This brochure will help you become familiar with the dosing and administration of PERJETA® (pertuzumab) in the following HER2+ treatment settings:

- Early breast cancer (neoadjuvant and adjuvant)
- Metastatic breast cancer

**Indications**

- PERJETA is indicated for use in combination with Herceptin® (trastuzumab) and chemotherapy for
  - the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node-positive) as part of a complete treatment regimen for early breast cancer (EBC)
  - the adjuvant treatment of patients with HER2-positive early breast cancer (EBC) at high risk of recurrence
- PERJETA is indicated for use in combination with Herceptin and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease

**IMPORTANT SAFETY INFORMATION**

**BOXED WARNINGS:** Left Ventricular Dysfunction and Embryo-Fetal Toxicity

- PERJETA can result in subclinical and clinical cardiac failure manifesting as decreased left ventricular ejection fraction (LVEF) and congestive heart failure (CHF). Evaluate cardiac function prior to and during treatment. Discontinue PERJETA treatment for a confirmed clinically significant decrease in left ventricular function.
- Exposure to PERJETA can result in embryo-fetal death and birth defects. Advise patients of these risks and the need for effective contraception.
  - Verify the pregnancy status of females of reproductive potential prior to the initiation of PERJETA. Advise pregnant women and females of reproductive potential that exposure to PERJETA in combination with trastuzumab during pregnancy or within 7 months prior to conception can result in fetal harm, including embryo-fetal death or birth defects. Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of PERJETA in combination with trastuzumab.
  - There is a pregnancy pharmacovigilance program for PERJETA. If PERJETA is administered during pregnancy, or if a patient becomes pregnant while receiving PERJETA or within 7 months following the last dose of PERJETA in combination with trastuzumab, healthcare providers and patients should immediately report PERJETA exposure to Genentech at 1-888-835-2555.

**Additional Important Safety Information**

PERJETA is contraindicated in patients with known hypersensitivity to pertuzumab or to any of its excipients.

Please see additional select Important Safety Information on pages 8 through 10, and the accompanying full Prescribing Information, including BOXED WARNINGS.
Early Breast Cancer (EBC) Dosing

**NEOADJUVANT DOSING**

Patients eligible to begin PERJETA® (pertuzumab) and Herceptin® (trastuzumab) and chemotherapy in the neoadjuvant setting: HER2+ locally advanced, inflammatory, or EBC (node-positive, and/or tumor size >2 cm)

![Diagram showing neoadjuvant treatment regimens and durations](image)

Patients who begin PERJETA and Herceptin in the neoadjuvant setting should continue to receive PERJETA and Herceptin, every 3 weeks, to complete 1 year (up to 18 cycles) or until disease recurrence or unmanageable toxicity, whichever occurs first.

**ADJUVANT DOSING**

Patients eligible to begin PERJETA and Herceptin and chemotherapy in the adjuvant setting: HER2+ EBC at high risk of recurrence

![Diagram showing adjuvant treatment regimens and durations](image)

Patients should receive a total of 1 year (up to 18 cycles) of PERJETA and Herceptin-based therapy, every 3 weeks, starting on Day 1 of the first taxane-containing cycle.

Adjuvant chemotherapy regimens as in APHINITY:

- **Non–anthracycline-based chemotherapy regimen**
  - 6 cycles of docetaxel** + carboplatin††

- **Anthracycline-based regimens**
  - 3 or 4 cycles of FEC**, or FAC,† followed by 3 or 4 cycles of docetaxel** or 12 cycles of weekly paclitaxel§§
  - 4 cycles of AC**, or EC,*** followed by 3 or 4 cycles of docetaxel** or 12 cycles of weekly paclitaxel§§

**Docetaxel dosing: 75 mg/m², which could be escalated to 100 mg/m² if initial dose was well-tolerated (not escalated in non–anthracycline-based regimens); docetaxel dosing following AC or EC administration: 100 mg/m² for 3 cycles or 75 mg/m² for first cycle and 100 mg/m² for subsequent 3 cycles, or 75 mg/m² for 4 cycles.

†Carboplatin dosing: AUC 6.

‡Docetaxel dosing: 80 mg/m².

§Paclitaxel dosing: 80 mg/m².

††Carboplatin dosing: AUC 6.

