2 or 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.
Before administering KADCYLA

Assess baseline characteristics
Some severe adverse reactions have been reported in clinical studies with KADCYLA. Before beginning treatment with KADCYLA, review guidelines below.

### SELECT PREADMINISTRATION GUIDELINES FOR KADCYLA*

#### Hepatotoxicity
- Establish baseline transaminases (aspartate transaminase [AST], alanine transaminase [ALT]) and total bilirubin
- Monitor liver function prior to each dose
- Modify dose, as appropriate, according to dose reduction guidelines

#### Cardiotoxicity
- Establish baseline left ventricular ejection fraction (LVEF)
- Perform standard cardiac assessment by echocardiogram or multigated acquisition (MUGA) scan at regular intervals (every 3 months)
- Modify dose, as appropriate, according to dose reduction guidelines

#### Thrombocytopenia
- Establish baseline hematologic parameters
- Monitor platelet counts prior to each dose
- Modify dose, as appropriate, according to dose reduction guidelines

*Per the KADCYLA Prescribing Information.

- 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

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How to administer KADCYLA

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 (0.2 or 0.22 micron) is required
- No loading dose

Dosing schedule for KADCYLA

- 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

Missed doses

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.
**DOSE MODIFICATION GUIDELINES FOR KADCYLA**

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

### Hepatotoxicity

<table>
<thead>
<tr>
<th>Increased serum transaminases (AST/ALT)</th>
<th>1) Treat at same dose level</th>
<th>1) Hold until recovery to ≤5× ULN</th>
<th>1) Permanently discontinue KADCYLA</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2.5 to ≤5× ULN (Grade 2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5 to ≤20× ULN (Grade 3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;20× ULN (Grade 4)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Hyperbilirubinemia

<table>
<thead>
<tr>
<th>&gt;1.5 to ≤3× ULN (Grade 2)</th>
<th>&gt;3 to ≤10× ULN (Grade 3)</th>
<th>&gt;10× ULN (Grade 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Hold until total bilirubin level recovers to ≤1.5× ULN</td>
<td>1) Hold until total bilirubin level recovers to ≤1.5× ULN</td>
<td>1) Permanently discontinue KADCYLA</td>
</tr>
<tr>
<td>2) Then treat at same dose level</td>
<td>2) Then reduce one dose level</td>
<td></td>
</tr>
</tbody>
</table>

**Permanently discontinue KADCYLA treatment in patients:**
- with serum transaminases >3× ULN and concomitant total bilirubin >2× ULN, OR
- diagnosed with nodular regenerative hyperplasia (NRH)

### Left ventricular cardiac dysfunction

<table>
<thead>
<tr>
<th>LVEF 40% to ≤45% AND &lt;10% point decline from baseline</th>
<th>LVEF 40% to ≤45% AND ≥10% point decline from baseline</th>
<th>LVEF &lt;40%</th>
<th>Symptomatic CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Continue KADCYLA</td>
<td>1) Do not administer KADCYLA</td>
<td>1) Do not administer KADCYLA</td>
<td>1) Discontinue KADCYLA</td>
</tr>
<tr>
<td>2) Repeat LVEF assessment within 3 weeks</td>
<td>2) Repeat LVEF assessment within 3 weeks</td>
<td>2) Repeat LVEF assessment within 3 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3) If LVEF has not recovered to within 10% points of absolute baseline, discontinue KADCYLA</td>
<td>3) If LVEF &lt;40% is confirmed, discontinue KADCYLA</td>
<td></td>
</tr>
</tbody>
</table>

AST=aspartate aminotransferase; ALT=alanine aminotransferase; ULN=upper limit of normal; CHF=congestive heart failure.

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For additional information about KADCYLA, visit KADCYLA.com.

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**Thrombocytopenia**

<table>
<thead>
<tr>
<th>25,000 to &lt;50,000 cells/mm³ (Grade 3)</th>
<th>&lt;25,000 cells/mm³ (Grade 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Hold until recovered to ≥75,000 cells/mm³</td>
<td>1) Hold until recovered to ≥75,000 cells/mm³</td>
</tr>
<tr>
<td>2) Then treat at same dose level</td>
<td>2) Then reduce one dose level</td>
</tr>
</tbody>
</table>

- **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**

- 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 never be re-escalated after a dose reduction has been made

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

*Dose reduction guidelines based on KADCYLA full Prescribing Information.*
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