***AC dosing: doxorubicin (60 mg/m²) and cyclophosphamide (500-600 mg/m²) every 3 weeks or 2 weeks with GCSF support.

### Managing diarrhea, as seen in the APHINITY trial²

- Early intervention with loperamide, fluids, and electrolyte replacement were considered for patients experiencing diarrhea
- The taxane dose was recommended to be reduced by 1 dose level if Grade 3 diarrhea had occurred or unresolved Grade 2 diarrhea had required delay of the next chemotherapy cycle

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*Please see additional select Important Safety Information on pages 8 through 10, and the accompanying full Prescribing Information, including BOXED WARNINGS.*
Metastatic Breast Cancer (MBC) Dosing

MBC DOSING FROM CLEOPATRA TRIAL

Patients eligible to begin PERJETA® (pertuzumab) and Herceptin® (trastuzumab) and docetaxel: HER2+ MBC, no previous anti-HER2 therapy or chemotherapy for MBC

START

MINIMUM OF 6 CYCLES

Docetaxel

PERJETA + Herceptin

CONTINUE until disease progression or unacceptable toxicity

- In CLEOPATRA, it was recommended that docetaxel be administered for a minimum of 6 cycles
  - The recommended initial dose of docetaxel is 75 mg/m²
  - The docetaxel dose could be decreased by 25% due to toxicity or increased to 100 mg/m² in those patients who could tolerate this dose
  - Fewer than 6 cycles were allowed for unmanageable toxicity
  - Comparable docetaxel exposure between the 2 treatment arms in CLEOPATRA
  - Docetaxel was administered for a median of 8 cycles in both treatment arms
- PERJETA and Herceptin should be continued until disease progression or unmanageable toxicity
- If docetaxel is discontinued, PERJETA and Herceptin may be continued on their own

Patient Selection, PERJETA Preparation, Storage and Handling

Patient selection

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

Prepare the infusion

Administer as an intravenous infusion only. Do not administer as an intravenous push or bolus. Do not mix PERJETA with other drugs.

Prepare the solution for infusion, using aseptic technique. Parenteral drug products should be inspected visually for particulates and discoloration prior to administration. Withdraw the appropriate volume of PERJETA solution from the single-use vial(s).

- Dilute into a 250-mL 0.9% sodium chloride PVC or non-PVC polyolefin infusion bag
  - Dilute with 0.9% sodium chloride injection only
  - Do not use dextrose (5%) to dilute PERJETA
- Mix diluted solution by gentle inversion. Do not shake
- Administer immediately once prepared. The diluted sodium chloride infusion solution of PERJETA may be stored at 2°C-8°C (36°F-46°F) for up to 24 hours

Storage and handling

- PERJETA injection is supplied as a 420-mg/14-mL (30-mg/mL) single-dose vial containing preservative-free solution
- Store vials in a refrigerator at 2°C-8°C (36°F-46°F) until time of use
- Keep vial in the outer carton to protect from light
- NDC 50242-145-01

DO NOT FREEZE. DO NOT SHAKE.

PVC=polyvinyl chloride.
**PERJETA® (pertuzumab) Dosing Considerations**

**PERJETA and Herceptin® (trastuzumab) are administered every 3 weeks**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Loading dose</th>
<th>Infusion time</th>
<th>Subsequent doses</th>
<th>Infusion time</th>
</tr>
</thead>
<tbody>
<tr>
<td>PERJETA</td>
<td>840 mg</td>
<td>60 min</td>
<td>420 mg</td>
<td>30-60 min</td>
</tr>
<tr>
<td>Herceptin</td>
<td>8 mg/kg</td>
<td>90 min</td>
<td>6 mg/kg</td>
<td>30-90 min</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Varies per regimen</td>
<td>Varies per regimen</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Close observation of the patient is recommended for 30-60 minutes after each PERJETA infusion and before any subsequent administration of Herceptin, Herceptin HYLECTA™ (trastuzumab and hyaluronidase-oysk), or chemotherapy.
- If a significant infusion-associated reaction occurs, slow or interrupt the infusion and administer appropriate medical therapies.
- The infusion should be discontinued immediately if the patient experiences a serious hypersensitivity reaction.

**Dose sequencing**

- PERJETA, Herceptin, and taxanes should be given sequentially.
- PERJETA and Herceptin can be given in any order.
- Taxane should be administered after PERJETA and Herceptin.
- In patients receiving an anthracycline-based regimen, PERJETA and Herceptin should be administered following completion of the anthracycline.

**If a delayed or missed dose of PERJETA with Herceptin occurs**

- If the time between two sequential infusion cycles is <6 weeks, the 420 mg dose of PERJETA and the 6 mg/kg dose of Herceptin should be administered. Do not wait until the next planned dose.
- If the time between two sequential infusion cycles is ≥6 weeks, a reloading dose of PERJETA and Herceptin (840 mg and 8 mg/kg, respectively) should be administered.

**Dose interruption or discontinuation of treatment**

- PERJETA should be discontinued if Herceptin treatment is discontinued.
- Dose reductions are not recommended for PERJETA.
- For chemotherapy dose modifications, see their respective prescribing information.
- If a significant infusion-associated reaction occurs, slow or interrupt the infusion and administer appropriate medical therapies.
- The infusion should be discontinued immediately if the patient experiences a serious hypersensitivity reaction.

**Left ventricular ejection fraction (LVEF)**

Assess LVEF prior to initiation of PERJETA and at regular intervals during treatment to ensure that LVEF is within normal limits, as indicated. If LVEF declines and has not improved, or has declined further at the subsequent assessment, discontinuation of PERJETA and trastuzumab should be strongly considered.

**Dose modifications for left ventricular dysfunction**

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment LVEF</th>
<th>WITHHOLD PERJETA and Herceptin for at least 3 weeks for an LVEF decrease to</th>
<th>RESUME PERJETA and Herceptin after 3 weeks if LVEF has recovered to</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early breast cancer</td>
<td>≥55%</td>
<td>&lt;50%, with a fall of ≥10% points below pretreatment value</td>
<td>≥50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Either</td>
<td>&lt;10% points below pretreatment value</td>
</tr>
<tr>
<td>Metastatic breast cancer</td>
<td>≥50%</td>
<td>&lt;40%, 40%-45%, with a fall of ≥10% points below pretreatment value</td>
<td>40%-45%, with a fall of &lt;10% points below pretreatment value</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Either</td>
<td>Either</td>
</tr>
</tbody>
</table>

*For patients receiving anthracycline-based chemotherapy, an LVEF ≥50% is required after completion of anthracyclines, before starting PERJETA and Herceptin.

**12** Monitor LVEF prior to initiation and then every ~12 weeks in MBC and EBC (once during neoadjuvant therapy).

A subcutaneous, fixed-dose combination with PERJETA + Herceptin is here. Contact your Genentech representative to learn more.
Important Safety Information

BOXED WARNINGS: Left Ventricular Dysfunction and Embryo-Fetal Toxicity

- PERJETA can result in subclinical and clinical cardiac failure manifesting as decreased left ventricular ejection fraction (LVEF) and congestive heart failure (CHF). Evaluate cardiac function prior to and during treatment. Discontinue PERJETA treatment for a confirmed clinically significant decrease in left ventricular function.

- Exposure to PERJETA can result in embryo-fetal death and birth defects. Advise patients of these risks and the need for effective contraception.
  - Verify the pregnancy status of females of reproductive potential prior to the initiation of PERJETA. Advise pregnant women and females of reproductive potential that exposure to PERJETA in combination with trastuzumab during pregnancy or within 7 months prior to conception can result in fetal harm, including embryo-fetal death or birth defects. Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of PERJETA in combination with trastuzumab.
  - There is a pregnancy pharmacovigilance program for PERJETA. If PERJETA is administered during pregnancy, or if a patient becomes pregnant while receiving PERJETA or within 7 months following the last dose of PERJETA in combination with trastuzumab, healthcare providers and patients should immediately report PERJETA exposure to Genentech at 1-888-835-2555.

Additional Important Safety Information

Left Ventricular Dysfunction (LVD)

- Assess LVEF prior to initiation of PERJETA and at regular intervals during treatment to ensure that LVEF is within normal limits. If LVEF declines and has not improved, or has declined further at the subsequent assessment, discontinuation of PERJETA and trastuzumab should be strongly considered.

- In the CLEOPATRA study, for patients with MBC, LVD occurred in 4% of patients in the PERJETA-treated group and in 8% of patients in the placebo-treated group. Symptomatic left ventricular systolic dysfunction (LVSD) (CHF) occurred in 1% of patients in the PERJETA-treated group and in 2% of patients in the placebo-treated group.

- In the NeoSphere study, for patients receiving neoadjuvant treatment, a LVEF decline >10% and a drop to <50% occurred in 2% of patients treated with neoadjuvant trastuzumab and docetaxel as compared to 8% of patients in the PERJETA-treated group. LVD occurred in 0.9% of patients treated with neoadjuvant trastuzumab and docetaxel as compared to 3% of patients in the PERJETA-treated group. Symptomatic LVSD occurred in 0.9% of patients treated with neoadjuvant PERJETA in combination with trastuzumab and in no patients in the other 3 arms.

- In the TRYPHAENA study, for patients receiving neoadjuvant treatment, in the overall treatment period, LVEF decline >10% and a drop to <50% occurred in 15% of patients treated with PERJETA plus trastuzumab and 5-fluorouracil, epirubicin, and cyclophosphamide (FcE), followed by PERJETA plus trastuzumab and docetaxel; in 16% of patients treated with PERJETA plus trastuzumab and docetaxel following FEC; in 11% of patients treated with PERJETA in combination with docetaxel, carboplatin, and trastuzumab (TCH). LVD occurred in 6% of patients treated with PERJETA plus trastuzumab and FEC, followed by PERJETA plus trastuzumab and docetaxel following FEC, in 4% of patients treated with PERJETA plus trastuzumab and FEC, followed by PERJETA plus trastuzumab and docetaxel following FEC, in 1% of patients treated with PERJETA in combination with TCH, and in none of the patients treated with PERJETA plus trastuzumab and FEC, followed by PERJETA plus trastuzumab and docetaxel following FEC.

In the CLEOPATRA study, the overall frequency of infusion reactions was 13% in the PERJETA-treated group and 10% in the placebo-treated group. Less than 1% were Grade 3 or 4. The most common infusion reactions (≥1.0%) were pyrexia, chills, fatigue, headache, asthenia, hypersensitivity, and vomiting. During the second cycle, when all drugs were administered on the same day, the most common infusion reactions in the PERJETA-treated group (≥1.0%) were fatigue, dysgeusia, hypersensitivity, myalgia, and vomiting.

- In the NeoSphere, TRYPHAENA, and APHINITY studies, PERJETA was administered on the same day as the other study treatment drugs. For APHINITY, infusion-related reactions occurred in 21% of patients in the PERJETA-treated group and in 18% of patients in the placebo arm. The incidence of Grades 3-4 National Cancer Institute—Common Terminology Criteria for Adverse Events (NCI-CTCAE v4.0) reactions was 1% for the PERJETA arm and 0.7% for the placebo arm.

- In the APHINITY study, patients treated in the adjuvant setting, the incidence of symptomatic heart failure with a LVEF decline ≥10% and a drop to <50% was <1% (0.6% of PERJETA-treated patients vs 0.2% of placebo-treated patients). Of the patients who experienced symptomatic heart failure, 47% of PERJETA-treated patients and 67% of placebo-treated patients had recovered (defined as 2 consecutive LVEF measurements above 50%) at the data cutoff. The majority of the events (86%) were reported in anthracycline-treated patients. Asymptomatic or mildly symptomatic declines in LVEF ≥10% and a drop to <50% were reported in 3% of PERJETA-treated patients and in 3% of placebo-treated patients, of whom 80% of PERJETA-treated patients and 81% of placebo-treated patients recovered at the data cutoff.

Infusion-Related Reactions

- PERJETA has been associated with infusion reactions, including fatal events.

- In the CLEOPATRA study, on the first day, when only PERJETA was administered, the overall frequency of infusion reactions was 13% in the PERJETA-treated group and 10% in the placebo-treated group. Less than 1% were Grade 3 or 4. The most common infusion reactions (≥1.0%) were fatigue, chills, headache, asthma, or hypovolemia. During the second cycle, when all drugs were administered on the same day, the most common infusion reactions in the PERJETA-treated group (≥1.0%) were fatigue, dysgeusia, hypersensitivity, myalgia, and vomiting.

Hypersensitivity Reactions/Anaphylaxis

- In the CLEOPATRA study, the overall frequency of hypersensitivity reaction/anaphylaxis was 11% in the PERJETA-treated group and 9% in the placebo-treated group. The incidence of Grades 3-4 hypersensitivity reaction/anaphylaxis was 2% in the PERJETA-treated group and 3% in the placebo-treated group according to NCI-CTCAE v3.0.

- In the NeoSphere, TRYPHAENA, BERENICE, and APHINITY studies, hypersensitivity/anaphylaxis events were consistent with those observed in CLEOPATRA.

- Patients should be observed closely for hypersensitivity reactions. Severe hypersensitivity, including anaphylaxis and fatal events, have been observed in patients treated with PERJETA. Angioedema has been described in post-marketing reports. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use.

Please see additional select Important Safety Information on pages 8 through 10, and the accompanying full Prescribing Information, including BOXED WARNINGS.
Most Common Adverse Reactions

\[\text{Neoadjuvant Treatment of Breast Cancer}\]

- The most common adverse reactions (>30%) with PERJETA in combination with trastuzumab and docetaxel administered for 4 cycles were alopecia, neutropenia, diarrhea, and nausea. The most common NCI-CTCAE v3.0 Grades 3-4 adverse reactions (>2%) were neutropenia, febrile neutropenia, leukopenia, and diarrhea.

- The most common adverse reactions (>30%) with PERJETA in combination with trastuzumab and docetaxel administered for 3 cycles following 3 cycles of FEC were diarrhea, nausea, alopecia, neutropenia, vomiting, and fatigue. The most common NCI-CTCAE v3.0 Grades 3-4 adverse reactions (>2%) were neutropenia, leukopenia, febrile neutropenia, diarrhea, left ventricular dysfunction, anemia, dyspnea, nausea, and vomiting.

- The most common adverse reactions (>30%) with PERJETA in combination with with anthracycline-based therapy (85% in the PERJETA-treated group vs 62% in the placebo-treated group) than with anthracycline-based therapy (67% in the placebo-treated group).

- The most common adverse reactions (>30%) with PERJETA in combination with TCH administered for 6 cycles were diarrhea, alopecia, neutropenia, nausea, fatigue, constipation, peripheral neuropathy, and headache. The most common Grades 3-4 adverse reactions (>2%) were neutropenia, febrile neutropenia, neutrophil count decreased, white blood cell count decreased, anemia, diarrhea, peripheral neuropathy, ALT increased, and nausea.

- The most common adverse reactions (>30%) with PERJETA in combination with TCH administered for 4 cycles following 4 cycles of ddAC were nausea, diarrhea, alopecia, fatigue, constipation, peripheral neuropathy, and headache. The most common Grades 3-4 adverse reactions (>2%) were neutropenia, febrile neutropenia, neutrophil count decreased, white blood cell count decreased, anemia, diarrhea, peripheral neuropathy, ALT increased, and nausea.

- The most common adverse reactions (>30%) with PERJETA in combination with TCH administered for 4 cycles following 4 cycles of FEC were diarrhea, nausea, alopecia, asthenia, constipation, fatigue, mucosal inflammation, vomiting, myalgia, and anemia. The most common Grades 3-4 adverse reactions (>2%) were febrile neutropenia, diarrhea, neutropenia, neutrophil count decreased, stomatitis, fatigue, vomiting, mucosal inflammation, neutropenic sepsis, and anemia.

\[\text{Adjuvant Treatment of Breast Cancer}\]

- The most common adverse reactions (>30%) with PERJETA in combination with trastuzumab and chemotherapy were diarrhea, nausea, alopecia, fatigue, peripheral neuropathy, and vomiting. The most common Grades 3-4 adverse reactions (>2%) were neutropenia, febrile neutropenia, diarrhea, neutrophil count decreased, anemia, white blood cell count decreased, leukopenia, fatigue, nausea, and stomatitis.

- The incidence of diarrhea, all Grades, was higher when chemotherapy was administered with targeted therapy (61% in the PERJETA-treated group vs 34% in the placebo-treated group) and was higher when administered with non–anthracycline-based therapy (85% in the PERJETA-treated group vs 62% in the placebo-treated group) than with anthracycline-based therapy (67% in the PERJETA-treated group vs 41% in the placebo-treated group). The incidence of diarrhea during the period that targeted therapy was administered without chemotherapy was 18% in the PERJETA-treated group vs 9% in the placebo-treated group.

\[\text{Metastatic Breast Cancer}\]

- The most common adverse reactions (>30%) seen with PERJETA in combination with trastuzumab and docetaxel were diarrhea, alopecia, neutropenia, nausea, fatigue, rash, and peripheral neuropathy. The most common NCI-CTCAE v3.0 Grades 3-4 adverse reactions (>2%) were neutropenia, febrile neutropenia, leukopenia, diarrhea, peripheral neuropathy, anemia, asthenia, and fatigue.

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at 1-888-835-2555.

References: