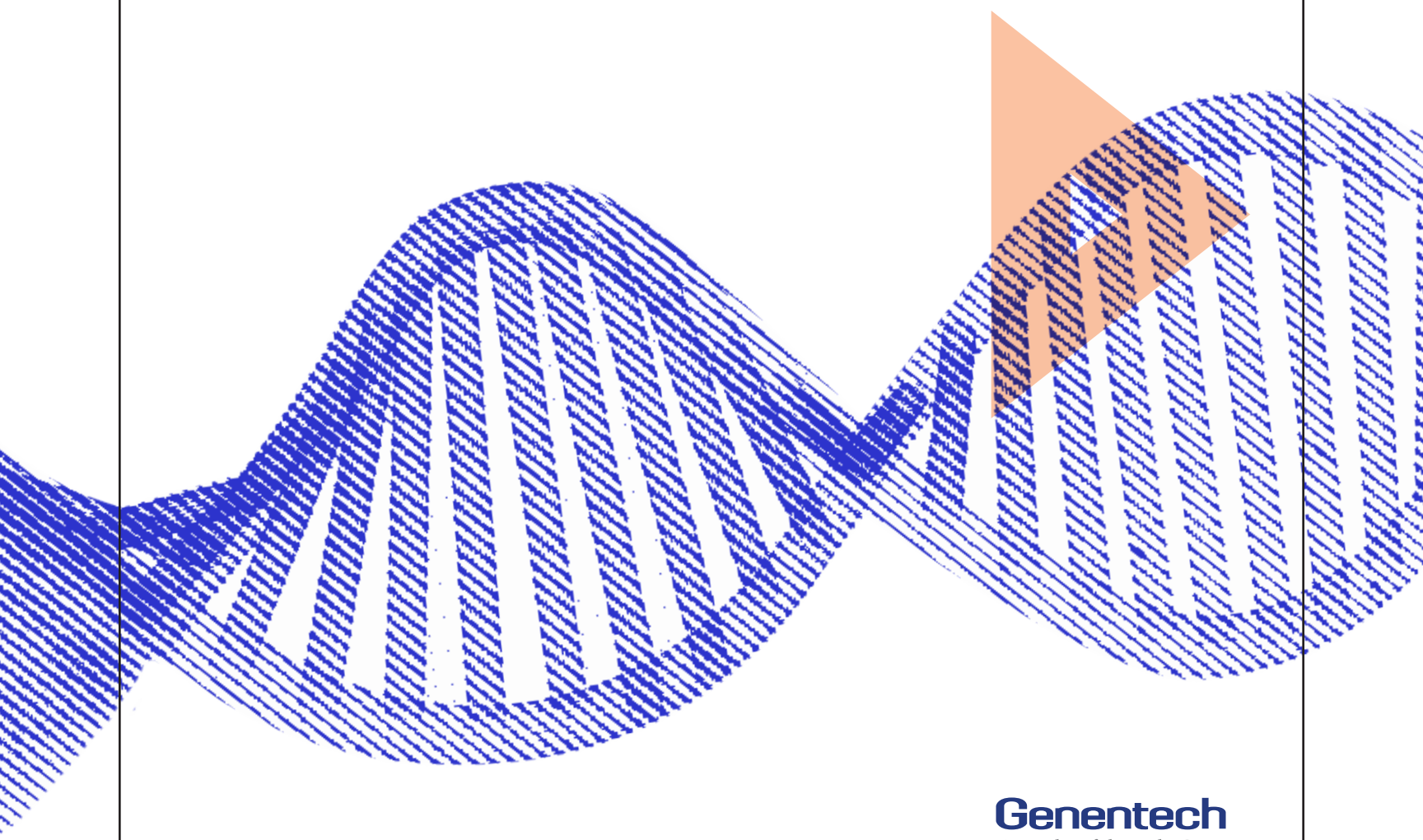
Regardless of the outcome of neoadjuvant treatment, **your patient with HER2+ early breast cancer (EBC) is still at risk of recurrence.**[1-3]

TRASTUZUMAB ALONE IS NOT ENOUGH

FOR YOUR PATIENTS WITH HER2+ EBC AT HIGH RISK OF RECURRENCE[4,5]

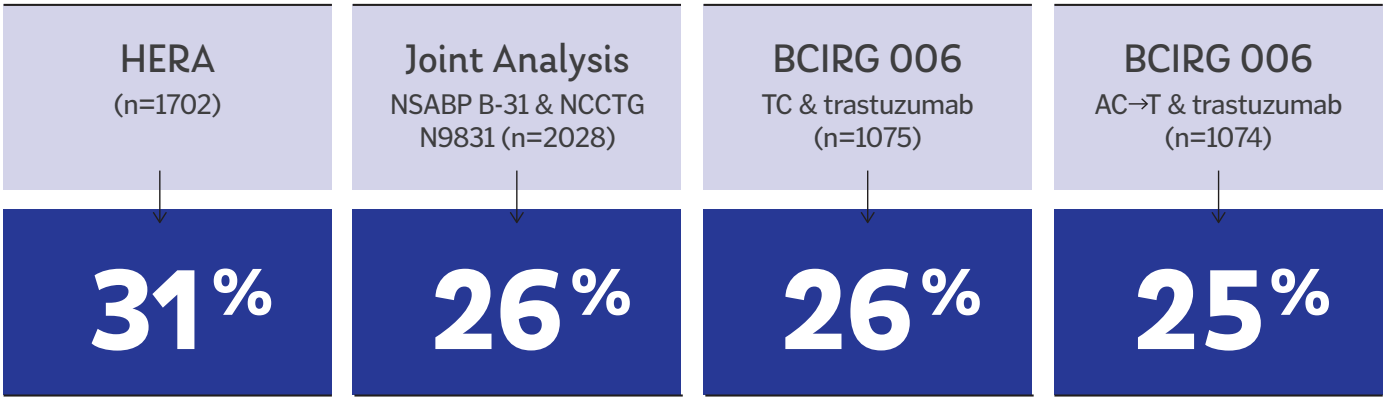


Genentech
A Member of the Roche Group

HER2=human epidermal growth factor receptor 2.

RISK OF RECURRENCE FOR PATIENTS WITH HER2+ EBC BASED ON HISTORICAL TRIALS

Percentages of patients with 10-year recurrence with the standard of care, based on historical HER2+ adjuvant clinical trials*†‡[2,6,7]



- 3-year and 10-year event-free rates were derived from Kaplan-Meier estimates[2,6-9]

*Recurrence was based on patient experience of a disease-free survival (DFS) event, which included recurrence or death. DFS was defined as time from randomization to the first occurrence of any of the following events: HERA: recurrence of breast cancer at any site; the development of ipsilateral or contralateral breast cancer, including ductal carcinoma in situ but not lobular carcinoma in situ; second nonbreast malignant disease other than basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix; or death from any cause without documentation of a cancer-related event; Joint Analysis: local, regional, and distant recurrence; contralateral breast cancer, including ductal carcinoma in situ; other second primary cancers; or death before recurrence or a second primary cancer; BCIRG 006: breast cancer recurrence, a second primary cancer (excluding contralateral ductal carcinoma in situ), or death from any cause, whichever came first.[2,6-11]

†Inclusion criteria for studies: HERA, node-positive or node-negative disease with tumor >1 cm; Joint Analysis, node-positive, or high-risk node-negative disease (tumor size >1 cm and hormone receptor–negative, or tumor size >2 cm and hormone receptor–positive); BCIRG 006, node-positive or high-risk node-negative disease (tumor size >2 cm, hormone receptor–negative, histologic and/or nuclear Grade 2 or 3, or age <35 years).[8-12]

‡Rates of recurrence at 3 years were 19% in HERA with trastuzumab (1 year) after completion of chemotherapy, 12% in the Joint Analysis with AC followed by T and trastuzumab, 13% in BCIRG 006 with TC and trastuzumab, and 12% in BCIRG 006 with AC followed by T and trastuzumab.[6,8,9]

AC=anthracycline (doxorubicin) plus cyclophosphamide; C=carboplatin (in the TC and trastuzumab regimen); T=taxane (paclitaxel in the Joint Analysis, docetaxel in BCIRG 006).

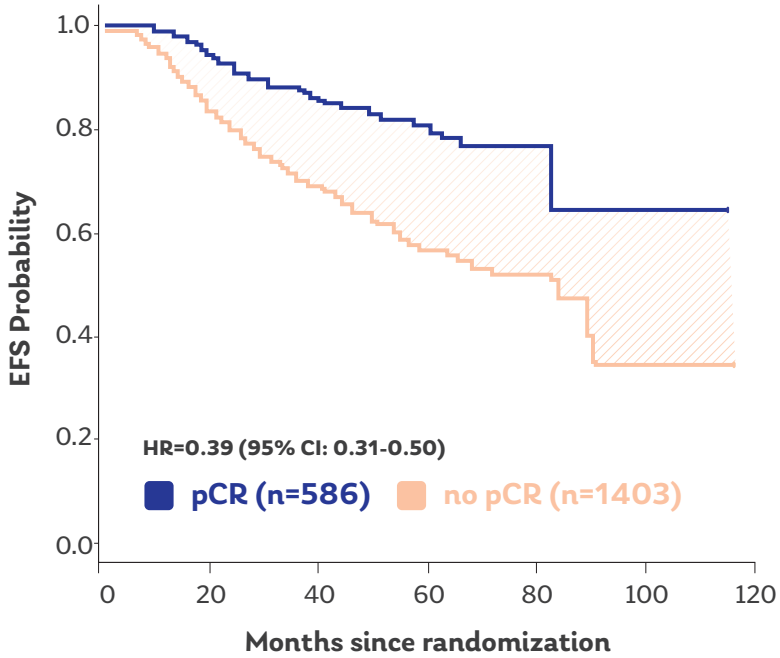
Despite improvement in the early stage treatment setting for HER2+ EBC

~1 in 4 PATIENTS

who received a year of adjuvant treatment with the standard of care in these 4 trials still **experienced recurrence** within 10 years*[2,6,7]

Even if patients achieved a pathological complete response (pCR) following neoadjuvant therapy, they were still at risk of recurrence and those with residual invasive disease were at an even higher risk of recurrence[3]

Association of pCR with event-free survival (EFS)* in the HER2+ subgroup analysis of the CTNeoBC study[3,13]



CTNeoBC: OVERVIEW[3]

- **CTNeoBC was a pooled analysis of 12 international trials published between Jan 1, 1990 and Aug 1, 2011**
- Studies had to meet three inclusion criteria: included at least 200 patients with primary breast cancer treated with preoperative chemotherapy followed by surgery; had available data for pathological complete response, EFS, and overall survival (OS); and had a media follow-up of at least 3 years

*EFS was calculated as the interval from randomization to occurrence of disease progression resulting in inoperability, loco-regional recurrence (after neoadjuvant therapy), distant metastases, or death from any cause.[3]

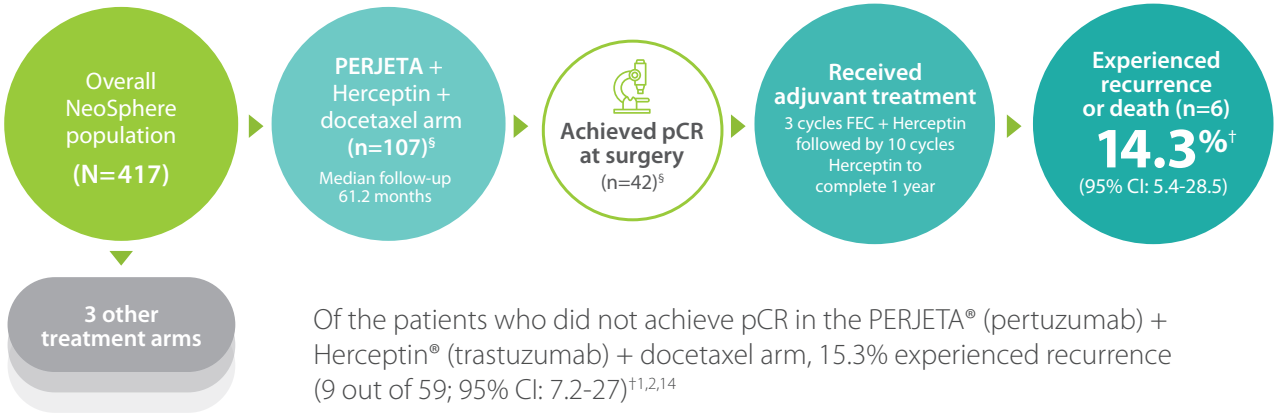
CTNeoBC: HER2+ SUBTYPE[3]

- The pooled analysis included patients across multiple breast cancer subtypes (hormone-receptor status, HER2 overexpression, and triple-negative)
- **Overall, 1,989 patients had HER2+ tumors and were included in the HER2+ subgroup analysis**
- 55% of these patients did not receive 1 year of adjuvant trastuzumab because they were treated before adjuvant trastuzumab trials were reported

Patients with HER2+ EBC remain at **risk of recurrence, even after pCR[1,2]**

In the 5-year analysis of the NeoSphere trial, 1 in 7 patients (6 out of 42) who achieved pCR with neoadjuvant therapy experienced recurrence.*†[1,2]

DFS‡ by pCR status was a predefined, exploratory subgroup analysis; therefore, results are considered descriptive only. A limitation of this analysis is the small number of patients included.[1,2]



Of the patients who did not achieve pCR in the PERJETA® (pertuzumab) + Herceptin® (trastuzumab) + docetaxel arm, 15.3% experienced recurrence (9 out of 59; 95% CI: 7.2-27)[†1,2,14]

NeoSphere was a multicenter, randomized, Phase II trial conducted in patients with operable, locally advanced, or inflammatory HER2+ EBC (T2-4d) who were scheduled for neoadjuvant therapy. Patients in the PERJETA + Herceptin + docetaxel (PHT) arm received 4 cycles of PHT before surgery, and received 3 cycles of FEC + Herceptin followed by 10 cycles of Herceptin after surgery to complete 1 year. The primary endpoint was pCR in the breast.[1,4,14]

*Recurrence is defined as disease progression based on investigator assessment.[2]
†The percentage of recurrence is based on the number of DFS events in the exploratory subgroup analysis.
‡Defined as the time from surgery to the first occurrence of disease progression or death.[1]
§Not all patients were evaluable for pCR. The number of patients who achieved pCR and the number of patients who did not achieve pCR does not total 107.[2]

FEC=fluorouracil, epirubicin, and cyclophosphamide.

With risk of recurrence remaining, is there more you can do?

Eligible patients with HER2+ EBC should receive **1 year (up to 18 cycles)*[4]**

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Indications

PERJETA is indicated for use in combination with Herceptin 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

Patients eligible to receive a total of 1 year (up to 18 cycles) of PERJETA + Herceptin-based therapy*†[4]

Appropriate patients who begin treatment in the neoadjuvant setting

After surgery, these patients **should** continue to receive **PERJETA + Herceptin** to complete 1 year

Patients at high risk of recurrence who begin treatment in the adjuvant setting

***Patients should discontinue treatment before 1 year if they experience disease recurrence or unmanageable toxicity.**

†Patients who begin PERJETA and Herceptin in the neoadjuvant setting should receive 3-6 cycles before surgery and should continue treatment after surgery, every 3 weeks, to complete 1 year (up to 18 cycles). Patients who begin treatment in the adjuvant setting 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.

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

Indication: PERJETA® (pertuzumab) is indicated for use in combination with Herceptin® (trastuzumab) and chemotherapy for the adjuvant treatment of patients with HER2-positive early breast cancer (EBC) at high risk of recurrence.

Trastuzumab alone is not enough for your patients at high risk of recurrence starting in the adjuvant setting or for those continuing after neoadjuvant treatment who achieve a pCR[4]

Give her PERJETA + Herceptin-based therapy in the adjuvant setting to reduce the risk of recurrence*[4]

APHINITY was a Phase III, randomized, double-blind, placebo-controlled study conducted in patients with HER2+ EBC after their primary tumor had been excised. Patients were randomized to receive PERJETA (n=2400) or placebo (n=2404), in combination with adjuvant Herceptin and chemotherapy. The trial excluded patients who had received neoadjuvant treatment. **The primary endpoint of the study was invasive disease-free survival (iDFS)**, defined as time from randomization to first occurrence of ipsilateral local or regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, or death from any cause. Investigators selected 1 of 3 chemotherapy regimens. PERJETA and Herceptin were administered intravenously every 3 weeks for a total of 52 weeks (up to 18 cycles) or until recurrence, withdrawal of consent, or unmanageable toxicity, whichever occurred first. The primary analysis was conducted with a clinical cutoff date of December 19, 2016. A pre-planned updated exploratory iDFS analysis with additional follow-up was conducted with a clinical cutoff date of June 19, 2019.[2,4,15]

Dual anti-HER2 adjuvant therapy with PERJETA + Herceptin + chemotherapy vs placebo + Herceptin + chemotherapy demonstrated a reduction in the risk of recurrence in patients with HER2+ EBC, based on the primary analysis.[4]

PRIMARY ANALYSIS†[4]

HR=0.82
(95% CI: 0.67-1.00; *P*=0.047)

18% REDUCTION in the risk of recurrence

after a median follow-up of **45.4 months**

3-year iDFS: 94.1% vs 93.2%
(95% CI: 93.1-95.0 vs 92.2-94.3, respectively)

EXPLORATORY iDFS FOLLOW-UP ANALYSIS[2]

HR=0.76
(95% CI: 0.64-0.91)

after a median follow-up of **74.1 months**

6-year iDFS: 90.6% vs 87.8%
(95% CI: 89.4-91.8 vs 86.4-89.1, respectively)

Limitations of data: The iDFS follow-up analysis was exploratory and the data are considered descriptive, therefore no formal conclusions may be drawn.

Secondary endpoints (PERJETA + Herceptin + chemotherapy vs placebo + Herceptin + chemotherapy)

Median follow-up: 45.4 months (primary analysis)[4]

- **iDFS including second primary non-breast cancer**: HR=0.83, 95% CI: 0.68-1.00†; *3-year event-free rate:* 93.5% (95% CI: 92.5-94.5) vs 92.5% (95% CI: 91.4-93.6)
- **DFS:** HR=0.82, 95% CI: 0.68-0.99†; *3-year event-free rate:* 93.4% (95% CI: 92.4-94.4) vs 92.3% (95% CI: 91.2-93.4)
- **OS:** HR=0.89, 95% CI: 0.66-1.21†; *3-year event-free rate:* 97.7% (95% CI: 97.0-98.3) vs 97.7% (95% CI: 97.1-98.3)

*Recurrence is defined as an invasive disease event or death.
†All analyses stratified by nodal status, protocol version, central hormone receptor status, and adjuvant chemotherapy regimen.

Important Safety Information (cont'd)

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 APHINITY study, for 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

APHINITY exploratory analysis:
iDFS by patient subgroup*†[2,4]

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		Primary Analysis			Follow-Up Analysis		
		HR *Number of events/N*	3 year iDFS % (95% CI)	3-Year Δ	HR *Number of events/N*	6 year iDFS % (95% CI)	6-Year Δ
Overall	**Overall (ITT)**	**0.82 (0.67-1.00)**			**0.76 (0.64-0.91)**		
	P+H+C	171/2400	**94.1%** (93.1-95.0)	**0.9%**	223/2400	**90.6%** (89.4-91.8)	**2.8%**
	Pla+H+C	210/2404	**93.2%** (92.2-94.3)		287/2404	**87.8%** (86.4-89.1)	
Nodal status	**Node+**	**0.77 (0.62-0.96)**			**0.72 (0.59-0.87)**		
	P+H+C	139/1503	**92.0%** (90.5-93.3)	**1.8%**	173/1503	**87.9%** (86.2-89.6)	**4.5%**
	Pla+H+C	181/1502	**90.2%** (88.5-91.6)		239/1502	**83.4%** (81.4-85.3)	
	Node-	**1.13 (0.68-1.86)**			**1.02 (0.69-1.53)**		
	P+H+C	32/897	**97.5%** (96.3-98.4)	**-0.9%**	48/897	**95.0%** (93.5-96.5)	**0.1%**
	Pla+H+C	29/902	**98.4%** (97.3-99.0)		48/902	**94.9%** (93.4-96.4)	
Hormone receptor status	**HR-**	**0.76 (0.56-1.04)**			**0.83 (0.63-1.10)**		
	P+H+C	71/864	**92.8%** (90.8-94.3)	**1.6%**	90/864	**89.5%** (87.4-91.6)	**2.5%**
	Pla+H+C	91/858	**91.2%** (89.0-92.9)		106/858	**87.0%** (84.7-89.4)	
	HR+	**0.86 (0.66-1.13)**			**0.73 (0.59-0.92)**		
	P+H+C	100/1536	**94.8%** (93.5-95.8)	**0.4%**	131/1536	**91.2%** (89.7-92.6)	**3.0%**
	Pla+H+C	119/1546	**94.4%** (93.1-95.4)		181/1546	**88.2%** (86.5-89.8)	
Chemotherapy regimens	**Anthracycline**	**0.82 (0.66-1.03)**			**0.79 (0.65-0.96)**		
	P+H+C	139/1865	**93.8%** (92.6-94.8)	**0.8%**	181/1865	**90.2%** (88.8-91.6)	**2.6%**
	Pla+H+C	171/1877	**93.0%** (91.8-94.1)		230/1877	**87.6%** (86.1-89.2)	
	Non-anthracycline	**0.82 (0.51-1.31)**			**0.71 (0.47-1.06)**		
	P+H+C	32/535	**94.9%** (92.6-96.6)	**0.9%**	40/535	**91.9%** (89.5-94.4)	**3.5%**
	Pla+H+C	39/527	**94.0%** (91.5-95.8)		57/527	**88.4%** (85.5-91.2)	

P+H+C = PERJETA + Herceptin + chemotherapy; **Pla+H+C = Placebo** + Herceptin + chemotherapy.

*Exploratory analyses without adjusting for multiple comparisons; therefore, results are considered descriptive.[4]

23% reduction in the risk of recurrence in the node-positive subgroup at primary analysis[4]
HR=0.77 (95% CI: 0.62-0.96)[4]

HR=0.72 (95% CI: 0.59-0.87; *P*=0.0008) at exploratory iDFS follow-up analysis[2]

There was an inability to show a reduction in risk of recurrence for the node-negative subgroup.[2,4]

†The primary analysis was conducted with a clinical cutoff date of 12/19/2016. An updated exploratory iDFS analysis was conducted with a clinical cutoff date of 6/19/2019.[2]

Select safety information from the APHINITY trial

Most common overall ARs (>20%, all Grades) in patients receiving PERJETA® (pertuzumab)[4]

	PERJETA + Herceptin® (trastuzumab) + chemotherapy (n=2364)		**Placebo** + Herceptin + chemotherapy (n=2405)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Diarrhea	71	10	45	4
Nausea	69	2	65	2
Alopecia	67	<0.1	67	<0.1
Fatigue	49	4	44	3
Neuropathy peripheral	33	1	32	1
Vomiting	32	2	30	2
Constipation	29	0.5	32	0.3
Arthralgia	29	0.9	33	1
Stomatitis	28	2	24	1
Anemia	28	7	23	5
Rash	26	0.4	20	0.2
Dysgeusia	26	0.1	22	<0.1
Myalgia	26	0.9	30	1
Neutropenia	25	16	23	16
Decreased appetite	24	0.8	20	0.4
Mucosal inflammation	23	2	19	0.7
Headache	22	0.3	23	0.4
Asthenia	21	1	21	2

Cardiac safety profile[4]

	PERJETA + Herceptin + chemotherapy (n=2364)	**Placebo** + Herceptin + chemotherapy (n=2405)
NYHA class III or IV heart failure and substantial decrease in LVEF*	0.6%	0.2%
Asymptomatic or mildly symptomatic (NYHA class II) heart failure and substantial decrease in LVEF*	3%	3%

*A substantial decrease in LVEF is defined as a decrease of 10 or more percentage points, to a value <50%.[15]

LVEF=left ventricular ejection fraction; NYHA=New York Heart Association.

Diarrhea rates during chemotherapy and after it was discontinued

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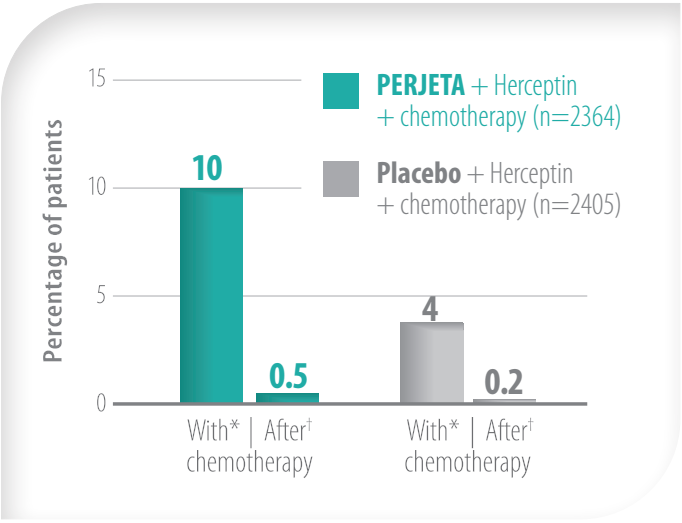
All Grades diarrhea[4]

- Overall incidence of diarrhea was 71% in the PERJETA-treated group and 45% in the placebo-treated group
- Incidence of diarrhea when targeted therapy was administered with chemotherapy:
  - 61% in the PERJETA-treated group
  - 34% in the placebo-treated group
- Incidence of diarrhea was higher when administered with non–anthracycline-based therapy vs with anthracycline-based therapy
- Incidence of diarrhea during targeted therapy after chemotherapy:
  - 18% in the PERJETA-treated group
  - 9% in the placebo-treated group

Grades 3-4 diarrhea[4,15]



*Includes Grade ≥3 ARs with onset from first dose of any study treatment through 28 days after last dose of study treatment.[15]

†Includes Grade ≥3 ARs with onset during the targeted therapy post-chemotherapy treatment period.[15]

Important Safety Information (cont'd)
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. The most common infusion reactions (≥1.0%) were pyrexia, chills, fatigue, headache, asthenia, hypersensitivity, 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
- If a significant infusion reaction occurs, slow or interrupt the infusion and administer appropriate medical therapies. Monitor patients carefully until complete resolution of signs and symptoms. Consider permanent discontinuation in patients with severe infusion reactions

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

Important Safety Information for **PERJETA® (pertuzumab)**

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**
  - Based on its mechanism of action and findings in animal studies, PERJETA can cause fetal harm when administered to a pregnant woman. PERJETA is a HER2/neu receptor antagonist. Cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death have been reported with use of another HER2/neu receptor antagonist (trastuzumab) during pregnancy. In an animal reproduction study, administration of pertuzumab to pregnant cynomolgus monkeys during the period of organogenesis resulted in oligohydramnios, delayed fetal kidney development, and embryo-fetal death at exposures 2.5 to 20 times the exposure in humans at the recommended dose, based on C_{max}
  - 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

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 APHINITY study, for patients treated in the adjuvant setting, the incidence of symptomatic heart failure (New York Heart Association [NYHA] Class III/IV) 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 (NYHA Class II) 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 pyrexia, chills, fatigue, headache, asthenia, hypersensitivity, 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 on the first day of PERJETA administration (in combination with trastuzumab and chemotherapy) 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

- Observe patients closely for 60 minutes after the first infusion and for 30 minutes after subsequent infusions of PERJETA. If a significant infusion reaction occurs, slow or interrupt the infusion and administer appropriate medical therapies. Monitor patients carefully until complete resolution of signs and symptoms. Consider permanent discontinuation in patients with severe infusion reactions

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. Overall, 4 patients in the PERJETA-treated group and 2 patients in the placebo-treated group experienced anaphylaxis
- In the NeoSphere, TRYPHAENA, BERENICE, and APHINITY studies, hypersensitivity/anaphylaxis events were consistent with those observed in CLEOPATRA. In NeoSphere, 2 patients in the PERJETA and docetaxel–treated group experienced anaphylaxis. In APHINITY, the overall frequency of hypersensitivity/anaphylaxis was 5% in the PERJETA-treated group vs 4% in the placebo-treated group. The incidence was highest in the PERJETA plus TCH–treated group (8%), of which 1% were NCI-CTCAE (v4.0) Grades 3-4
- 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. PERJETA is contraindicated in patients with known hypersensitivity to pertuzumab or to any of its excipients

Most Common Adverse Reactions

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. The median duration of all Grades diarrhea was 8 days for the PERJETA-treated group vs. 6 days for the placebo-treated group. The median duration of Grade ≥3 diarrhea was 20 days for the PERJETA-treated group vs. 8 days for the placebo-treated group. More patients required hospitalization for diarrhea as a serious adverse event in the PERJETA-treated group (2.4%) than in the placebo-treated group (0.7%)

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.

Please see full Prescribing Information for additional Important Safety Information, including BOXED WARNINGS.

Indication: KADCYLA® (ado-trastuzumab emtansine), 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.

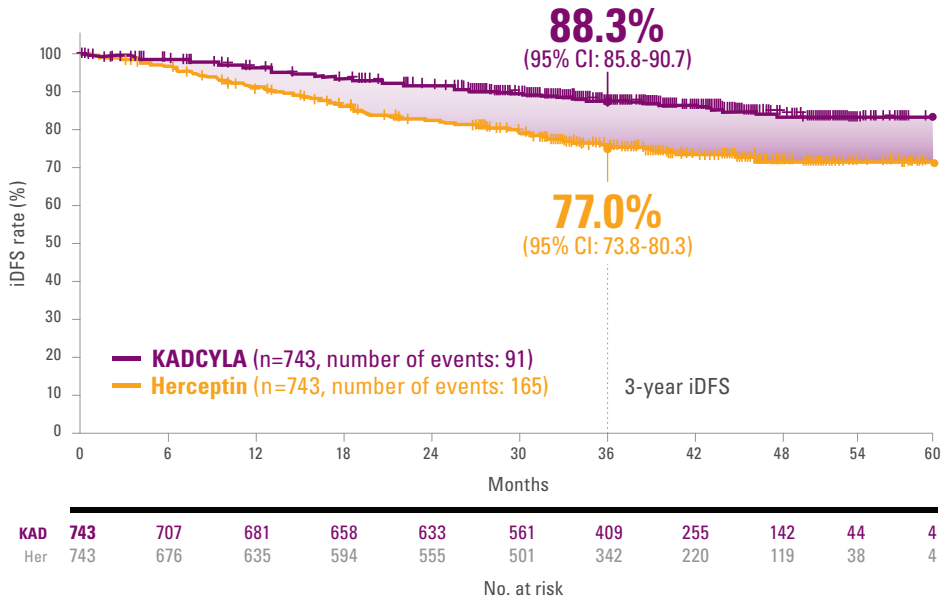
Trastuzumab alone is not enough for your patients with HER2+ EBC who have residual invasive disease[5]

Choose KADCYLA in the adjuvant setting for greater reduction in the risk of recurrence vs Herceptin® (trastuzumab)*[5]

KATHERINE was a Phase III randomized, open-label trial in 1486 patients with HER2+ EBC who had residual invasive disease in the breast and/or axillary lymph nodes following neoadjuvant treatment with taxane + trastuzumab-based therapy. Patients received either KADCYLA (3.6 mg/kg) or Herceptin (6 mg/kg), intravenously, every 3 weeks for a total of 14 cycles or until recurrence, withdrawal of consent, or unmanageable toxicity. Patients received radiotherapy and/or hormonal therapy concurrent with study treatment as per local guidelines. **The primary endpoint was invasive disease-free survival (iDFS)**, defined as the time from randomization to first occurrence of ipsilateral invasive breast tumor recurrence, ipsilateral local or regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, or death from any cause.[5,16]

Nearly 90% of patients who received KADCYLA remained disease free at 3 years[5]

iDFS in the overall study population after a median follow-up of 40 months[5]



50% **REDUCTION** in the risk of recurrence
HR=0.50; 95% CI: 0.39-0.64; *P*<0.0001

*Recurrence is defined as an invasive-disease event or death.

Important Safety Information

BOXED WARNINGS: HEPATOTOXICITY

- **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**

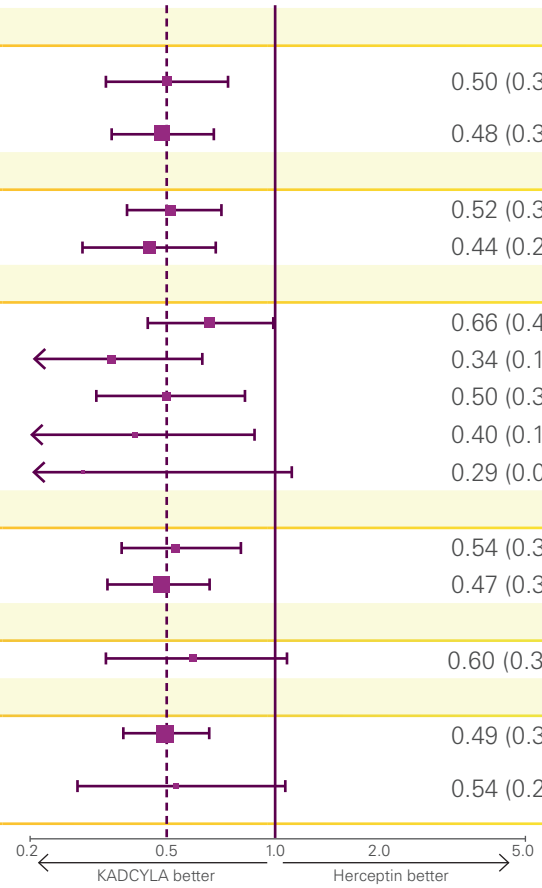
Consistent iDFS benefit was observed with KADCYLA across subgroups[5]

Kadcyla®
ado-trastuzumab emtansine
20 mg/mL INJECTION FOR INTRAVENOUS USE

Based on stratification factors, key baseline demographics and disease characteristics, and prior treatments[5]

Exploratory analysis of pre-specified subgroups[2,16,17]

	KADCYLA	Herceptin
	No. of patients with an invasive-disease event/total no.	
Hormone receptor status		
Negative (ER negative & PgR negative/unknown)	38/209	61/203
Positive (ER and/or PgR positive)	53/534	104/540
Pathological nodal status after pre-operative therapy		
Node positive	62/343	103/346
Node negative/not done	29/400	62/397
Primary tumor stage (at definitive surgery)		
ypT0, ypT1a, ypT1b, ypT1mic, ypTis	40/331	52/306
ypT1, ypT1c	14/175	42/184
ypT2	25/174	44/185
ypT3	9/51	21/57
ypT4	3/12	6/11
Clinical stage at presentation		
Inoperable	42/185	70/190
Operable	49/558	95/553
Residual disease ≤1 cm with negative axillary lymph nodes		
ypT1a, ypT1b or ypT1mic and ypN0	17/170	25/161
Pre-operative HER2-directed therapy		
Herceptin alone	78/600	141/596
Herceptin plus additional HER2-directed agent(s)*	13/143	24/147



*18.3% (n=272) of patients were treated with PERJETA® (pertuzumab) + Herceptin-based therapy in the neoadjuvant setting, and had an iDFS hazard ratio of 0.50 (95% CI: 0.25-1.00). The other 18 patients received Herceptin and either neratinib, dacomitinib, afatinib, or lapatinib.[16]

Important Safety Information

BOXED WARNINGS: CARDIAC TOXICITY, EMBRYO-FETAL TOXICITY

- **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 throughout and on pages 16-17, and accompanying Prescribing Information, including BOXED WARNINGS.

Adverse reactions (ARs) in KATHERINE were **consistent with the known safety profile for KADCYLA® (ado-trastuzumab emtansine)**[16]

Summary of ARs occurring in ≥10% of patients[5]

	KADCYLA (n=740)		Herceptin® (trastuzumab) (n=720)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Fatigue	50	1.1	34	0.1
Nausea	42	0.5	13	0.3
Transaminases increased	32	1.5	8	0.4
Musculoskeletal pain	30	0.7	29	0.7
Hemorrhage	29	0.4*	10	0.3
Thrombocytopenia	29	6	2.4	0.3
Headache	28	0	17	0.1
Peripheral neuropathy	28	1.6	14	0.1
Arthralgia	26	0.1	21	0
Epistaxis	22	0	3.5	0
Constipation	17	0.1	8	0
Myalgia	15	0.4	11	0
Stomatitis	15	0.1	8	0.1
Vomiting	15	0.5	5	0.3
Insomnia	14	0	12	0.1
Dry mouth	14	0.1	1.3	0
Cough	14	0.1	12	0
Diarrhea	12	0.8	13	0.3
Abdominal pain	11	0.4	7	0.3
Pyrexia	10	0	4	0
Urinary tract infection	10	0.3	6	0.1
Anemia	10	1.1	9	0.1
Dizziness	10	0.1	8	0.3

*Included one fatal hemorrhage.

The most common Grade ≥3 ARs (>2%) were thrombocytopenia and hypertension.

Select Important Safety Information

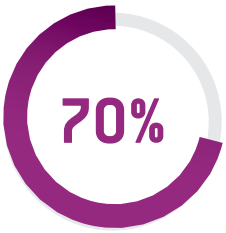
Warnings and Precautions

KADCYLA has warnings and precautions for Hepatotoxicity, Left Ventricular Dysfunction, Embryo-Fetal Toxicity, Pulmonary Toxicity, Infusion-Related/Hypersensitivity Reactions, Hemorrhage, Thrombocytopenia, Neurotoxicity, and Extravasation.

Understanding peripheral neuropathy in KATHERINE

Kadcyla®
ado-trastuzumab emtansine
20 mg/mL INJECTION FOR INTRAVENOUS USE

- In the KATHERINE trial, 32% of patients in the KADCYLA arm experienced any Grade peripheral neuropathy vs 17% in the Herceptin arm*[5]
- 1.6% of patients in the KADCYLA arm experienced Grade ≥3 peripheral neuropathy vs 0.1% in the Herceptin arm[5]



of cases of peripheral neuropathy in the KADCYLA arm, including sensory and motor peripheral neuropathy, were resolved at the time of primary iDFS analysis[5]

An additional 9% of cases of peripheral neuropathy were resolving at the time of primary iDFS analysis.[2]

*These numbers differ from those noted in the AR table because a broader set of safety terms were included in this definition of neuropathy.[5]

Give patients **a full course of KADCYLA treatment**

Eligible patients should receive KADCYLA:

- For a total of 14 cycles in the adjuvant setting unless there is disease recurrence or unmanageable toxicity[5]

14 CYCLES
once every 3 weeks

The majority of patients in the trial (71.4% of 740) completed all 14 cycles of KADCYLA treatment[16]

CATEGORY 1, PREFERRED
NCCN
GUIDELINES®
RECOMMENDED
OPTION

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend ado-trastuzumab emtansine (KADCYLA) monotherapy for the adjuvant treatment of HER2+ patients with residual invasive disease after neoadjuvant treatment (category 1, preferred).†[18]

- NCCN Guidelines recommend treatment with ado-trastuzumab emtansine (KADCYLA) for 14 cycles in this setting

†Category 1: Based upon high-level evidence, there is uniform National Comprehensive Cancer Network® (NCCN®) consensus that the intervention is appropriate. NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

Please see Important Safety Information throughout and on pages 16-17, and accompanying Prescribing Information, including BOXED WARNINGS.

Important Safety Information for **KADCYLA® (ado-trastuzumab emtansine)**

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 clinical trials with KADCYLA. Serious hepatotoxicity, including 3 fatal cases, has been observed in clinical trials (n=1624) with KADCYLA as single-agent. The two fatal cases of severe drug-induced liver injury and associated hepatic encephalopathy occurred in MBC clinical trials with KADCYLA. Some of the patients experiencing hepatotoxicity had comorbidities and/or 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 liver disease (such as hepatitis B virus or hepatitis C virus) were excluded from the KATHERINE (for patients with early breast cancer [EBC]) study. 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 >3 × ULN and concomitant total bilirubin >2 × ULN.

In clinical trials of KADCYLA, cases of nodular regenerative hyperplasia (NRH) of the liver have been identified from liver biopsies (5 cases out of 1624, 1 of which was fatal). Two of these five cases of NRH were observed in KATHERINE. Diagnosis can be confirmed only by histopathology. 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. Upon NRH diagnosis, KADCYLA treatment must be permanently discontinued.

Left Ventricular Dysfunction

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. Serious cases of heart failure, with no fatal cases, have been observed in clinical trials with KADCYLA.

In KATHERINE, left ventricular dysfunction 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 (e.g. every 3 months) during treatment to ensure the LVEF is within the institution's normal limits. Treatment with KADCYLA has not been studied in patients with LVEF <50% prior to treatment.

For patients with EBC, if at routine monitoring LVEF is <45%, or is 45% to 49% with a ≥10% 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

KADCYLA can cause fetal harm when administered to a pregnant woman. Cases of oligohydramnios, and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities and neonatal death were observed in the post-marketing setting in patients treated with trastuzumab, the antibody component of KADCYLA. DM1, the cytotoxic component of KADCYLA, can cause embryo-fetal toxicity, based on its mechanism of action.

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 with KADCYLA and for 4 months following the last dose.

If KADCYLA is administered during pregnancy, or if a 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 clinical trials with KADCYLA. Signs and symptoms include dyspnea, cough, fatigue, and pulmonary infiltrates.

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.

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.

Patients with dyspnea at rest due to complications of advanced malignancy and comorbidities and receiving concurrent pulmonary radiation therapy may be at increased risk of pulmonary toxicity.

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 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 observed closely for IRR, especially during the first infusion.

One case of a serious, allergic/anaphylactic-like 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 KATHERINE, the overall incidence of hemorrhage was 29% in the KADCYLA group and 10% in the trastuzumab group. The incidence of Grade ≥ 3 hemorrhage was 0.4% in the KADCYLA group, with one fatal case of intracranial hemorrhage, and 0.3% in the trastuzumab 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. 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 KATHERINE, the overall incidence of thrombocytopenia was 29% in the KADCYLA group and 2.4% in the trastuzumab group. The incidence of Grade ≥ 3 thrombocytopenia was 6% in the KADCYLA group and 0.3% in the trastuzumab group. In Asian patients, the incidence of Grade ≥ 3 thrombocytopenia was 19% and 0%, respectively. The overall incidence of thrombocytopenia in the KADCYLA group for Asian patients was 50%.

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 (<50,000/mm^3), do not administer KADCYLA until platelet counts recover to Grade 1 (≥75,000/mm^3). Closely monitor patients with thrombocytopenia (< 100,000/mm^3) and patients on anti-coagulant treatment during treatment with KADCYLA.

Neurotoxicity

Peripheral neuropathy, mainly as Grade 1 and predominantly sensory, was reported in clinical trials of KADCYLA.

In KATHERINE, the overall incidence of peripheral neuropathy was 32% in the KADCYLA group and 17% in the trastuzumab group. Peripheral neuropathy, including sensory and motor peripheral neuropathy, were not resolved in 30% of cases for KADCYLA treated patients at the time of the primary IDFS analysis for KATHERINE. The incidence of Grade ≥ 3 peripheral neuropathy was 1.6% in the KADCYLA group and 0.1% in the trastuzumab group.

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

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 erythema, tenderness, skin irritation, pain, or swelling at the infusion site. Specific treatment for KADCYLA extravasation is unknown. Closely monitor the infusion site for possible subcutaneous infiltration during drug administration.

Adverse Reactions

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

There is no information regarding the presence of ado-trastuzumab emtansine in human milk, the effects on the breastfed infant, or the effects on milk production. DM1, the cytotoxic component of KADCYLA, may cause serious adverse reactions in breastfed infants based on its mechanism of action. 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 accompanying full Prescribing Information for additional Important Safety Information, including BOXED WARNINGS.

PERJETA®
pertuzumab
420 mg INJECTION FOR INTRAVENOUS USE

Indications & Important Safety Information for PERJETA® (pertuzumab)

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

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**

Kadcyla®
ado-trastuzumab emtansine
20 mg/mL INJECTION FOR INTRAVENOUS USE

Indication & Important Safety Information for KADCYLA® (ado-trastuzumab emtansine)

Indication

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.

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 for PERJETA on pages 10-11 and for KADCYLA on pages 16-17, and the accompanying full Prescribing Information, including BOXED WARNINGS.

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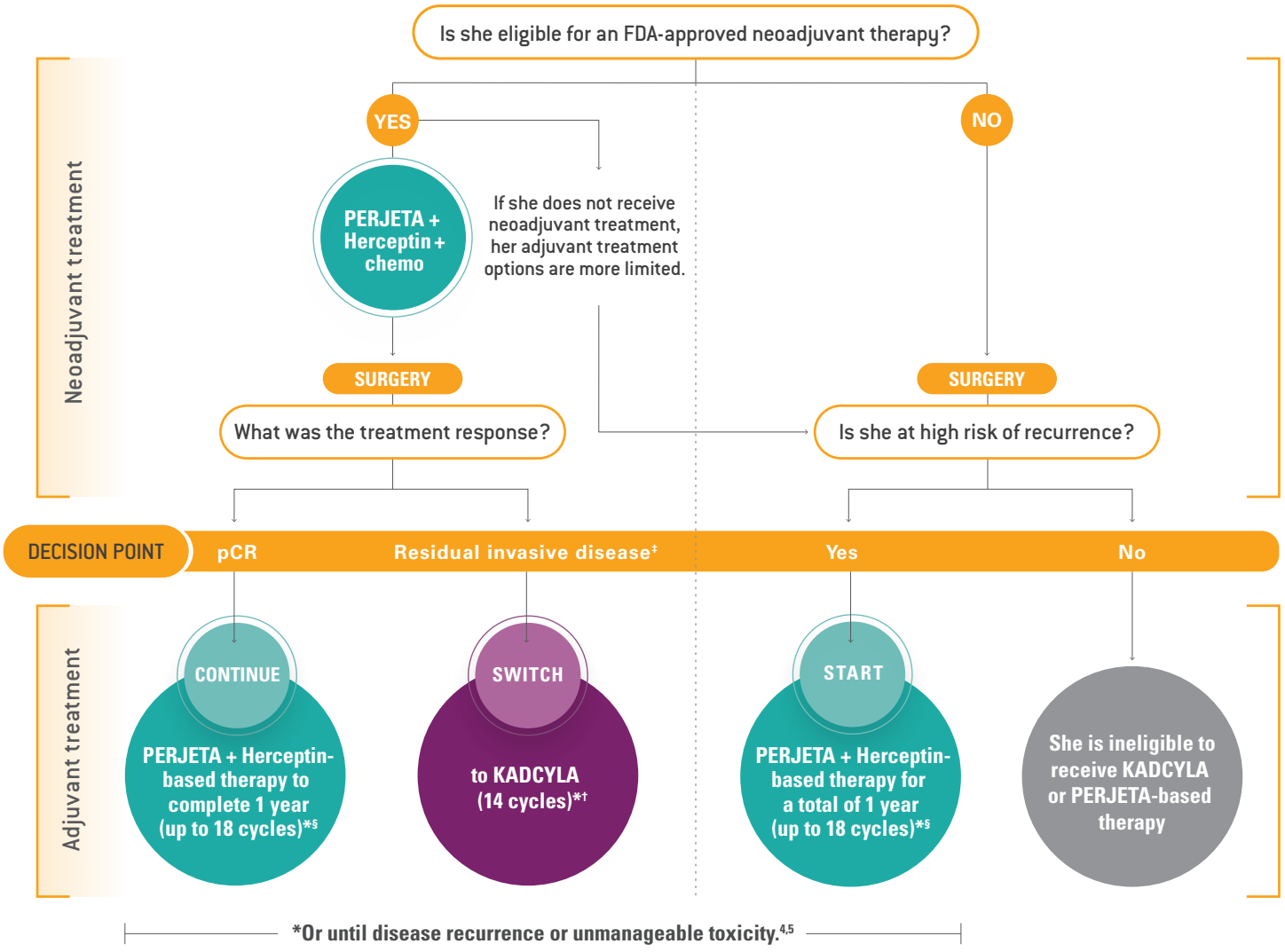
Targeted treatments for HER2+ EBC have advanced in the last 20 years, **but this is still an aggressive disease**[19]

At any point along the treatment journey, there is still a risk of recurrence[1-3]

WHAT TREATMENT CHOICES WILL YOU MAKE?

Consider these approved treatment options for your eligible patients with HER2+ EBC[4,5]



†Based on the Prescribing Information, PERJETA + Herceptin remains an option for patients with residual invasive disease following neoadjuvant treatment with PERJETA + Herceptin-based therapy. In the adjuvant setting, there have been no studies that compare KADCYLA to PERJETA + Herceptin-based therapy.[4,5]

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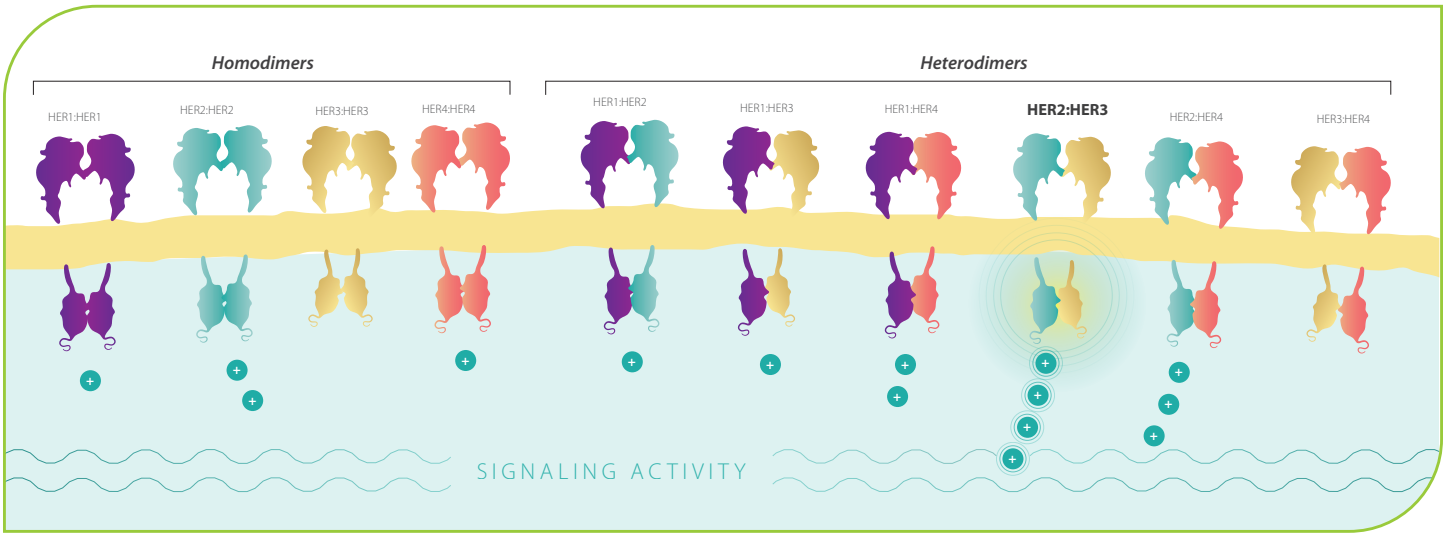
PERJETA is designed to work with Herceptin **for a dual-HER2 blockade**[4,20]

In preclinical models, PERJETA targeted a different subdomain on the HER2 receptor than Herceptin, to block dimerization with HER1, HER3, and HER4 receptors and provide a dual blockade of HER2-driven signaling pathways[4,20,21]

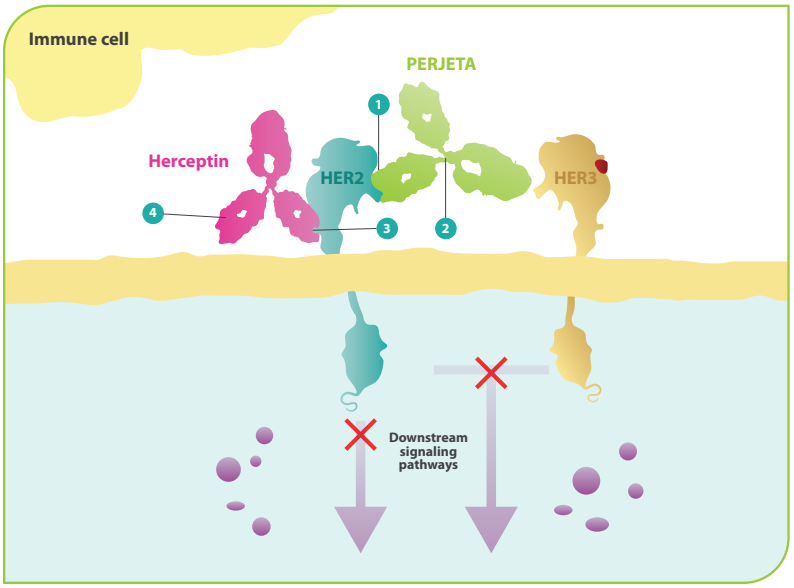
HER2:HER3 dimerization[22-24]



HER2:HER3 dimerization is believed to produce the strongest oncogenic signaling in HER2+ breast cancer[25-27]

- Activates two key pathways that regulate cell growth and survival
  - The mitogen-activated protein kinase (MAPK) pathway[26,27]
  - The phosphoinositide 3-kinase (PI3K) pathway[28,29]

Proposed mechanism of action



PERJETA activities[4]

1. **HER2 binding:** Selectively binds to the HER2 receptor at subdomain II
2. **HER2+ antitumor activities**
   - Inhibits HER2:HER3 dimer formation to disrupt ligand-dependent signaling
   - Mediates antibody-dependent cell-mediated cytotoxicity (ADCC)

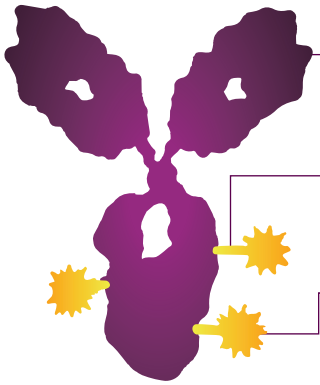
Herceptin activities[20,21,30]

3. **HER2 binding:** Selectively binds to the HER2 receptor at subdomain IV
4. **HER2+ antitumor activities**
   - Disrupts ligand-independent HER2 signaling (antiproliferative and apoptotic effects)
   - Mediates ADCC
   - Inhibits HER2 shedding

KADCYLA is designed to perform multiple antitumor activities **as a single drug**[5]

In preclinical studies, KADCYLA maintained the HER2 suppression and anticancer activities of trastuzumab while delivering cytotoxic DM1 inside HER2-expressing cells[5]

KADCYLA structure



Trastuzumab–monoclonal antibody[5]

- Selectively binds to HER2

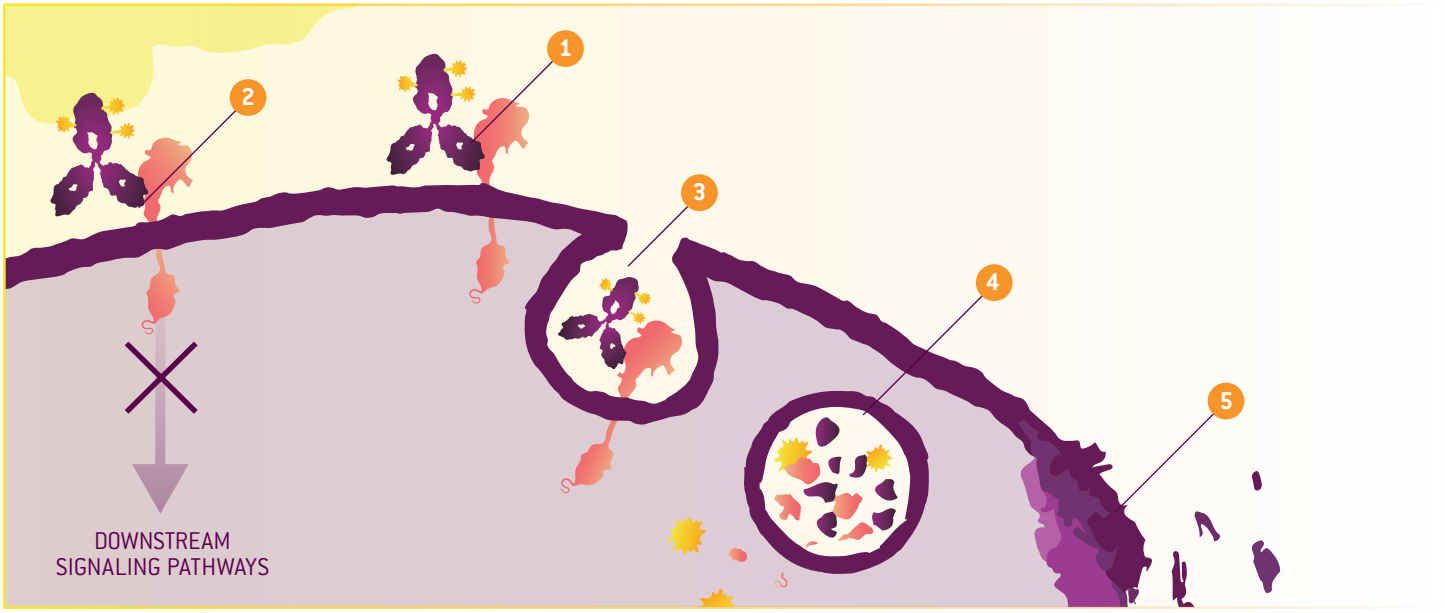
MCC*–stable linker[5,31]

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

DM1*–cytotoxic agent[5,32]

- Approximately 20 to 200 times more potent than taxanes and vinca alkaloids
- Provides cytotoxicity previously unavailable for clinical use

Proposed mechanism of action



Trastuzumab antibody activities[5,30]

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2. **HER2+ antitumor activities**
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   - Mediates ADCC
   - Inhibits HER2 shedding

DM1† cytotoxic activity[5]

3. **Internalization:** Once bound, the KADCYLA/HER2-receptor complex is internalized via endocytosis.
4. **DM1 release:** KADCYLA is degraded inside the tumor to release DM1.
5. **DM1 cytotoxicity:** DM1 binds to microtubules and inhibits their polymerization, causing cell-cycle arrest and cell death.

*Emtansine is the combination of DM1, a cytotoxic maytansinoid, and the stable MCC linker.[5]
†Cytotoxic DM1-containing catabolites (primarily lysine-bound emtansine).[5]

DM1=derivative of maytansine; MCC=4-(N-maleimidomethyl) cyclohexane-1-carboxylate.

For your patients with HER2+ EBC,

GO BEYOND TRASTUZUMAB ALONE.[4,5]

Genentech
A Member of the Roche Group

PERJETA® pertuzumab
420 mg INJECTION FOR INTRAVENOUS USE

Indications & Important Safety Information for **PERJETA® (pertuzumab)**

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

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**

Kadcyla® ado-trastuzumab emtansine
20 mg/mL INJECTION FOR INTRAVENOUS USE

Indication & Important Safety Information for **KADCYLA® (ado-trastuzumab emtansine)**

Indication

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.

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 for PERJETA on pages 10-11 and for KADCYLA on pages 16-17, and the accompanying full Prescribing Information, including BOXED WARNINGS.

References: 1. Gianni L, et al. *Lancet Oncol.* 2016;17(6):791-800. **2.** Data on file. Genentech, Inc. **3.** Cortazar P, et al. *Lancet.* 2014;384(9938):164-172. **4.** PERJETA Prescribing Information. Genentech, Inc. 2020. **5.** KADCYLA Prescribing Information. Genentech, Inc. 2019. **6.** Cameron D, et al. *Lancet.* 2017;389(10075):1195-1205. **7.** Perez EA, et al. *J Clin Oncol.* 2014;32(33):3744-3752. **8.** Perez EZ, et al. *J Clin Oncol.* 2011;29(25):3366-3373. **9.** Slamon D, et al. *N Engl J Med.* 2011;365(14):1273-1283. **10.** Piccart-Gebhart MJ, et al. *N Engl J Med.* 2005;353(16):1659-1672. **11.** Romond EH, et al. *N Engl J Med.* 2005;353(16):1673-1684. **12.** Combination chemotherapy with or without trastuzumab in treating women with breast cancer. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT00021255. Accessed December 1, 2019. **13.** Cortazar P. Meta-analysis results from the collaborative trials in neoadjuvant breast cancer (CTNeoBC). Presented at the San Antonio Breast Cancer Symposium, December 4-8, 2012. **14.** Gianni L, et al. *Lancet Oncol.* 2012;13(1):25-32. **15.** von Minckwitz G, et al. *N Engl J Med.* 2017;377(2):122-131. **16.** von Minckwitz G, et al. *N Engl J Med.* 2019;380(7):617-628. **17.** Geyer CE, et al. Phase III study of trastuzumab emtansine (T-DM1) vs trastuzumab as adjuvant therapy in patients with HER2-positive early breast cancer with residual invasive disease after neoadjuvant chemotherapy and HER2-targeted therapy including trastuzumab: primary results from KATHERINE (NSABP B-50-I, GBG 77 and Roche BO27938). Presented at San Antonio Breast Cancer Symposium December 4–8, 2018. **18.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V1.2020. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed January 17, 2020. To view the most recent and complete version of the guideline, go online to NCCN.org. **19.** Witton CJ, et al. *J Pathol.* 2003;200(3):290-297. **20.** Scheuer W, et al. *Cancer Res.* 2009;69(24):9330-9336. **21.** Lee-Hoeflich ST, et al. *Cancer Res.* 2008;68(14):5878-5887. **22.** Tzahar E, et al. *Mol Cell Biol.* 1996;16(10):5276-5287. **23.** Citri A, et al. *Exp Cell Res.* 2003;284(1):54-65. **24.** Lenferink AE, et al. *EMBO J.* 1998;17(12):3385-3397. **25.** Baselga J, et al. *Nat Rev Cancer.* 2009;9(7):463-475. **26.** Hynes NE, et al. *Nat Rev Cancer.* 2005;5(5):341-354. **27.** Yarden Y, et al. *Nat Rev Mol Cell Biol.* 2001;2(2):127-137. **28.** Hsieh AC, et al. *Br J Cancer.* 2007;97(4):453-457. **29.** Soltoff SP, et al. *Mol Cell Biol.* 1994;14(6):3550-3558. **30.** Nahta R, et al. *Cancer Lett.* 2006;232(2):123-138. **31.** Verma S, et al. *N Engl J Med.* 2012;367(19):1783-1791. Erratum, 2013;368:2442. **32.** Junttila TT, et al. *Breast Cancer Res Treat.* 2011;128(2):347-356.

Targeted treatments for HER2+ EBC have advanced in the last 20 years, **but this is still an aggressive disease[19]**

At any point along the treatment journey, there is still a risk of recurrence[1-3]

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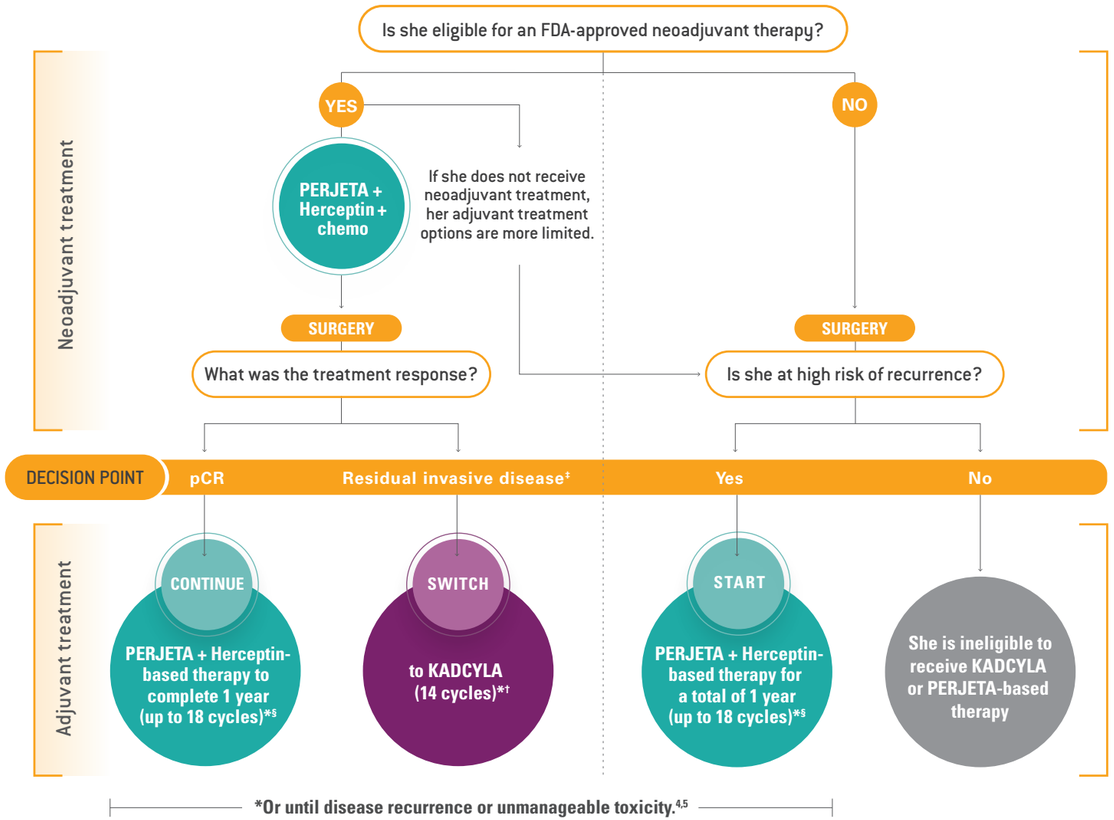

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FLIP OPEN

PERJETA® pertuzumab 420 mg INJECTION FOR INTRAVENOUS USE

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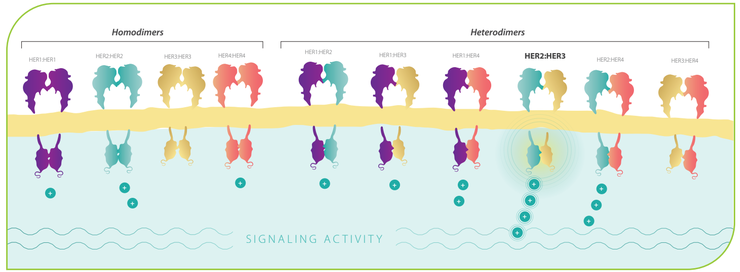

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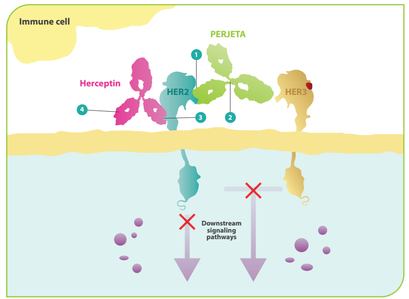

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Herceptin activities[20,21,30]

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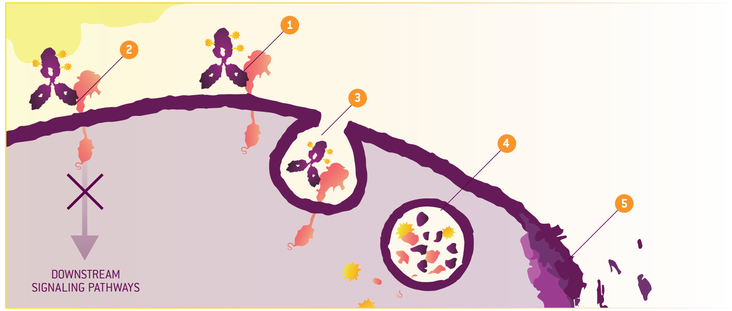

Trastuzumab antibody activities[5,30]

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DM1† cytotoxic activity[5]

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DM1=derivative of maytansine; MCC=4-(N-maleimidomethyl) cyclohexane-1-carboxylate.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PERJETA safely and effectively. See full prescribing information for PERJETA.

PERJETA® (pertuzumab) injection, for intravenous use
Initial U.S. Approval: 2012

WARNING: LEFT VENTRICULAR DYSFUNCTION and EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning.

- **Left Ventricular Dysfunction: PERJETA can result in subclinical and clinical cardiac failure manifesting as decreased LVEF and CHF. Evaluate cardiac function prior to and during treatment. Discontinue PERJETA treatment for a confirmed clinically significant decrease in left ventricular function. (2.3, 5.1, 6.1)**
- **Embryo-fetal Toxicity: Exposure to PERJETA can result in embryo-fetal death and birth defects. Advise patients of these risks and the need for effective contraception. (5.2, 8.1, 8.3)**

---------- RECENT MAJOR CHANGES ----------

Dosage and Administration (2.2, 2.3) 01/2020

---------- INDICATIONS AND USAGE ----------

PERJETA is a HER2/neu receptor antagonist indicated for:

- Use in combination with trastuzumab and docetaxel for treatment of patients with HER2-positive metastatic breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. (1.1)
- Use in combination with trastuzumab and chemotherapy as
  - 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. (1.2, 2.2, 14.2)
  - adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence (1.2, 2.2, 14.3)

---------- DOSAGE AND ADMINISTRATION ----------

- **For intravenous infusion only.** Do not administer as an intravenous push or bolus. (2.4)
- HER2 testing: Perform using FDA-approved tests by laboratories with demonstrated proficiency. (2.1)
- The initial PERJETA dose is 840 mg administered as a 60-minute intravenous infusion, followed every 3 weeks thereafter by 420 mg administered as a 30 to 60 minute intravenous infusion. (2.2)
- MBC: Administer PERJETA, trastuzumab or trastuzumab hyaluronidase-oysk, and docetaxel every 3 weeks. (2.2)
- Neoadjuvant: Administer PERJETA, trastuzumab or trastuzumab hyaluronidase-oysk, and chemotherapy preoperatively every 3 weeks for 3 to 6 cycles. (2.2)
- Adjuvant: Administer PERJETA, trastuzumab or trastuzumab hyaluronidase-oysk, and chemotherapy postoperatively every 3 weeks for a total of 1 year (up to 18 cycles). (2.2)

---------- DOSAGE FORMS AND STRENGTHS ----------

- Injection: 420 mg/14 mL single-dose vial. (3)

---------- CONTRAINDICATIONS ----------

PERJETA is contraindicated in patients with known hypersensitivity to pertuzumab or to any of its excipients. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Infusion-Related Reactions: Monitor for signs and symptoms. If a significant infusion-associated reaction occurs, slow or interrupt the infusion and administer appropriate medical therapies. (5.3)
- Hypersensitivity Reactions/Anaphylaxis: Monitor for signs and symptoms, including angioedema. If a severe hypersensitivity reaction/anaphylaxis occurs, discontinue the infusion immediately and administer appropriate medical therapies. (5.4)

---------- ADVERSE REACTIONS ----------

Metastatic Breast Cancer

- The most common adverse reactions (> 30%) with PERJETA in combination with trastuzumab and docetaxel were diarrhea, alopecia, neutropenia, nausea, fatigue, rash, and peripheral neuropathy. (6.1)

Neoadjuvant Treatment of Breast Cancer

- The most common adverse reactions (> 30%) with PERJETA in combination with trastuzumab and docetaxel were alopecia, diarrhea, nausea, and neutropenia. (6.1)
- The most common adverse reactions (>30%) with PERJETA in combination with trastuzumab and docetaxel when given for 3 cycles following 3 cycles of FEC were fatigue, alopecia, diarrhea, nausea, vomiting, and neutropenia. (6.1)
- The most common adverse reactions (>30%) with PERJETA in combination with docetaxel, carboplatin, and trastuzumab (TCH) were fatigue, alopecia, diarrhea, nausea, vomiting, neutropenia, thrombocytopenia, and anemia. (6.1)
- The most common adverse reactions (>30%) with PERJETA in combination with trastuzumab and paclitaxel when given for 4 cycles following 4 cycles of ddAC were nausea, diarrhea, alopecia, fatigue, constipation, peripheral neuropathy, and headache. (6.1)
- The most common adverse reactions (>30%) with PERJETA in combination with trastuzumab and docetaxel when given for 4 cycles following 4 cycles of FEC were diarrhea, nausea, alopecia, asthenia, constipation, fatigue, mucosal inflammation, vomiting, myalgia, and anemia. (6.1)

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. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

---------- USE IN SPECIFIC POPULATIONS ----------

Females and Males of Reproductive Potential: Verify the pregnancy status of females prior to initiation of PERJETA. (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 01/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: LEFT VENTRICULAR DYSFUNCTION and EMBRYO-FETAL TOXICITY

- **Left Ventricular Dysfunction: PERJETA can result in subclinical and clinical cardiac failure manifesting as decreased LVEF and CHF. Evaluate cardiac function prior to and during treatment. Discontinue PERJETA treatment for a confirmed clinically significant decrease in left ventricular function *[see Dosage and Administration (2.3), Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.**
- **Embryo-fetal Toxicity: Exposure to PERJETA can result in embryo-fetal death and birth defects. Advise patients of these risks and the need for effective contraception *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.1) (8.3)]*.**

1 INDICATIONS AND USAGE

1.1 Metastatic Breast Cancer (MBC)

PERJETA is indicated for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease *[see Dosage and Administration (2.2) and Clinical Studies (14.1)]*.

1.2 Early Breast Cancer (EBC)

PERJETA is indicated for use in combination with 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 *[see Dosage and Administration (2.2) and Clinical Studies (14.2)]*.
- the adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence *[see Dosage and Administration (2.2) and Clinical Studies (14.3)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients based on HER2 protein overexpression or HER2 gene amplification in tumor specimens *[see Indications and Usage (1) and Clinical Studies (14)]*. Assessment of HER2 protein overexpression and HER2 gene amplification should be performed using FDA-approved tests specific for breast cancer by laboratories with demonstrated proficiency. Information on the FDA-approved tests for the detection of HER2 protein overexpression and HER2 gene amplification is available at: http://www.fda.gov/CompanionDiagnostics.

Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results.

2.2 Recommended Doses and Schedules

The initial dose of PERJETA is 840 mg administered as a 60-minute intravenous infusion, followed every 3 weeks by a dose of 420 mg administered as an intravenous infusion over 30 to 60 minutes.

When administered with PERJETA, the recommended initial dose of trastuzumab is 8 mg/kg administered as a 90-minute intravenous infusion, followed every 3 weeks by a dose of 6 mg/kg administered as an intravenous infusion over 30 to 90 minutes.

When administered with PERJETA, the recommended initial dose of trastuzumab hyaluronidase-oysk is 600 mg/10,000 units (600 mg trastuzumab and 10,000 units hyaluronidase) administered subcutaneously over approximately 2 to 5 minutes once every three weeks irrespective of the patient's body weight.

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

In patients receiving an anthracycline-based regimen, PERJETA and trastuzumab or trastuzumab hyaluronidase-oysk should be administered following completion of the anthracycline.

Metastatic Breast Cancer (MBC)

When administered with PERJETA, the recommended initial dose of docetaxel is 75 mg/m^2 administered as an intravenous infusion. The dose may be escalated to 100 mg/m^2 administered every 3 weeks if the initial dose is well tolerated.

Neoadjuvant Treatment of Breast Cancer

PERJETA should be administered every 3 weeks for 3 to 6 cycles as part of one of the following treatment regimens for early breast cancer *[see Clinical Studies (14.2)]*:

- Four preoperative cycles of PERJETA in combination with trastuzumab or trastuzumab hyaluronidase-oysk and docetaxel followed by 3 postoperative cycles of fluorouracil, epirubicin, and cyclophosphamide (FEC) as given in NeoSphere
- Three or four preoperative cycles of FEC alone followed by 3 or 4 preoperative cycles of PERJETA in combination with docetaxel and trastuzumab or trastuzumab hyaluronidase-oysk as given in TRYPHAENA and BERENICE, respectively
- Six preoperative cycles of PERJETA in combination with docetaxel, carboplatin, and trastuzumab (TCH) or trastuzumab hyaluronidase-oysk (escalation of docetaxel above 75 mg/m^2 is not recommended) as given in TRYPHAENA
- Four preoperative cycles of dose-dense doxorubicin and cyclophosphamide (ddAC) alone followed by 4 preoperative cycles of PERJETA in combination with paclitaxel and trastuzumab or trastuzumab hyaluronidase-oysk as given in BERENICE

Following surgery, patients should continue to receive PERJETA and trastuzumab or trastuzumab hyaluronidase-oysk to complete 1 year of treatment (up to 18 cycles).

Adjuvant Treatment of Breast Cancer

PERJETA should be administered in combination with trastuzumab or trastuzumab hyaluronidase-oysk every 3 weeks for a total of 1 year (up to 18 cycles) or until disease recurrence or unmanageable toxicity, whichever occurs first, as part of a complete regimen for early breast cancer, including standard anthracycline- and/or taxane-based chemotherapy as given in APHINITY. PERJETA and trastuzumab or trastuzumab hyaluronidase-oysk should start on Day 1 of the first taxane-containing cycle *[see Clinical Studies (14.3)]*.

2.3 Dose Modification

For recommendations on delayed or missed doses, please refer to Table 1.

Table 1 Recommendations regarding delayed or missed doses

Time between two sequential doses	PERJETA	Trastuzumab (intravenous)	Trastuzumab hyaluronidase-oysk
< 6 weeks	Administer PERJETA 420 mg intravenously as soon as possible. Do not wait until the next planned dose.	Administer trastuzumab 6 mg/kg intravenously as soon as possible. Do not wait until the next planned dose.	Administer trastuzumab hyaluronidase-oysk 600 mg/10,000 units subcutaneously as soon as possible. Do not wait until the next planned dose.
≥ 6 weeks	Readminister PERJETA loading dose of 840 mg intravenously as a 60 minute infusion, followed by a maintenance dose of 420 mg administered intravenously over a period of 30 to 60 minutes every 3 weeks thereafter.	Readminister trastuzumab loading dose of 8 mg/kg intravenously over approximately 90 minutes, followed by a maintenance dose of 6 mg/kg administered intravenously over a period of 30 or 90 minutes every 3 weeks thereafter.	

PERJETA should be discontinued if trastuzumab or trastuzumab hyaluronidase-oysk treatment is discontinued.

Dose reductions are not recommended for PERJETA.

For chemotherapy dose modifications, see relevant prescribing information.

Left Ventricular Ejection Fraction (LVEF):

Assess left ventricular ejection fraction (LVEF) prior to initiation of PERJETA and at regular intervals during treatment as indicated in Table 2. The recommendations on dose modifications in the event of LVEF dysfunction are also indicated in Table 2 *[see Warnings and Precautions (5.1)]*.

Table 2 Dose Modifications for Left Ventricular Dysfunction

	Pre-treatment LVEF:	Monitor LVEF every:	Withhold PERJETA and trastuzumab or trastuzumab hyaluronidase-oysk for at least 3 weeks for an LVEF decrease to:	Resume PERJETA and trastuzumab or trastuzumab hyaluronidase-oysk after 3 weeks if LVEF has recovered to:
	≥ 50%	~12 weeks	Either	Either

<table>
<tr><td>Metastatic Breast Cancer</td><td></td><td></td><td><40%</td><td>40%-45% with a fall of ≥10%-points below pre-treatment value</td><td>>45%</td><td>40%-45% with a fall of <10%-points below pre-treatment value</td></tr>
<tr><td rowspan="2">Early Breast Cancer</td><td rowspan="2">≥ 55%*</td><td rowspan="2">~12 weeks (once during neoadjuvant therapy)</td><td colspan="2" rowspan="2"><50% with a fall of ≥10%-points below pre-treatment value</td><td colspan="2">Either</td></tr>
<tr><td>≥50%</td><td><10% points below pre-treatment value</td></tr>
</table>

*For patients receiving anthracycline-based chemotherapy, a LVEF of ≥ 50% is required after completion of anthracyclines, before starting PERJETA and trastuzumab or trastuzumab hyaluronidase-oysk.

Infusion-Related Reactions

The infusion rate of PERJETA may be slowed or interrupted if the patient develops an infusion-related reaction *[see Warnings and Precautions (5.3)]*.

Hypersensitivity Reactions/Anaphylaxis

The infusion should be discontinued immediately if the patient experiences a serious hypersensitivity reaction *[see Warnings and Precautions (5.4)]*.

2.4 Preparation for Administration

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

Preparation

Prepare the solution for infusion, using aseptic technique, as follows:

- Parenteral drug products should be inspected visually for particulates and discoloration prior to administration.
- Withdraw the appropriate volume of PERJETA solution from the vial(s).
- Dilute into a 250 mL 0.9% sodium chloride PVC or non-PVC polyolefin infusion bag.
- Mix diluted solution by gentle inversion. Do not shake.
- Administer immediately once prepared.
- If the diluted infusion solution is not used immediately, it can be stored at 2°C to 8°C for up to 24 hours.
- Dilute with 0.9% Sodium Chloride injection only. Do not use dextrose (5%) solution.

3 DOSAGE FORMS AND STRENGTHS

Injection: 420 mg/14 mL (30 mg/mL) in a single-dose vial

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Left Ventricular Dysfunction

Decreases in LVEF have been reported with drugs that block HER2 activity, including PERJETA. Assess LVEF prior to initiation of PERJETA and at regular intervals during treatment to ensure that LVEF is within normal limits. If the LVEF declines and has not improved, or has declined further at the subsequent assessment, discontinuation of PERJETA and trastuzumab should be strongly considered *[Dosage and Administration (2.3)*].

In CLEOPATRA, for patients with MBC, PERJETA in combination with trastuzumab and docetaxel was not associated with increases in the incidence of symptomatic left ventricular systolic dysfunction (LVSD) or decreases in LVEF compared with placebo in combination with trastuzumab and docetaxel *[see Clinical Studies (14.1)]*. Left ventricular dysfunction occurred in 4% of patients in the PERJETA-treated group and 8% of patients in the placebo-treated group. Symptomatic left ventricular systolic dysfunction (congestive heart failure) occurred in 1% of patients in the PERJETA-treated group and 2% of patients in the placebo-treated group *[see Adverse Reactions (6.1)]*. Patients who have received prior anthracyclines or prior radiotherapy to the chest area may be at higher risk of decreased LVEF.

In patients receiving neoadjuvant treatment in NeoSphere, the incidence of LVSD was higher in the PERJETA-treated groups compared to the trastuzumab- and docetaxel-treated group. An increased incidence of LVEF declines was observed in patients treated with PERJETA in combination with trastuzumab and docetaxel. In the overall treatment period, LVEF decline > 10% and a drop to less than 50% occurred in 2% of patients treated with neoadjuvant trastuzumab and docetaxel as compared to 8% of patients treated with neoadjuvant PERJETA in combination with trastuzumab and docetaxel. Left ventricular dysfunction occurred in 0.9% of patients treated with neoadjuvant trastuzumab and docetaxel as compared to 3% of patients treated with neoadjuvant PERJETA in combination with trastuzumab and docetaxel. Symptomatic LVSD occurred in 0.9% of patients treated with neoadjuvant PERJETA in combination with trastuzumab and no patients in the other 3 arms. LVEF recovered to ≥ 50% in all patients.

In patients receiving neoadjuvant PERJETA in TRYPHAENA, in the overall treatment period, LVEF decline > 10% and a drop to less than 50% occurred in 7% of patients treated with PERJETA plus trastuzumab and FEC followed by PERJETA plus trastuzumab and docetaxel, 16% of patients treated with PERJETA plus trastuzumab and docetaxel following FEC, and 11% of patients treated with PERJETA in combination with TCH. Left ventricular dysfunction occurred in 6% of patients treated with PERJETA plus trastuzumab and FEC followed by PERJETA plus trastuzumab and docetaxel, 4% of patients treated with PERJETA plus trastuzumab and docetaxel following FEC, and 3% of patients treated with PERJETA in combination with TCH. Symptomatic LVSD occurred in 4% of patients treated with PERJETA plus trastuzumab and docetaxel following FEC, 1% of patients treated with PERJETA in combination with TCH, and none of the patients treated with PERJETA plus trastuzumab and FEC followed by PERJETA plus trastuzumab and docetaxel. LVEF recovered to ≥ 50% in all but one patient.

In patients receiving neoadjuvant PERJETA in BERENICE, in the neoadjuvant period, LVEF decline ≥ 10% and a drop to less than 50% as measured by ECHO/MUGA assessment occurred

in 7% of patients treated with PERJETA plus trastuzumab and paclitaxel following ddAC, and 2% of patients treated with PERJETA plus trastuzumab and docetaxel following FEC. Ejection fraction decreased (asymptomatic LVD) occurred in 7% of patients treated with PERJETA plus trastuzumab and paclitaxel following ddAC and 4% of the patients treated with PERJETA plus trastuzumab and docetaxel following FEC in the neoadjuvant period. Symptomatic LVSD (NYHA Class III/IV Congestive Heart Failure) occurred in 2% of patients treated with PERJETA plus trastuzumab and paclitaxel following ddAC and none of the patients treated with PERJETA plus trastuzumab and docetaxel following FEC in the neoadjuvant period.

In patients receiving adjuvant PERJETA in APHINITY, the incidence of symptomatic heart failure (NYHA Class III/IV) with a LVEF decline ≥ 10% and a drop to less than 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 (NYHA Class II) declines in LVEF ≥ 10% and a drop to less than 50% were reported in 3% of PERJETA-treated patients and 3% of placebo-treated patients, of whom 80% of PERJETA-treated patients and 81% of placebo-treated patients recovered at the data cutoff.

PERJETA has not been studied in patients with a pretreatment LVEF value of < 50%, a prior history of CHF, decreases in LVEF to < 50% during prior trastuzumab therapy, or conditions that could impair left ventricular function such as uncontrolled hypertension, recent myocardial infarction, serious cardiac arrhythmia requiring treatment or a cumulative prior anthracycline exposure to > 360 mg/m^2 of doxorubicin or its equivalent.

5.2 Embryo-Fetal Toxicity

Based on its mechanism of action and findings in animal studies, PERJETA can cause fetal harm when administered to a pregnant woman. PERJETA is a HER2/neu receptor antagonist. Cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death have been reported with use of another HER2/neu receptor antagonist (trastuzumab) during pregnancy. In an animal reproduction study, administration of pertuzumab to pregnant cynomolgus monkeys during the period of organogenesis resulted in oligohydramnios, delayed fetal kidney development, and embryo-fetal death at exposures 2.5 to 20 times the exposure in humans at the recommended dose, based on C_{max}.

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 *[see Use in Specific Populations (8.1, 8.3)]*.

5.3 Infusion-Related Reactions

PERJETA has been associated with infusion reactions, including fatal events. *[see Adverse Reactions (6.1)]*. An infusion reaction was defined in CLEOPATRA as any event described as hypersensitivity, anaphylactic reaction, acute infusion reaction, or cytokine release syndrome occurring during an infusion or on the same day as the infusion. The initial dose of PERJETA

was given the day before trastuzumab and docetaxel to allow for the examination of PERJETA-associated reactions. 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 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 NeoSphere, TRYPHAENA, and APHINITY, PERJETA was administered on the same day as the other study treatment drugs. For APHINITY, infusion-related reactions occurred in 21% of patients on the first day of PERJETA administration (in combination with trastuzumab and chemotherapy) and in 18% of patients in the placebo arm. The incidence of Grade 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.

Observe patients closely for 60 minutes after the first infusion and for 30 minutes after subsequent infusions of PERJETA. If a significant infusion-related reaction occurs, slow or interrupt the infusion, and administer appropriate medical therapies. Monitor patients carefully until complete resolution of signs and symptoms. Consider permanent discontinuation in patients with severe infusion reactions *[see Dosage and Administration (2.2)]*.

5.4 Hypersensitivity Reactions/Anaphylaxis

In CLEOPATRA, the overall frequency of hypersensitivity/anaphylaxis reactions was 11% in the PERJETA-treated group and 9% in the placebo-treated group. The incidence of Grade 3 – 4 hypersensitivity/anaphylaxis reactions was 2% in the PERJETA-treated group and 3% in the placebo-treated group according to NCI - CTCAE v3.0. Overall, 4 patients in the PERJETA-treated group and 2 patients in the placebo-treated group experienced anaphylaxis.

In NeoSphere, TRYPHAENA, BERENICE, and APHINITY, hypersensitivity/anaphylaxis events were consistent with those observed in CLEOPATRA. In NeoSphere, two patients in the PERJETA- and docetaxel-treated group experienced anaphylaxis. In APHINITY, the overall frequency of hypersensitivity/anaphylaxis was 5% in the PERJETA treated group vs. 4% in the placebo-treated group. The incidence was highest in the PERJETA plus TCH treated group (8%) of which 1% were NCI-CTCAE (v4.0) Grade 3 – 4.

Patients should be observed closely for hypersensitivity reactions. Severe hypersensitivity, including anaphylaxis and fatal events, have been observed in patients treated with PERJETA *[see Clinical Trials Experience (6.1)]*. Angioedema has been described in post-marketing reports. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. PERJETA is contraindicated in patients with known hypersensitivity to pertuzumab or to any of its excipients *[see Contraindications (4)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Left Ventricular Dysfunction *[see Warnings and Precautions (5.1)]*
- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.2)]*
- Infusion-Related Reactions *[see Warnings and Precautions (5.3)]*
- Hypersensitivity Reactions/Anaphylaxis *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Metastatic Breast Cancer (MBC)

The adverse reactions described in Table 3 were identified in 804 patients with HER2-positive metastatic breast cancer treated in CLEOPATRA. Patients were randomized to receive either PERJETA in combination with trastuzumab and docetaxel or placebo in combination with trastuzumab and docetaxel. The median duration of study treatment was 18.1 months for patients in the PERJETA-treated group and 11.8 months for patients in the placebo-treated group. No dose adjustment was permitted for PERJETA or trastuzumab. Adverse reactions resulting in permanent discontinuation of all study therapy were 6% in the PERJETA-treated group and 5% for patients in the placebo-treated group. The most common adverse reactions (>1%) that led to discontinuation of all study therapy was left ventricular dysfunction (1% for patients in the PERJETA-treated group and 2% for patients in the placebo-treated group). The most common adverse reactions that led to discontinuation of docetaxel alone were edema, fatigue, edema peripheral, neuropathy peripheral, neutropenia, nail disorder and pleural effusion. Table 3 reports the adverse reactions that occurred in at least 10% of patients in the PERJETA-treated group. The safety profile of PERJETA remained unchanged with an additional 2.75 years of follow-up (median total follow-up of 50 months) in CLEOPATRA.

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 Grade 3 – 4 adverse reactions (> 2%) were neutropenia, febrile neutropenia, leukopenia, diarrhea, peripheral neuropathy, anemia, asthenia, and fatigue. An increased incidence of febrile neutropenia was observed for Asian patients in both treatment arms compared with patients of other races and from other geographic regions. Among Asian patients, the incidence of febrile neutropenia was higher in the pertuzumab-treated group (26%) compared with the placebo-treated group (12%).

Table 3 Summary of Adverse Reactions Occurring in ≥ 10% of Patients on the PERJETA Treatment Arm in CLEOPATRA

Body System/ Adverse Reactions	PERJETA + trastuzumab + docetaxel n=407 Frequency rate %		Placebo + trastuzumab + docetaxel n=397 Frequency rate %	
	All Grades %	Grades 3 – 4 %	All Grades %	Grades 3 – 4 %
General disorders and administration site conditions				
Fatigue	37	2	37	3
Mucosal inflammation	28	1	20	1
Asthenia	26	2	30	2
Edema peripheral	23	0.5	30	0.8
Pyrexia	19	1	18	0.5
Skin and subcutaneous tissue disorders				
Alopecia	61	0	60	0.3
Rash	34	0.7	24	0.8
Nail disorder	23	1	23	0.3
Pruritus	14	0	10	0
Dry skin	11	0	4	0
Gastrointestinal disorders				
Diarrhea	67	8	46	5
Nausea	42	1	42	0.5
Vomiting	24	1	24	2
Stomatitis	19	0.5	15	0.3
Constipation	15	0	25	1
Blood and lymphatic system disorders				
Neutropenia	53	49	50	46
Anemia	23	2	19	4
Leukopenia	18	12	20	15
Febrile neutropenia*	14	13	8	7
Nervous system disorders				
Neuropathy peripheral	32	3	34	2
Headache	21	1	17	0.5

Dysgeusia	18	0	16	0
Dizziness	13	0.5	12	0
Musculoskeletal and connective tissue disorders				
Myalgia	23	1	24	0.8
Arthralgia	15	0.2	16	0.8
Infections and infestations				
Upper respiratory tract infection	17	0.7	13	0
Nasopharyngitis	12	0	13	0.3
Respiratory, thoracic, and mediastinal disorders				
Dyspnea	14	1	16	2
Metabolism and nutrition disorders				
Decreased appetite	29	2	26	2
Eye disorders				
Lacrimation increased	14	0	14	0
Psychiatric disorders				
Insomnia	13	0	13	0

* In this table this denotes an adverse reaction that has been reported in association with a fatal outcome

The following clinically relevant adverse reactions were reported in < 10% of patients in the PERJETA-treated group in CLEOPATRA:

Infections and infestations: Paronychia (7% in the PERJETA-treated group vs. 4% in the placebo-treated group)

Adverse Reactions Reported in Patients Receiving PERJETA and Trastuzumab After Discontinuation of Docetaxel

In CLEOPATRA, adverse reactions were reported less frequently after discontinuation of docetaxel treatment. All adverse reactions in the PERJETA and trastuzumab treatment group occurred in < 10% of patients with the exception of diarrhea (19%), upper respiratory tract infection (13%), rash (12%), headache (11%), and fatigue (11%).

Neoadjuvant Treatment of Breast Cancer (NeoSphere)

In NeoSphere, the most common adverse reactions seen with PERJETA in combination with trastuzumab and docetaxel administered for 4 cycles were similar to those seen in the PERJETA-treated group in CLEOPATRA. The most common adverse reactions (> 30%) were alopecia, neutropenia, diarrhea, and nausea. The most common NCI – CTCAE v3.0 Grade 3 – 4 adverse reactions (> 2%) were neutropenia, febrile neutropenia, leukopenia, and diarrhea. In this group, one patient permanently discontinued neoadjuvant treatment due to an adverse event. Table 4 reports the adverse reactions that occurred in patients who received neoadjuvant treatment with PERJETA for breast cancer in NeoSphere.

Table 4 Summary of Adverse Reactions Occurring in ≥ 10% in the Neoadjuvant Setting for Patients Receiving PERJETA in NeoSphere

Body System/ Adverse Reactions	Trastuzumab + docetaxel n=107 Frequency rate %		PERJETA + trastuzumab + docetaxel n=107 Frequency rate %		PERJETA + trastuzumab n=108 Frequency rate %		PERJETA + docetaxel n=108 Frequency rate %	
	All Grades %	Grades 3 – 4 %	All Grades %	Grades 3 – 4 %	All Grades %	Grades 3 – 4 %	All Grades %	Grades 3 – 4 %
General disorders and administration site conditions								
Fatigue	27	0	26	0.9	12	0	26	1
Mucosal inflammation	21	0	26	2	3	0	26	0
Asthenia	18	0	21	2	3	0	16	2
Pyrexia	10	0	17	0	8	0	9	0
Edema peripheral	10	0	3	0	0.9	0	5	0
Skin and subcutaneous tissue disorders								
Alopecia	66	0	65	0	3	0	67	0
Rash	21	2	26	0.9	11	0	29	1
Gastrointestinal disorders								
Diarrhea	34	4	46	6	28	0	54	4
Nausea	36	0	39	0	14	0	36	1
Stomatitis	7	0	18	0	5	0	10	0
Vomiting	12	0	13	0	5	0	16	2
Blood and lymphatic system disorders								
Neutropenia	64	59	50	45	0.9	0.9	65	57
Leukopenia	21	11	9	5	0	0	14	9
Nervous system disorders								
Dysgeusia	10	0	15	0	5	0	7	0
Headache	11	0	11	0	14	0	13	0
Peripheral Sensory Neuropathy	12	0.9	8	0.9	2	0	11	0
Musculoskeletal and connective tissue disorders								
Myalgia	22	0	22	0	9	0	21	0
Arthralgia	8	0	10	0	5	0	10	0
Metabolism and nutrition disorders								
Decreased appetite	7	0	14	0	2	0	15	0

Psychiatric disorders								
Insomnia	11	0	8	0	4	0	9	0

The following adverse reactions were reported in < 10% of patients receiving neoadjuvant treatment and occurred more frequently in PERJETA-treated groups in NeoSphere: (Ptz=pertuzumab; H=trastuzumab; D=docetaxel)

Blood and lymphatic system disorders: Anemia (7% in the H+D arm, 3% in the Ptz+H+D arm, 5% in the Ptz+H arm and 9% in the Ptz+D arm), Febrile neutropenia (7% in the H+D arm, 8% in the Ptz+H+D arm, 0% in the Ptz+H arm and 7% in the Ptz+D arm)

Nervous system disorders: Dizziness (4% in the H+D arm, 3% in the Ptz+H+D arm, 6% in the Ptz+H arm and 3% in the Ptz+D arm)

Infections and infestations: Upper respiratory tract infection (3% in the H+D arm, 5% in the Ptz+H+D arm, 2% in the Ptz+H arm and 7% in the Ptz+D arm)

Eye disorders: Lacrimation increased (2% in the H+D arm, 4% in the Ptz+H+D arm, 0.9% in the Ptz+H arm, and 4% in the Ptz+D arm)

Neoadjuvant Treatment of Breast Cancer (TRYPHAENA)

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

Similarly, when PERJETA was administered in combination with docetaxel, carboplatin, and trastuzumab (TCH) for 6 cycles, the most common adverse reactions (> 30%) were diarrhea, alopecia, neutropenia, nausea, fatigue, vomiting, anemia, and thrombocytopenia. The most common NCI-CTCAE (version 3) Grade 3 – 4 adverse reactions (> 2%) were neutropenia, febrile neutropenia, anemia, leukopenia, diarrhea, thrombocytopenia, vomiting, fatigue, ALT increased, hypokalemia, and hypersensitivity.

Adverse reactions resulting in permanent discontinuation of any component of neoadjuvant treatment occurred in 7% of patients receiving PERJETA in combination with trastuzumab and docetaxel following FEC, and 8% for patients receiving PERJETA in combination with TCH. The most common adverse reactions (>2%) resulting in permanent discontinuation of PERJETA were left ventricular dysfunction, drug hypersensitivity, and neutropenia. Table 5 reports the adverse reactions that occurred in patients who received neoadjuvant treatment with PERJETA for breast cancer in TRYPHAENA.

Table 5 Summary of Adverse Reactions Occurring in ≥ 10% of Patients Receiving Neoadjuvant Treatment with PERJETA in TRYPHAENA

Body System/Adverse Reactions	PERJETA + trastuzumab + FEC followed by PERJETA + trastuzumab + docetaxel n=72 Frequency rate %		PERJETA + trastuzumab + docetaxel following FEC n=75 Frequency rate %		PERJETA + TCH n=76 Frequency rate %	
	All Grades %	Grades 3 – 4 %	All Grades %	Grades 3 – 4 %	All Grades %	Grades 3 – 4 %
General disorders and administration site conditions						
Fatigue	36	0	36	0	42	4
Mucosal inflammation	24	0	20	0	17	1
Pyrexia	17	0	9	0	16	0
Asthenia	10	0	15	1	13	1
Edema peripheral	11	0	4	0	9	0
Skin and subcutaneous tissue disorders						
Alopecia	49	0	52	0	55	0
Rash	19	0	11	0	21	1
Palmar-Plantar Erythrodysaesthesia Syndrome	7	0	11	0	8	0
Dry skin	6	0	9	0	11	0
Gastrointestinal disorders						
Diarrhea	61	4	61	5	72	12
Nausea	53	0	53	3	45	0
Vomiting	40	0	36	3	39	5
Dyspepsia	25	1	8	0	22	0
Constipation	18	0	23	0	16	0
Stomatitis	14	0	17	0	12	0
Blood and lymphatic system disorders						
Neutropenia	51	47	47	43	49	46

Leukopenia	22	19	16	12	17	12
Anemia	19	1	9	4	38	17
Febrile neutropenia	18	18	9	9	17	17
Thrombocytopenia	7	0	1	0	30	12
Immune system disorders						
Hypersensitivity	10	3	1	0	12	3
Nervous system disorders						
Headache	22	0	15	0	17	0
Dysgeusia	11	0	13	0	21	0
Dizziness	8	0	8	1	16	0
Neuropathy peripheral	6	0	1	0	11	0
Musculoskeletal and connective tissue disorders						
Myalgia	17	0	11	1	11	0
Arthralgia	11	0	12	0	7	0
Respiratory, thoracic, and mediastinal disorders						
Dyspnea	13	0	8	3	11	1
Epistaxis	11	0	11	0	16	1
Cough	10	0	5	0	12	0
Oropharyngeal pain	8	0	7	0	12	0
Metabolism and nutrition disorders						
Decreased appetite	21	0	11	0	21	0
Eye disorders						
Lacrimation increased	13	0	5	0	8	0
Psychiatric disorders						
Insomnia	11	0	13	0	21	0
Investigations						
ALT increased	7	0	3	0	11	4

FEC=5-fluorouracil, epirubicin, cyclophosphamide, TCH=docetaxel, carboplatin, trastuzumab

The following selected adverse reactions were reported in < 10% of patients receiving neoadjuvant treatment in TRYPHAENA: (Ptz=pertuzumab; H=trastuzumab; D=docetaxel; FEC= fluorouracil, epirubicin, and cyclophosphamide; TCH=docetaxel, carboplatin, and trastuzumab)

Skin and subcutaneous tissue disorders: Nail disorder (10% in the Ptz+H+FEC/Ptz+H+D arm, 7% in the FEC/Ptz+H+D arm, and 9% in the Ptz+TCH arm), Paronychia (0% in the Ptz+H+FEC/Ptz+H+D arm, and 1% in both the FEC/Ptz+H+D and Ptz+TCH arms), Pruritus

(3% in the Ptz+H+FEC/Ptz+H+D arm, 4% in the FEC/Ptz+H+D arm, and 4% in the Ptz+TCH arm)

Infections and infestations: Upper respiratory tract infection (8.3% in the Ptz+H+FEC/Ptz+H+D arm, 4.0% in the FEC/Ptz+H+D arm, and 2.6% in the Ptz+TCH arm), Nasopharyngitis (6.9% in the Ptz+H+FEC/Ptz+H+D arm, 6.7% in the FEC/Ptz+H+D arm, and 7.9% in the Ptz+TCH arm)

Neoadjuvant Treatment of Breast Cancer (BERENICE)

In BERENICE, when PERJETA was administered in combination with trastuzumab and paclitaxel for 4 cycles following 4 cycles of ddAC, the most common adverse reactions (> 30%) were nausea, diarrhea, alopecia, fatigue, constipation, peripheral neuropathy and headache. The most common Grade 3 – 4 adverse reactions (> 2%) were neutropenia, febrile neutropenia, neutrophil count decreased, white blood cell count decreased, anemia, diarrhea, peripheral neuropathy, alanine aminotransferase increased and nausea.

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

Adverse reactions resulting in permanent discontinuation of any component of neoadjuvant treatment were 14% for patients receiving PERJETA in combination with trastuzumab and paclitaxel following ddAC and 8% for patients receiving PERJETA in combination with trastuzumab and docetaxel following FEC. The most common adverse reactions (>1%) resulting in permanent discontinuation of any component of neoadjuvant treatment were neuropathy peripheral, ejection fraction decreased, diarrhea, neutropenia and infusion related reaction. Table 6 reports the adverse reactions that occurred in patients who received neoadjuvant treatment with PERJETA for breast cancer in BERENICE.

Table 6 Summary of Adverse Reactions Occurring in ≥ 10% of Patients Receiving Neoadjuvant Treatment with PERJETA in BERENICE

Body System/Adverse Reactions	**PERJETA + trastuzumab + paclitaxel following ddAC n=199 Frequency rate %**		**PERJETA + trastuzumab + docetaxel following FEC n=198 Frequency rate %**	
	All Grades %	**Grades 3 – 4 %**	**All Grades %**	**Grades 3 – 4 %**
General disorders and administration site conditions				
Fatigue	58	1	38	5
Asthenia	19	2	41	0

Mucosal inflammation	22	1	37	4
Pyrexia	15	0	18	0
Edema peripheral	9	0	12	1
Skin and subcutaneous tissue disorders				
Alopecia	62	0	59	0
Rash	14	0	11	0
Dry skin	14	0	10	0
Nail discoloration	15	0	2	0
Palmar-Plantar Erythrodysaesthesia Syndrome	6	0	10	0.5
Gastrointestinal disorders				
Nausea	71	3	69	2
Diarrhea	67	3	69	10
Constipation	35	0.5	38	0.5
Vomiting	23	1	35	4
Stomatitis	25	0	27	5
Dyspepsia	19	0	16	0
Abdominal pain upper	6	0	13	0
Abdominal pain	5	0	10	0
Gastroesophageal reflux disease	12	0	2	0
Blood and lymphatic system disorders				
Anemia	27	3	30	3
Neutropenia	22	12	16	9
Febrile neutropenia	7	7	17	17
Nervous system disorders				
Headache	30	0.5	14	0.5
Dysgeusia	20	0	19	0.5
Neuropathy peripheral	42	3	26	0.5
Paresthesia	15	0	9	0
Dizziness	12	0	8	0
Musculoskeletal and connective tissue disorders				
Myalgia	20	0	33	1
Arthralgia	20	0	21	1
Back pain	10	0	9	0
Pain in extremity	10	0	8	0
Bone pain	12	0.5	5	0
Infections and infestations				
Urinary tract infection	11	1	2	0
Respiratory, thoracic, and mediastinal disorders				
Epistaxis	25	0	19	0
Dyspnea	15	0.5	15	0.5
Cough	20	0.5	9	0
Oropharyngeal pain	10	0	8	0.5
Metabolism and nutrition disorders				
Decreased appetite	20	0	23	0

Eye disorders				
Lacrimation increased	9	0	18	0
Psychiatric disorders				
Insomnia	19	0	13	0
Vascular disorders				
Hot flush	19	0	13	0
Investigations				
White blood cell count decreased	11	4	3	2
Injury, poisoning and procedural complications				
Infusion related reaction	16	1	13	1

ddAC = dose-dense doxorubicin, cyclophosphamide, FEC=5-fluorouracil, epirubicin, cyclophosphamide

The following selected adverse reactions were reported in < 10% of patients receiving neoadjuvant treatment in BERENICE: (Ptz=pertuzumab; H=trastuzumab; P=paclitaxel; ddAC=dose-dense doxorubicin and cyclophosphamide; D=docetaxel; FEC= fluorouracil, epirubicin, and cyclophosphamide)

Skin and Subcutaneous tissue disorders: Pruritus (9% in the ddAC/Ptz+H+P arm, and 8% in the FEC/Ptz+H+D arm), Nail disorder (7% in the ddAC/Ptz+H+P arm, and 10% in the FEC/Ptz+H+D arm)

Infections and infestations: Upper respiratory tract infection (7% in the ddAC/Ptz+H+P arm, and 2% in the FEC/Ptz+H+D arm), nasopharyngitis (7% in the ddAC/Ptz+H+P arm, and 9% in the FEC/Ptz+H+D arm), paronychia (0.5% in the ddAC/Ptz+H+P arm, and 1% in the FEC/Ptz+H+D arm)

Adjuvant Treatment of Breast Cancer (APHINITY)

The adverse reactions described in Table 7 were identified in 4769 patients with HER2-positive early breast cancer treated in APHINITY. Patients were randomized to receive either PERJETA in combination with trastuzumab and chemotherapy or placebo in combination with trastuzumab and chemotherapy.

Adverse reactions resulting in permanent discontinuation of any study therapy were 13% for patients in the PERJETA-treated group and 12% for patients in the placebo-treated group. Adverse reactions resulting in permanent discontinuation of PERJETA or placebo was 7% and 6%, respectively. The most common adverse reactions (>0.5%) resulting in permanent discontinuation of any study treatment were ejection fraction decreased, neuropathy peripheral, diarrhea, and cardiac failure. Table 7 reports the adverse reactions that occurred in at least 10% of patients in the PERJETA-treated group.

When PERJETA was administered in combination with trastuzumab and chemotherapy, the most common adverse reactions (> 30%) were diarrhea, nausea, alopecia, fatigue, peripheral neuropathy, and vomiting. The most common Grade 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. The median duration of all Grades diarrhea was 8 days for the PERJETA-treated group vs. 6 days for the placebo-treated group. The median duration of Grade ≥3 diarrhea was 20 days for the PERJETA-treated group vs. 8 days for the placebo-treated group. More patients required hospitalization for diarrhea as a serious adverse event in the PERJETA-treated group (2.4%) than in the placebo-treated group (0.7%).

Table 7 Summary of Adverse Reactions Occurring in ≥ 10% of Patients Receiving Adjuvant Treatment with PERJETA in APHINITY

Body System/ Adverse Reactions	**PERJETA + trastuzumab + chemotherapy n=2364 Frequency rate %**		**Placebo + trastuzumab + chemotherapy n=2405 Frequency rate %**	
	All Grades %	**Grades 3 – 4 %**	**All Grades %**	**Grades 3 – 4 %**
General disorders and administration site conditions				
Fatigue	49	4	44	3
Mucosal inflammation	23	2	19	0.7
Asthenia	21	1	21	2
Pyrexia	20	0.6	20	0.7
Edema peripheral	17	0	20	0.2
Skin and subcutaneous tissue disorders				
Alopecia	67	<0.1	67	<0.1
Rash	26	0.4	20	0.2
Pruritus	14	0.1	9	<0.1
Dry skin	13	0.1	11	<0.1
Nail disorder	12	0.2	12	0.1
Gastrointestinal disorders				
Diarrhea	71	10	45	4
Nausea	69	2	65	2
Vomiting	32	2	30	2
Constipation	29	0.5	32	0.3
Stomatitis	28	2	24	1
Dyspepsia	14	0	14	0
Abdominal pain	12	0.5	11	0.6
Abdominal pain upper	10	0.3	9	0.2
Blood and lymphatic system disorders				
Anemia	28	7	23	5
Neutropenia	25	16	23	16
Febrile neutropenia*	12	12	11	11
Nervous system disorders				

Dysgeusia	26	0.1	22	<0.1
Neuropathy peripheral	33	1	32	1
Headache	22	0.3	23	0.4
Paresthesia	12	0.5	10	0.2
Dizziness	11	0	11	0.2
Musculoskeletal and connective tissue disorders				
Arthralgia	29	0.9	33	1
Myalgia	26	0.9	30	1
Pain in extremity	10	0.2	10	0.2
Infections and infestations				
Nasopharyngitis	13	<0.1	12	0.1
Respiratory, thoracic, and mediastinal disorders				
Epistaxis	18	<0.1	14	0
Cough	16	<0.1	15	<0.1
Dyspnea	12	0.4	12	0.5
Metabolism and nutrition disorders				
Decreased appetite	24	0.8	20	0.4
Vascular disorders				
Hot flush	20	0.2	21	0.4
Eye disorders				
Lacrimation increased	13	0	13	<0.1
Psychiatric disorders				
Insomnia	17	0.3	17	<0.1
Investigations				
Neutrophil count decreased	14	10	14	10
Injury, poisoning and procedural complications				
Radiation skin injury	13	0.3	11	0.3

* In this table this denotes an adverse reaction that has been reported in association with a fatal outcome

For the adverse reactions that were reported in ≥10% of patients with at least 5% difference between the PERJETA-treated group and the placebo-treated group in APHINITY, the breakdown per chemotherapy regimen is provided: (Ptz=pertuzumab; H=trastuzumab; AC=anthracyclines; TCH=docetaxel, carboplatin, and trastuzumab)

Gastrointestinal disorders: Diarrhea (67% in the Ptz+H+AC chemo arm, 85% in the Ptz+TCH arm, 41% in the Pla+H+AC chemo arm, 62% in the Pla+TCH arm)

Skin and subcutaneous disorders: Rash (26% in the Ptz+H+AC chemo arm, 25% in the Ptz+TCH arm, 21% in the Pla+H+AC chemo arm, 19% in the Pla+TCH arm), Pruritus (14% in the Ptz+H+AC chemo arm, 15% in the Ptz+TCH arm, 9% in the Pla+H+AC chemo arm, 9% in the Pla+TCH arm)

The following clinically relevant adverse reactions were reported in < 10% of patients in the PERJETA-treated group in APHINITY:

Blood and lymphatic system disorders: Leukopenia (9% in the PERJETA-treated group vs. 9% in the placebo-treated group)

Infections and infestations: Upper respiratory tract infection (8% in the PERJETA-treated group vs. 7% in the placebo-treated group), paronychia (4% in the PERJETA-treated group vs. 2% in the placebo-treated group)

Adverse Reactions Reported in Patients Receiving PERJETA and Trastuzumab After Discontinuation of Chemotherapy

In the APHINITY study, during the targeted treatment alone phase, all adverse reactions in the PERJETA treatment group occurred in < 10% of patients with the exception of diarrhea (18%), arthralgia (15%), radiation skin injury (12%), and hot flush (12%).

6.2 Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to pertuzumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Patients in CLEOPATRA were tested at multiple time-points for antibodies to PERJETA. 3% (13/389) of patients in the PERJETA-treated group and 7% (25/372) of patients in the placebo-treated group tested positive for anti-PERJETA antibodies. Of these 38 patients, none experienced anaphylactic/hypersensitivity reactions that were clearly related to the anti-drug antibodies (ADA). The presence of pertuzumab in patient serum at the levels expected at the time of ADA sampling can interfere with the ability of this assay to detect anti-pertuzumab antibodies. In addition, the assay may be detecting antibodies to trastuzumab. As a result, data may not accurately reflect the true incidence of anti-pertuzumab antibody development.

In the neoadjuvant period of BERENICE, 0.3% (1/383) of patients treated with PERJETA tested positive for anti-PERJETA antibodies. This patient did not experience any anaphylactic/hypersensitivity reactions.

6.3 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of PERJETA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Tumor lysis syndrome (TLS): Cases of possible TLS have been reported in patients treated with PERJETA. Patients with significant tumor burden (e.g., bulky metastases) may be at a higher risk. Patients could present with hyperuricemia, hyperphosphatemia, and acute renal failure which may represent possible TLS. Providers should consider additional monitoring and/or treatment as clinically indicated.

7 DRUG INTERACTIONS

No drug-drug interactions were observed between pertuzumab and trastuzumab, or between pertuzumab and docetaxel, paclitaxel, or carboplatin.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Pharmacovigilance Program

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, health care providers and patients should immediately report PERJETA exposure to Genentech at 1-888-835-2555.

Risk Summary

Based on its mechanism of action and findings in animal studies, PERJETA can cause fetal harm when administered to a pregnant woman. There are no available data on the use of PERJETA in pregnant women. However, in post-marketing reports, use of another HER2/neu receptor antagonist (trastuzumab) during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. In an animal reproduction study, administration of pertuzumab to pregnant cynomolgus monkeys during the period of organogenesis resulted in oligohydramnios, delayed fetal kidney development, and embryo-fetal deaths at clinically relevant exposures that were 2.5 to 20-fold greater than exposures in humans receiving the recommended dose, based on C_{max} *[see Data]*. Apprise the patient of the potential risks to a fetus. There are clinical considerations if PERJETA in combination with trastuzumab is used during pregnancy or within 7 months prior to conception *[see Clinical Considerations]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Monitor women who received PERJETA in combination with trastuzumab during pregnancy or within 7 months prior to conception for oligohydramnios. If oligohydramnios occurs, perform fetal testing that is appropriate for gestational age and consistent with community standards of care.

Data

Animal Data

Pregnant cynomolgus monkeys were treated on Gestational Day (GD)19 with loading doses of 30 to 150 mg/kg pertuzumab, followed by bi-weekly doses of 10 to 100 mg/kg. These dose levels resulted in clinically relevant exposures of 2.5 to 20-fold greater than exposures in humans receiving the recommended dose, based on C_{max}. Intravenous administration of pertuzumab from GD19 through GD50 (period of organogenesis) was embryotoxic, with dose-dependent increases in embryo-fetal death between GD25 to GD70. The incidences of embryo-fetal loss were 33, 50, and 85% for dams treated with bi-weekly pertuzumab doses of 10, 30, and 100 mg/kg, respectively (2.5 to 20-fold greater than the recommended human dose, based on C_{max}). At Caesarean section on GD100, oligohydramnios, decreased relative lung and kidney weights, and microscopic evidence of renal hypoplasia consistent with delayed renal

development were identified in all pertuzumab dose groups. Pertuzumab exposure was reported in offspring from all treated groups, at levels of 29% to 40% of maternal serum levels at GD100.

8.2 Lactation

Risk Summary

There is no information regarding the presence of pertuzumab in human milk, the effects on the breastfed infant or the effects on milk production. Published data suggest that human IgG is present in human milk but does not enter the neonatal and infant circulation in substantial amounts. Consider the developmental and health benefits of breast feeding along with the mother's clinical need for PERJETA treatment and any potential adverse effects on the breastfed child from PERJETA or from the underlying maternal condition. This consideration should also take into account the elimination half-life of pertuzumab and the trastuzumab wash out period of 7 months.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to the initiation of PERJETA.

Contraception

Females

Based on the mechanism of action and animal data, PERJETA can cause embryo-fetal harm when administered during pregnancy. 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 *[see Use in Specific Populations (8.1)]*.

8.4 Pediatric Use

The safety and effectiveness of PERJETA have not been established in pediatric patients.

8.5 Geriatric Use

In studies in the indicated populations, CLEOPATRA, NeoSphere, TRYPHAENA, BERENICE, and APHINITY, 464 patients who received PERJETA were ≥65 years of age and 47 were ≥75 years of age. The most common (≥10%) Grade 3-4 adverse reactions in both age groups were neutropenia (22% ≥65 years, 23% ≥75 years), febrile neutropenia (12% ≥65 years, 13% ≥75 years), diarrhea (15% ≥65 years, 17% ≥75 years) and anemia (15% ≥75 years).

The incidence of the following all grade adverse events was at least 5% higher in patients aged ≥65 years of age, compared to patients aged < 65 years of age: decreased appetite (13% higher), anemia (7% higher), weight decreased (7% higher), asthenia (7% higher), dysgeusia (7% higher), neuropathy peripheral and hypomagnesemia (both 5% higher).

No overall differences in efficacy of PERJETA were observed in patients aged ≥65 and <65 years of age. There are too few patients aged ≥75 years to draw conclusions on efficacy in this age group.

Based on a population pharmacokinetic analysis, no significant difference was observed in the pharmacokinetics of pertuzumab between patients < 65 years (n=306) and patients ≥ 65 years (n=175).

8.6 Renal Impairment

Dose adjustments of PERJETA are not needed in patients with mild (creatinine clearance [CLcr] 60 to 90 mL/min) or moderate (CLcr 30 to 60 mL/min) renal impairment. No dose adjustment can be recommended for patients with severe renal impairment (CLcr less than 30 mL/min) because of the limited pharmacokinetic data available *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of pertuzumab.

11 DESCRIPTION

Pertuzumab is a recombinant humanized monoclonal antibody that targets the extracellular dimerization domain (Subdomain II) of the human epidermal growth factor receptor 2 protein (HER2). Pertuzumab is produced by recombinant DNA technology in a mammalian cell (Chinese Hamster Ovary) culture that may contain the antibiotic, gentamicin. Gentamicin is not detectable in the final product. Pertuzumab has an approximate molecular weight of 148 kDa.

PERJETA injection is a sterile, clear to slightly opalescent, colorless to pale brown liquid for intravenous infusion. Each single-dose vial contains 420 mg of pertuzumab at a concentration of 30 mg/mL in 20 mM L-histidine acetate (pH 6.0), 120 mM sucrose and 0.02% polysorbate 20.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pertuzumab targets the extracellular dimerization domain (Subdomain II) of the human epidermal growth factor receptor 2 protein (HER2) and, thereby, blocks ligand-dependent heterodimerization of HER2 with other HER family members, including EGFR, HER3, and HER4. As a result, pertuzumab inhibits ligand-initiated intracellular signaling through two major signal pathways, mitogen-activated protein (MAP) kinase, and phosphoinositide 3-kinase (PI3K). Inhibition of these signaling pathways can result in cell growth arrest and apoptosis, respectively. In addition, pertuzumab mediates antibody-dependent cell-mediated cytotoxicity (ADCC).

While pertuzumab alone inhibited the proliferation of human tumor cells, the combination of pertuzumab and trastuzumab augmented anti-tumor activity in HER2-overexpressing xenograft models.

12.3 Pharmacokinetics

Pertuzumab demonstrated linear pharmacokinetics at a dose range of 2 – 25 mg/kg. Based on a population PK analysis that included 481 patients, the median clearance (CL) of pertuzumab was 0.24 L/day and the median half-life was 18 days. With an initial dose of 840 mg followed by a maintenance dose of 420 mg every three weeks thereafter, the steady-state concentration of pertuzumab was reached after the first maintenance dose.

The population PK analysis suggested no PK differences based on age, gender, ethnicity (Japanese vs. non-Japanese), or disease status (neoadjuvant or adjuvant vs. metastatic setting). Baseline serum albumin level and lean body weight as covariates only exerted a minor influence on PK parameters. Therefore, no dose adjustments based on body weight or baseline albumin level are needed.

No dedicated renal impairment trial for PERJETA has been conducted. Based on the results of the population pharmacokinetic analysis, pertuzumab exposure in patients with mild (CLcr

60 to 90 mL/min, n=200) and moderate renal impairment (CLcr 30 to 60 mL/min, n=71) were similar to those in patients with normal renal function (CLcr greater than 90 mL/min, n=200). No relationship between CLcr and pertuzumab exposure was observed over the range of observed CLcr (27 to 244 mL/min).

12.6 Cardiac Electrophysiology

The effect of pertuzumab with an initial dose of 840 mg followed by a maintenance dose of 420 mg every three weeks on QTc interval was evaluated in a subgroup of 20 patients with HER2-positive breast cancer in CLEOPATRA. No large changes in the mean QT interval (i.e., greater than 20 ms) from placebo based on Fridericia correction method were detected in the trial. A small increase in the mean QTc interval (i.e., less than 10 ms) cannot be excluded because of the limitations of the trial design.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of pertuzumab.

Studies have not been performed to evaluate the mutagenic potential of pertuzumab.

No specific fertility studies in animals have been performed to evaluate the effect of pertuzumab. No adverse effects on male and female reproductive organs were observed in repeat-dose toxicity studies of up to six months duration in cynomolgus monkeys.

14 CLINICAL STUDIES

14.1 Metastatic Breast Cancer

CLEOPATRA (NCT00567190) was a multicenter, double-blind, placebo-controlled trial of 808 patients with HER2-positive metastatic breast cancer. HER2 overexpression was defined as a score of 3+ IHC or FISH amplification ratio of 2.0 or greater as determined by a central laboratory. Patients were randomly allocated 1:1 to receive placebo plus trastuzumab and docetaxel or PERJETA plus trastuzumab and docetaxel. Randomization was stratified by prior treatment (prior or no prior adjuvant/neoadjuvant anti-HER2 therapy or chemotherapy) and geographic region (Europe, North America, South America, and Asia). Patients with prior adjuvant or neoadjuvant therapy were required to have a disease-free interval of greater than 12 months before trial enrollment.

PERJETA was given intravenously at an initial dose of 840 mg, followed by 420 mg every 3 weeks thereafter. Trastuzumab was given intravenously at an initial dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks thereafter. Patients were treated with PERJETA and trastuzumab until progression of disease, withdrawal of consent, or unacceptable toxicity. Docetaxel was given as an initial dose of 75 mg/m^2 by intravenous infusion every 3 weeks for at least 6 cycles. The docetaxel dose could be escalated to 100 mg/m^2 at the investigator's discretion if the initial dose was well tolerated. At the time of the primary analysis, the mean number of cycles of study treatment administered was 16.2 in the placebo-treated group and 19.9 in the PERJETA-treated group.

The primary endpoint of CLEOPATRA was progression-free survival (PFS) as assessed by an independent review facility (IRF). PFS was defined as the time from the date of randomization to the date of disease progression or death (from any cause) if the death occurred within 18 weeks of the last tumor assessment. Additional endpoints included overall survival (OS), PFS (investigator-assessed), objective response rate (ORR), and duration of response.

Patient demographic and baseline characteristics were balanced between the treatment arms. The median age was 54 (range 22 to 89 years), 59% were White, 32% were Asian, and 4% were Black. All were women with the exception of 2 patients. Seventeen percent of patients were enrolled in North America, 14% in South America, 38% in Europe, and 31% in Asia. Tumor prognostic characteristics, including hormone receptor status (positive 48%, negative 50%), presence of visceral disease (78%) and non-visceral disease only (22%) were similar in the study arms. Approximately half of the patients received prior adjuvant or neoadjuvant anti-HER2 therapy or chemotherapy (placebo 47%, PERJETA 46%). Among patients with hormone receptor positive tumors, 45% received prior adjuvant hormonal therapy and 11% received hormonal therapy for metastatic disease. Eleven percent of patients received prior adjuvant or neoadjuvant trastuzumab.

CLEOPATRA demonstrated a statistically significant improvement in IRF-assessed PFS in the PERJETA-treated group compared with the placebo-treated group [hazard ratio (HR)=0.62 (95% CI: 0.51, 0.75), $p < 0.0001$] and an increase in median PFS of 6.1 months (median PFS of 18.5 months in the PERJETA-treated group vs. 12.4 months in the placebo-treated group) (see Figure 1). The results for investigator-assessed PFS were comparable to those observed for IRF-assessed PFS.

Consistent results were observed across several patient subgroups including age (< 65 or ≥ 65 years), race, geographic region, prior adjuvant/neoadjuvant anti-HER2 therapy or chemotherapy (yes or no), and prior adjuvant/neoadjuvant trastuzumab (yes or no). In the subgroup of patients with hormone receptor-negative disease (n=408), the hazard ratio was 0.55 (95% CI: 0.42, 0.72). In the subgroup of patients with hormone receptor-positive disease (n=388), the hazard ratio was 0.72 (95% CI: 0.55, 0.95). In the subgroup of patients with disease limited to non-visceral metastasis (n=178), the hazard ratio was 0.96 (95% CI: 0.61, 1.52).

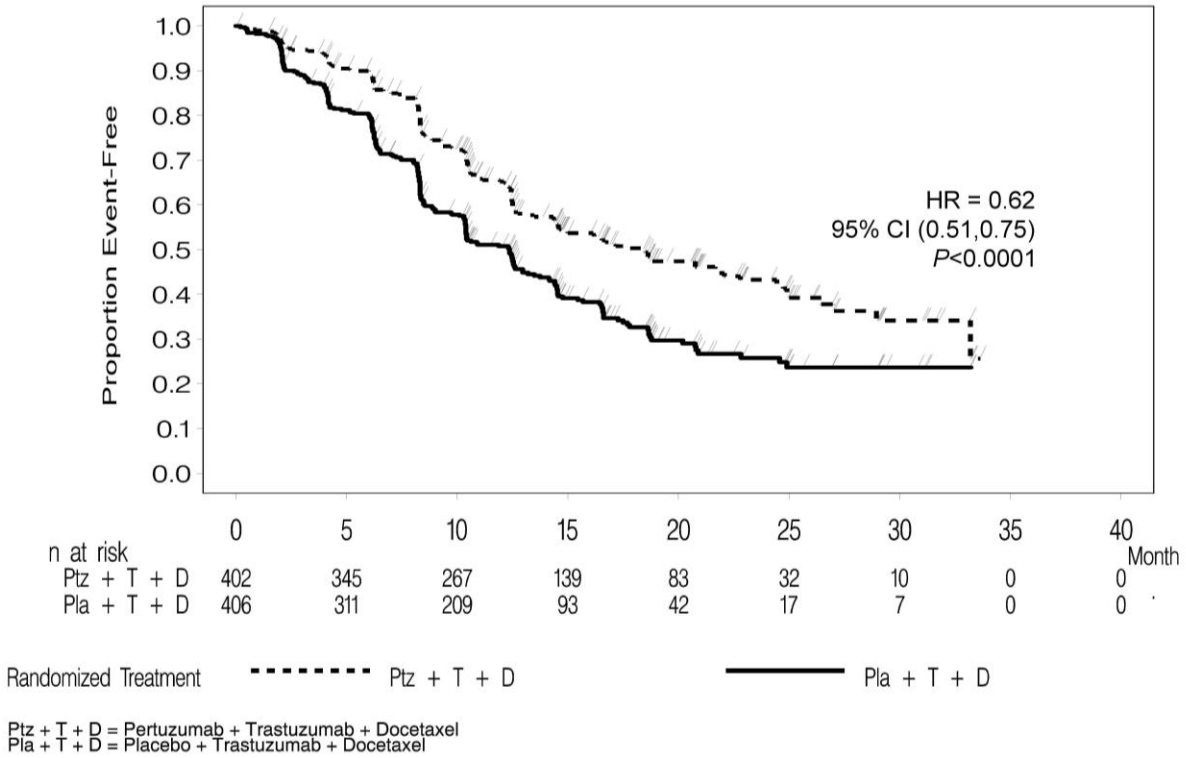
At the time of the final PFS analysis, 165 patients had died, and more deaths had occurred in the placebo-treated group (23.6%) compared with the PERJETA-treated group (17.2%); OS was not mature and interim OS analysis results did not meet the pre-specified stopping boundary for statistical significance. The final analysis of OS (Table 8, Figure 2) was performed when 389 patients had died (221 in the placebo-treated group and 168 in the PERJETA-treated group). A statistically significant OS improvement in favor of the PERJETA-treated group was demonstrated [HR=0.68 (95% CI; 0.56, 0.84), p=0.0002] with an increase in median OS of 15.7 months (median OS of 56.5 months in the PERJETA-treated group vs. 40.8 months in the placebo-treated group). OS results in patient subgroups were consistent with those observed for IRF-assessed PFS with the exception of the subgroup of patients with disease limited to non-visceral metastasis [HR=1.11 (95% CI: 0.66, 1.85)].

Table 8 Summary of Efficacy from CLEOPATRA

Parameter	PERJETA + trastuzumab + docetaxel n=402	Placebo + trastuzumab + docetaxel n=406	HR (95% CI)	p-value
Progression-Free Survival (independent review)				
No. of patients with an event	191 (47.5%)	242 (59.6%)	0.62	
Median months	18.5	12.4	(0.51, 0.75)	< 0.0001
Overall Survival* (final analysis)				
No. of patients who died	168 (41.8%)	221 (54.4%)	0.68	
Median months	56.5	40.8	(0.56, 0.84)	0.0002
Objective Response Rate (ORR, independent review)				
No. of patients analyzed	343	336		
Objective response (CR + PR)	275 (80.2%)	233 (69.3%)		
Complete response (CR)	19 (5.5%)	14 (4.2%)		
Partial Response (PR)	256 (74.6%)	219 (65.2%)		
Median Duration of Response (months)	20.2	12.5		
Difference in ORR	10.8%			
95% CI	(4.2%, 17.5%)			0.0011

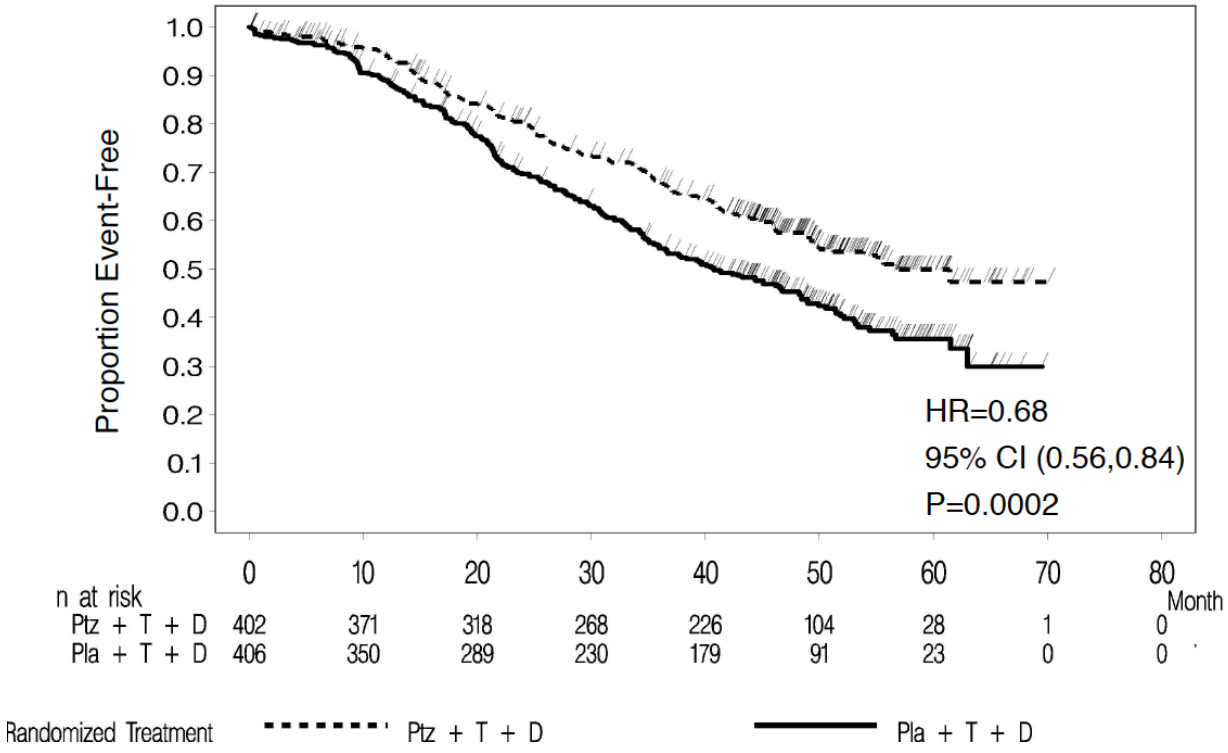
* Final analysis of overall survival, cutoff date Feb 2014
CI=Confidence Interval

Figure 1 Kaplan-Meier Curve of IRF-Assessed Progression-Free Survival for CLEOPATRA



Ptz + T + D = Pertuzumab + Trastuzumab + Docetaxel
Pla + T + D = Placebo + Trastuzumab + Docetaxel

Figure 2 Kaplan-Meier Curve of Overall Survival for CLEOPATRA (Final Analysis)



14.2 Neoadjuvant Treatment of Breast Cancer

NeoSphere

NeoSphere (NCT00545688) was a multicenter, randomized trial conducted in 417 patients with operable, locally advanced, or inflammatory HER2-positive breast cancer (T2-4d) who were scheduled for neoadjuvant therapy. HER2 overexpression was defined as a score of 3+ IHC or FISH amplification ratio of 2.0 or greater as determined by a central laboratory. Patients were randomly allocated to receive 1 of 4 neoadjuvant regimens prior to surgery as follows: trastuzumab plus docetaxel, PERJETA plus trastuzumab and docetaxel, PERJETA plus trastuzumab, or PERJETA plus docetaxel. Randomization was stratified by breast cancer type (operable, locally advanced, or inflammatory) and estrogen receptor (ER) or progesterone receptor (PgR) positivity.

PERJETA was given intravenously at an initial dose of 840 mg, followed by 420 mg every 3 weeks for 4 cycles. Trastuzumab was given intravenously at an initial dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks for 4 cycles. Docetaxel was given as an initial dose of 75 mg/m^2 by intravenous infusion every 3 weeks for 4 cycles. The docetaxel dose could be escalated to 100 mg/m^2 at the investigator's discretion if the initial dose was well tolerated. Following surgery all patients received 3 cycles of 5-fluorouracil (600 mg/m^2), epirubicin (90 mg/m^2), and cyclophosphamide (600 mg/m^2) (FEC) given intravenously every 3 weeks and trastuzumab administered intravenously every 3 weeks to complete 1 year of therapy. After surgery, patients in the PERJETA plus trastuzumab arm received docetaxel every 3 weeks for 4 cycles prior to FEC.

The primary endpoint of the study was pathological complete response (pCR) rate in the breast (ypT0/is). The FDA-preferred definition of pCR is the absence of invasive cancer in the breast and lymph nodes (ypT0/is ypN0).

Demographics were well balanced (median age was 49 – 50 years old, the majority were Caucasian (71%) and all were female. Overall, 7% of patients had inflammatory cancer, 32% had locally advanced cancer, and 61% had operable cancer. Approximately half the patients in each treatment group had hormone receptor-positive disease (defined as ER-positive and/or PgR-positive).

The efficacy results are summarized in Table 9. Statistically significant improvements in pCR rates by both the study and FDA-preferred definitions were observed in patients receiving PERJETA plus trastuzumab and docetaxel compared to patients receiving trastuzumab plus docetaxel. The pCR rates and magnitude of improvement with PERJETA were lower in the subgroup of patients with hormone receptor-positive tumors compared to patients with hormone receptor-negative tumors.

Table 9 Summary of Efficacy from NeoSphere

Endpoint/Study Population	**H+T**	**Ptz+H+T**	**Ptz+H**	**Ptz+T**
Overall ITT	**N=107**	**N=107**	**N=107**	**N=96**
pCR[1], n **(%)** **[95% CI][2]**	23 (21.5%) [14.1, 30.5]	42 (39.3%) [30.0, 49.2]	12 (11.2%) [5.9, 18.8]	17 (17.7%) [10.7, 26.8]
p-value (with Simes correction for CMH test)[3]		0.0063 (vs. H+T)	0.0223 (vs. H+T)	0.0018 (vs. Ptz+H+T)

Hormone receptor-positive subgroup	N=50	N=50	N=51[4]	N=46
pCR[1], n **(%)** **[95% CI][2]**	6 (12.0%) [4.5, 24.3]	11 (22.0%) [11.5, 36.0]	1 (2.0%) [0.1, 10.5]	4 (8.7%) [2.4, 20.8]
Hormone receptor-negative subgroup	N=57	N=57	N=55[4]	N=50
pCR[1], n **(%)** **[95% CI][2]**	17 (29.8%) [18.4, 43.4]	31 (54.4%) [40.7, 67.6]	11 (20.0%) [10.4, 33.0]	13 (26.0%) [14.6, 40.3]

T=docetaxel, Ptz=PERJETA, H=trastuzumab
CI=Confidence Interval
[1] ypT0/is ypN0 (absence of invasive cancer in the breast and lymph nodes)
[2] 95% CI for one sample binomial using Pearson-Clopper method.
[3] p-value from Cochran-Mantel-Haenszel (CMH) test, with Simes multiplicity adjustment
[4] One patient had unknown hormone receptor status. The patient did not achieve a pCR.

TRYPHAENA
An additional neoadjuvant study (TRYPHAENA, NCT00976989) was conducted in 225 patients with HER2-positive locally advanced, operable, or inflammatory (T2-4d) breast cancer designed primarily to assess cardiac safety in which all arms included PERJETA. HER2 overexpression was defined as a score of 3+ IHC or FISH amplification ratio of 2.0 or greater as determined by a central laboratory.

Patients were randomly allocated to receive 1 of 3 neoadjuvant regimens prior to surgery as follows: 3 cycles of FEC followed by 3 cycles of docetaxel all in combination with PERJETA and trastuzumab, 3 cycles of FEC alone followed by 3 cycles of docetaxel and trastuzumab in combination with PERJETA, or 6 cycles of docetaxel, carboplatin, and trastuzumab (TCH) in combination with PERJETA. Randomization was stratified by breast cancer type (operable, locally advanced, or inflammatory) and ER and/or PgR positivity.

PERJETA was given by intravenous infusion at an initial dose of 840 mg, followed by 420 mg every 3 weeks. Trastuzumab was given by intravenous infusion at an initial dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks. 5-Fluorouracil (500 mg/m^2), epirubicin (100 mg/m^2), and cyclophosphamide (600 mg/m^2) were given intravenously every 3 weeks for 3 cycles. In the PERJETA plus trastuzumab, docetaxel, and FEC arms, docetaxel was given as an initial dose of 75 mg/m^2 by intravenous infusion every 3 weeks for 3 cycles with the option to escalate to 100 mg/m^2 at the investigator's discretion if the initial dose was well tolerated. However, in the PERJETA plus TCH arm, docetaxel was given intravenously at 75 mg/m^2 (no escalation was permitted) and carboplatin (AUC 6) was given intravenously every 3 weeks for 6 cycles. Following surgery all patients received trastuzumab to complete 1 year of therapy, which was administered intravenously every 3 weeks.

Demographics were well balanced (median age was 49-50 years old, the majority were Caucasian [76%]) and all were female. Overall 6% of patients had inflammatory cancer, 25% had locally advanced cancer and 69% had operable cancer, with approximately half the patients in each treatment group having ER-positive and/or PgR-positive disease.

The pCR (ypT0/is ypN0) rates were 56.2% (95% CI: 44.1%, 67.8%), 54.7% (95% CI: 42.7%, 66.2%), and 63.6% (95% CI: 51.9%, 74.3%) for patients treated with PERJETA plus trastuzumab and FEC followed by PERJETA plus trastuzumab and docetaxel, PERJETA plus trastuzumab and docetaxel following FEC, or PERJETA plus TCH, respectively. The pCR rates were lower in the subgroups of patients with hormone receptor-positive tumors: 41.0% (95% CI: 25.6%, 57.9%), 45.7% (95% CI: 28.8%, 63.4%), and 47.5% (95% CI: 31.5%, 63.9%) than with hormone receptor-negative tumors: 73.5% (95% CI: 55.6%, 87.1%), 62.5% (95% CI: 45.8%, 77.3%), and 81.1% (95% CI: 64.8%, 92.0%), respectively.

BERENICE

A two-arm non-randomized study (BERENICE, NCT02132949) was conducted in 401 patients with HER2-positive locally advanced, inflammatory, or early-stage HER2-positive breast cancer. HER2 overexpression was defined as a score of 3+ IHC or ISH amplification ratio of 2.0 or greater as determined by a central laboratory.

Patients received 1 of 2 neoadjuvant regimens prior to surgery as follows: 4 cycles of dose dense doxorubicin and cyclophosphamide (ddAC) followed by 4 cycles of PERJETA in combination with trastuzumab and weekly paclitaxel for 12 weeks or 4 cycles of 5-fluorouracil, epirubicin and cyclophosphamide (FEC) followed by 4 cycles of PERJETA in combination with trastuzumab and docetaxel. The choice of neoadjuvant treatment regimen was made by the Investigator on a site-specific basis. Dosing for the regimens was as follows:

- PERJETA was given by intravenous infusion at an initial dose of 840 mg, followed by 420 mg every 3 weeks. Trastuzumab was given by intravenous infusion at an initial dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks.
- In the ddAC cohort, (doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2) were given intravenously every 2 weeks (ddAC) for 4 cycles with G-CSF (granulocyte colony stimulating factor) support at investigator discretion, followed by paclitaxel 80 mg/m^2 given intravenously weekly for 12 weeks, with PERJETA and trastuzumab every 3 weeks from the start of paclitaxel for 4 cycles.
- In the FEC cohort, 5-Fluorouracil (5-FU) (500 mg/m^2), epirubicin (100 mg/m^2), and cyclophosphamide (600 mg/m^2) were given intravenously every 3 weeks for 4 cycles, followed by docetaxel given as an initial dose of 75 mg/m^2 by intravenous infusion every 3 weeks for 4 cycles with PERJETA and trastuzumab, and with the option to escalate to 100 mg/m^2 at the investigator's discretion if the initial dose was well tolerated.

Following surgery, all patients received PERJETA and trastuzumab administered intravenously every 3 weeks to complete 1 year of therapy.

The median age of the overall study population was 49 years old (range 21-78), 12% of patients were 65 or older, 83% were Caucasian, and all but one patient was female. Overall 3% of patients had inflammatory cancer, 23% had locally advanced cancer (Stage 3A or greater), 5% were not classified per TNM staging, with approximately two thirds of the patients in each treatment group having ER-positive and/or PgR-positive disease. All patients had an ECOG performance status of 0 or 1.

The pCR (ypT0/is ypN0) rates were 61.8% (95% CI: 54.7, 68.6) and 60.7% (95% CI: 53.6, 67.5) for patients treated with ddAC followed by PERJETA plus trastuzumab and paclitaxel, or FEC followed by PERJETA plus trastuzumab and docetaxel, respectively. The pCR rates were lower in the subgroups of patients with hormone receptor-positive tumors: 51.6% (95% CI: 42.6,

60.5%) and 57.3% (95% CI: 48.1, 66.1%) than with hormone receptor-negative tumors: 81.5% (95% CI: 70.0, 90.1%) and 68.0% (95% CI: 56.2, 78.3%), respectively.

14.3 Adjuvant Treatment of Breast Cancer

APHINITY (NCT01358877) was a multicenter, randomized, double-blind, placebo-controlled study conducted in 4804 patients with HER2-positive early breast cancer who had their primary tumor excised prior to randomization. Patients were then randomized to receive PERJETA or placebo, in combination with adjuvant trastuzumab and chemotherapy. Randomization was stratified by the following factors: region, nodal status, protocol version, central hormone receptor status, and adjuvant chemotherapy regimen.

Investigators selected one of the following anthracycline-based or non-anthracycline-based chemotherapy regimens for individual patients:

- 3 or 4 cycles of FEC (5-FU 500-600 mg/m^2, epirubicin 90-120 mg/m^2, cyclophosphamide 500-600 mg/m^2) or FAC (5-FU 500-600 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500-600 mg/m^2), followed by 3 or 4 cycles of docetaxel (75 mg/m^2 which could be escalated to 100 mg/m^2 every 3 weeks) or 12 cycles of weekly paclitaxel (80 mg/m^2).
- 4 cycles of AC (doxorubicin 60 mg/m^2 and cyclophosphamide 500-600 mg/m^2) or EC (epirubicin 90-120 mg/m^2 and cyclophosphamide 500-600 mg/m^2) either every 3 weeks or every 2 weeks with GCSF support, followed by docetaxel (100 mg/m^2 for 3 cycles or 75 mg/m^2 for first cycle and 100 mg/m^2 for subsequent three cycles, or 75 mg/m^2 for four cycles) or 12 cycles of weekly paclitaxel (80 mg/m^2).
- 6 cycles of docetaxel (75 mg/m^2) in combination with carboplatin (AUC 6)

PERJETA and trastuzumab were administered intravenously every 3 weeks starting on Day 1 of the first taxane-containing cycle, for a total of 52 weeks (up to 18 cycles) or until recurrence, withdrawal of consent, or unmanageable toxicity.

After completion of chemotherapy, patients received radiotherapy and/or hormone therapy as per investigator's discretion.

The major efficacy outcome of the study was invasive disease-free survival (IDFS), defined as the time from randomization to first occurrence of ipsilateral local or regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, or death from any cause. Additional efficacy endpoints were IDFS including second primary non-breast cancer, disease-free survival (DFS), and overall survival (OS).

Demographics were generally balanced between the two treatment arms. The median age was 51 years (range 18-86), 13% of patients were 65 or older, and over 99% of patients were female. Sixty-three percent of patients had node-positive disease, 64% had hormone receptor-positive disease, and 71% were Caucasian. All patients had an ECOG performance status of 0 or 1. Seventy-eight percent received an anthracycline containing regimen.

PERJETA-treated patients and placebo-treated patients both received a median number of 18 cycles of anti-HER2 therapy. After a median follow-up of 45.4 months, a statistically significant improvement in IDFS was demonstrated in patients randomized to receive PERJETA compared with patients randomized to receive placebo. The efficacy results from APHINITY are summarized in Tables 10 and 11 and in Figure 3.

Table 10 Efficacy Results from APHINITY

	PERJETA + trastuzumab + chemotherapy N=2400	**Placebo + trastuzumab + chemotherapy N=2404**
Invasive Disease Free Survival (IDFS)		
Number (%) of patients with event	171 (7.1%)	210 (8.7%)
HR [95% CI] [1]	0.82 [0.67, 1.00]	
p-value (Log-Rank test, stratified[1])	0.047	
3 year event-free rate[2], % [95% CI]	94.1 [93.1, 95.0]	93.2 [92.2, 94.3]
IDFS including second primary non-breast cancer		
Number (%) of patients with event	189 (7.9%)	230 (9.6%)
HR [95% CI] [1]	0.83 [0.68, 1.00]	
3 year event-free rate[2], % [95% CI]	93.5 [92.5, 94.5]	92.5 [91.4, 93.6]
Disease Free Survival (DFS)		
Number (%) of patients with event	192 (8.0%)	236 (9.8%)
HR [95% CI] [1]	0.82 [0.68, 0.99]	
3 year event-free rate[2], % [95% CI]	93.4 [92.4, 94.4]	92.3 [91.2, 93.4]
Overall Survival (OS)[3]		
Number (%) of patients with event	80 (3.3%)	89 (3.7%)
HR [95% CI] [1]	0.89 [0.66, 1.21]	
3 year event-free rate[2], % [95% CI]	97.7 [97.0, 98.3]	97.7 [97.1, 98.3]

HR=Hazard Ratio, CI=Confidence Interval

[1] All analyses stratified by nodal status, protocol version, central hormone receptor status, and adjuvant chemotherapy regimen. Stratification factors are defined according to the randomization data for IDFS.

[2] 3-year event-free rate derived from Kaplan-Meier estimates

[3] Data from first interim analysis

Figure 3 Kaplan-Meier Curve of Invasive Disease Free Survival from APHINITY (ITT Population)

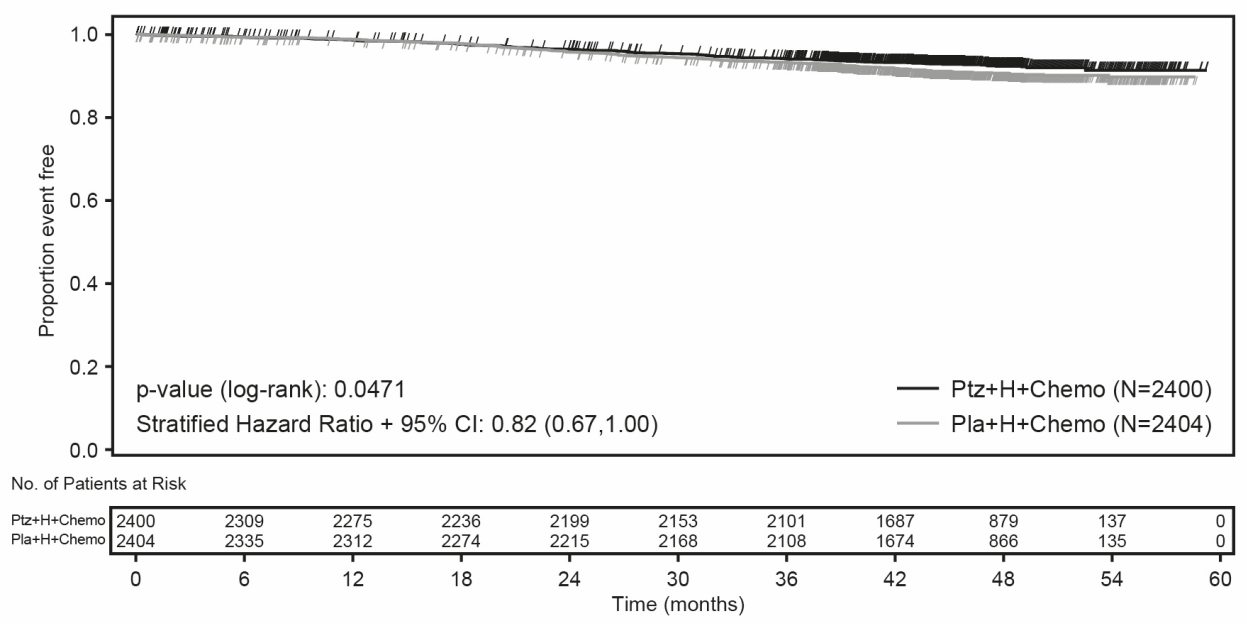


Table 11 Efficacy Results by Baseline Disease Characteristics and Adjuvant Chemotherapy from APHINITY[1]

Population	Number of events/Total N (%)		IDFS at 3 year (%, 95% CI)		Unstratified HR (95% CI)
	PERJETA + trastuzumab + chemotherapy	Placebo + trastuzumab + chemotherapy	PERJETA + trastuzumab + chemotherapy	Placebo + trastuzumab + chemotherapy	
Hormone Receptor Status					
Negative	71/864 (8.2%)	91/858 (10.6%)	92.8 (90.8, 94.3)	91.2 (89.0, 92.9)	0.76 (0.56, 1.04)
Positive	100/1536 (6.5%)	119/1546 (7.7%)	94.8 (93.5, 95.8)	94.4 (93.1, 95.4)	0.86 (0.66, 1.13)
Nodal Status					
Negative	32/897 (3.6%)	29/902 (3.2%)	97.5 (96.3, 98.4)	98.4 (97.3, 99.0)	1.13 (0.68, 1.86)
Positive	139/1503 (9.2%)	181/1502 (12.1%)	92.0 (90.5, 93.3)	90.2 (88.5, 91.6)	0.77 (0.62, 0.96)
Adjuvant Chemotherapy Regimen					
Anthracycline	139/1865 (7.4%)	171/1877 (9.1%)	93.8 (92.6, 94.8)	93.0 (91.8, 94.1)	0.82 (0.66, 1.03)
Non-Anthracycline	32/535 (6.0%)	39/527 (7.4%)	94.9 (92.6, 96.6)	94.0 (91.5, 95.8)	0.82 (0.51, 1.31)

[1]Exploratory analyses without adjusting multiple comparisons, therefore, results are considered descriptive.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

PERJETA injection is supplied as a 420 mg/14 mL (30 mg/mL) single-dose vial containing preservative-free solution. NDC 50242-145-01.

Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F) until time of use.

Keep vial in the outer carton in order to protect from light.

DO NOT FREEZE. DO NOT SHAKE.

17 PATIENT COUNSELING INFORMATION

Left Ventricular Dysfunction

- Advise patients to contact a health care professional immediately for any of the following: new onset or worsening shortness of breath, cough, swelling of the ankles/legs, swelling of the face, palpitations, weight gain of more than 5 pounds in 24 hours, dizziness or loss of consciousness [*see Warnings and Precautions (5.1)]*.

Embryo-Fetal Toxicity

- 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. Advise female patients to contact their healthcare provider with a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.
- Advise women who are exposed to PERJETA in combination with trastuzumab during pregnancy or within 7 months prior to conception that there is a pregnancy pharmacovigilance program that monitors pregnancy outcomes. Encourage these patients to report their pregnancy to Genentech *[see Use in Specific Populations (8.1)]*.
- 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 *[see Use in Specific Populations (8.3)]*.

PERJETA® (pertuzumab)

Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990
U.S. License No. 1048

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use KADCYLA safely and effectively. See full prescribing information for KADCYLA.

KADCYLA® (ado-trastuzumab emtansine) for injection, for intravenous use
Initial U.S. Approval: 2013

WARNING: HEPATOTOXICITY, CARDIAC TOXICITY, EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning

- **Hepatotoxicity, liver failure and death have occurred in KADCYLA-treated patients. Monitor hepatic function prior to initiation and prior to each dose. Institute dose modifications or permanently discontinue as appropriate. (2.3, 5.1)**
- **KADCYLA may lead to reductions in left ventricular ejection fraction (LVEF). Assess LVEF prior to initiation. Monitor and withhold dosing or discontinue as appropriate. (2.3, 5.2)**
- **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. (5.3, 8.1, 8.3)**

RECENT MAJOR CHANGES

Warnings and Precautions (5.2) 09/2020

INDICATIONS AND USAGE

KADCYLA is a HER2-targeted antibody and microtubule inhibitor conjugate indicated, as a single agent, 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. (1.1)
- the adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment. (1.2)

Select patients for therapy based on an FDA-approved companion diagnostic for KADCYLA *[see Dosage and Administration (2.1)]*

DOSAGE AND ADMINISTRATION

- **Do not substitute KADCYLA for or with trastuzumab.**
- HER2 Testing: Perform using FDA-approved tests by laboratories with demonstrated proficiency. (2.1)
- *For intravenous infusion only*. Do not administer as an intravenous push or bolus. Do not use Dextrose (5%) solution. (2.4)
- The recommended dose of KADCYLA is 3.6 mg/kg given as an intravenous infusion every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity, or a total of 14 cycles for patients with EBC. *Do not administer KADCYLA at doses greater than 3.6 mg/kg.* (2.2)
- Management of adverse reactions (infusion-related reactions, hepatotoxicity, left ventricular cardiac dysfunction, thrombocytopenia, pulmonary toxicity or peripheral neuropathy) may require temporary interruption, dose reduction, or treatment discontinuation of KADCYLA. (2.3)

DOSAGE FORMS AND STRENGTHS

Lyophilized powder in single-dose vials containing 100 mg per vial or 160 mg per vial. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Pulmonary Toxicity: Permanently discontinue KADCYLA in patients diagnosed with interstitial lung disease or pneumonitis. For patients with radiation pneumonitis in the adjuvant setting, permanently discontinue KADCYLA for Grade ≥ 3 or for Grade 2 not responding to standard treatment. (2.2, 5.4)
- Infusion-Related Reactions, Hypersensitivity Reactions: Monitor for signs and symptoms during and after infusion. If significant infusion-related reactions or hypersensitivity reactions occur, slow or interrupt the infusion and administer appropriate medical therapies. Permanently discontinue KADCYLA for life threatening infusion-related reaction. (2.1, 2.2, 5.5)
- 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 anti-coagulation and antiplatelet therapy. Use caution with these agents and consider additional monitoring when concomitant use is medically necessary**.** (5.6)
- Thrombocytopenia: Monitor platelet counts prior to each KADCYLA dose. Institute dose modifications as appropriate. (2.2, 5.7)
- Neurotoxicity: Monitor for signs or symptoms. Withhold dosing temporarily for patients experiencing Grade 3 or 4 peripheral neuropathy. (2.2, 5.8, 13.2)

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. (6.1)

Early Breast Cancer

- The most common adverse reactions (≥ 25%) with KADCYLA were fatigue, nausea, increased transaminases, musculoskeletal pain, hemorrhage, thrombocytopenia, headache, peripheral neuropathy, and arthralgia.

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed. (8.2)
- Females and Males of Reproductive Potential: Verify pregnancy status of females prior to initiation of KADCYLA. (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 09/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

*** Sections or subsections omitted from the Full Prescribing Information are not listed.**

FULL PRESCRIBING INFORMATION

WARNING: 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. (2.3, 5.1)**
- **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. (2.3, 5.2)**
- **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. (5.3, 8.1, 8.3)**

1 INDICATIONS AND USAGE

1.1 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 [*see Dosage and Administration (2.1)*].

1.2 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 [*see Dosage and Administration (2.1)*].

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients based on HER2 protein overexpression or HER2 gene amplification in tumor specimens *[see Indications and Usage (1), Clinical Studies (14)]*. 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. Information on the FDA-approved tests for the

detection of HER2 protein overexpression and HER2 gene amplification is available at: http://www.fda.gov/CompanionDiagnostics.

Improper assay performance, including use of sub-optimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results.

2.2 Recommended Doses and Schedules

Do not substitute trastuzumab for or with KADCYLA.

The recommended dose of KADCYLA is 3.6 mg/kg given as an intravenous infusion every 3 weeks (21-day cycle). *Do not administer KADCYLA at doses greater than 3.6 mg/kg*.

Closely monitor the infusion site for possible subcutaneous infiltration during drug administration *[see Warnings and Precautions (5.9)]*.

First infusion: Administer infusion over 90 minutes. Observe patients during the infusion and for at least 90 minutes following the initial dose for fever, chills, or other infusion-related reactions *[see Warnings and Precautions (5.5)]*.

Subsequent infusions: Administer over 30 minutes if prior infusions were well tolerated. Observe patients during the infusion and for at least 30 minutes after infusion.

Metastatic Breast Cancer (MBC)

Patients with MBC should receive treatment until disease progression or unmanageable toxicity.

Early Breast Cancer (EBC)

Patients with EBC should receive treatment for a total of 14 cycles unless there is disease recurrence or unmanageable toxicity.

2.3 Dose Modifications

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

If a planned dose is delayed or missed, 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.

Slow or interrupt the infusion rate of KADCYLA if the patient develops an infusion-related reaction. Permanently discontinue KADCYLA for life-threatening infusion-related reactions *[see Warnings and Precautions (5.5)]*.

Management of increased serum transaminases, hyperbilirubinemia, left ventricular dysfunction, thrombocytopenia, pulmonary toxicity or peripheral neuropathy may require temporary interruption, dose reduction or treatment discontinuation of KADCYLA as per guidelines provided in Tables 1 and 2.

Table 1 Recommended Dose Reduction Schedule for Adverse Reactions

Dose Reduction Schedule	Dose Level
Starting dose	3.6 mg/kg
First dose reduction	3 mg/kg
Second dose reduction	2.4 mg/kg
Requirement for further dose reduction	Discontinue treatment

Table 2 Dose Modification Guidelines for KADCYLA

Dose Modifications for Patients with MBC		
Adverse reaction	**Severity**	**Treatment modification**
Increased Transaminase (AST/ALT)	Grade 2 (> 2.5 to ≤ 5× the ULN)	Treat at the same dose level.
	Grade 3 (> 5 to ≤ 20× the ULN)	Do not administer KADCYLA until AST/ALT recovers to Grade ≤ 2, and then reduce one dose level
	Grade 4 (> 20× the ULN)	Discontinue KADCYLA
Hyperbilirubinemia	Grade 2 (> 1.5 to ≤ 3× the ULN)	Do not administer KADCYLA until total bilirubin recovers to Grade ≤ 1, and then treat at the same dose level.
	Grade 3 (> 3 to ≤ 10× the ULN)	Do not administer KADCYLA until total bilirubin recovers to Grade ≤ 1 and then reduce one dose level.
	Grade 4 (> 10× the ULN)	Discontinue KADCYLA
Drug Induced Liver Injury (DILI)	Serum transaminases > 3 x ULN and concomitant total bilirubin > 2 × ULN	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
Nodular Regenerative Hyperplasia (NRH)	All Grades	Permanently discontinue KADCYLA
Thrombocytopenia	Grade 3 (25,000 to < 50,000/mm^3)	Do not administer KADCYLA until platelet count recovers to Grade ≤ 1 (≥ 75,000/mm^3), and then treat at the same dose level
	Grade 4 (< 25,000/mm^3)	Do not administer KADCYLA until platelet count recovers to Grade ≤ 1 (≥ 75,000/mm^3), and then reduce one dose level
Left Ventricular Dysfunction	Symptomatic CHF	Discontinue KADCYLA
	LVEF < 40%	Do not administer KADCYLA Repeat LVEF assessment within 3 weeks. If LVEF < 40% is confirmed, discontinue KADCYLA

	LVEF 40% to ≤ 45% and decrease is ≥ 10% points from baseline	Do not administer KADCYLA Repeat LVEF assessment within 3 weeks. If the LVEF has not recovered to within 10% points from baseline, discontinue KADCYLA
	LVEF 40% to ≤ 45% and decrease is < 10% points from baseline	Continue treatment with KADCYLA. Repeat LVEF assessment within 3 weeks.
	LVEF > 45%	Continue treatment with KADCYLA.
Pulmonary Toxicity	Interstitial lung disease (ILD) or pneumonitis	Permanently discontinue KADCYLA
Peripheral Neuropathy	Grade 3-4	Do not administer KADCYLA until resolution Grade ≤ 2
Dose Modification Guidelines for EBC		
Adverse reaction	**Severity**	**Treatment modification**
Increased Alanine Transaminase (ALT)	Grade 2-3 (> 3.0 to ≤ 20 × ULN on day of scheduled treatment)	Do not administer KADCYLA until ALT recovers to Grade ≤ 1, and then reduce one dose level
	Grade 4 (> 20 × ULN at any time)	Discontinue KADCYLA
Increased Aspartate Transaminase (AST)	Grade 2 (> 3.0 to ≤ 5 × ULN on day of scheduled treatment)	Do not administer KADCYLA until AST recovers to Grade ≤ 1, and then treat at the same dose level
	Grade 3 (> 5 to ≤ 20 × ULN on day of scheduled treatment)	Do not administer KADCYLA until AST recovers to Grade ≤ 1, and then reduce one dose level
	Grade 4 (> 20 × ULN at any time)	Discontinue KADCYLA
Hyperbilirubinemia	TBILI > 1.0 to ≤ 2.0 × the ULN on day of scheduled treatment	Do not administer KADCYLA until total bilirubin recovers to ≤ 1.0 × ULN, and then reduce one dose level

	TBILI > 2 × ULN at any time	Discontinue KADCYLA
Nodular Regenerative Hyperplasia (NRH)	All Grades	Permanently discontinue KADCYLA
Thrombocytopenia	Grade 2-3 on day of scheduled treatment (25,000 to < 75,000/mm^3)	Do not administer KADCYLA until platelet count recovers to Grade ≤ 1 (≥ 75,000/mm^3), and then treat at the same dose level. If a patient requires 2 delays due to thrombocytopenia, consider reducing dose by one level.
	Grade 4 at any time < 25,000/mm^3	Do not administer KADCYLA until platelet count recovers to Grade ≤ 1 (≥ 75,000/mm^3), and then reduce one dose level.
Left Ventricular Dysfunction	LVEF < 45%	Do not administer KADCYLA Repeat LVEF assessment within 3 weeks. If LVEF < 45% is confirmed, discontinue KADCYLA.
	LVEF 45% to < 50% and decrease is ≥ 10% points from baseline*	Do not administer KADCYLA Repeat LVEF assessment within 3 weeks. If the LVEF remains < 50% and has not recovered to < 10% points from baseline, discontinue KADCYLA.
	LVEF 45% to < 50% and decrease is < 10% points from baseline*	Continue treatment with KADCYLA. Repeat LVEF assessment within 3 weeks.
	LVEF ≥ 50%	Continue treatment with KADCYLA.
Heart Failure	Symptomatic CHF, Grade 3-4 LVSD or Grade 3-4 heart failure, or Grade 2 heart failure accompanied by LVEF < 45%	Discontinue KADCYLA
Peripheral Neuropathy	Grade 3-4	Do not administer KADCYLA until resolution Grade ≤ 2
Pulmonary Toxicity	Interstitial lung disease (ILD) or pneumonitis	Permanently discontinue KADCYLA
Radiotherapy-Related Pneumonitis	Grade 2	Discontinue KADCYLA if not resolving with standard treatment
	Grade 3-4	Discontinue KADCYLA

ALT = alanine transaminase; AST = aspartate transaminase, CHF = congestive heart failure, DILI = Drug Induced Liver Injury; LVEF = left ventricular ejection fraction, LVSD = left ventricular systolic dysfunction, TBILI = Total Bilirubin, ULN = upper limit of normal

*Prior to starting KADCYLA treatment

2.4 Preparation for Administration

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.

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 medicinal products.

Reconstitution:

- Use aseptic technique for reconstitution and preparation of dosing solution. Appropriate procedures for the preparation of chemotherapeutic drugs should be used.
- 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.* 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.
- The reconstituted lyophilized vials should be used immediately following reconstitution with Sterile Water for Injection. If not used immediately, the reconstituted KADCYLA vials can be stored for up to 24 hours in a refrigerator at 2ºC to 8ºC (36°F to 46°F); discard unused KADCYLA after 24 hours. *Do not freeze.*
- The reconstituted product contains no preservative and is intended for single-dose only.

Dilution:

Determine the correct dose (mg) of KADCYLA *[see Dosage and Administration (2.1)]*.

- Calculate the volume of the 20 mg/mL reconstituted KADCYLA solution needed.
- Withdraw this amount from the vial and add it to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection. *Do not use Dextrose (5%) solution.*
- Gently invert the bag to mix the solution in order to avoid foaming.
- 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.*

3 DOSAGE FORMS AND STRENGTHS

Lyophilized powder in single-dose vials: 100 mg per vial or 160 mg per vial of ado-trastuzumab emtansine.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

Hepatotoxicity, predominantly in the form of asymptomatic, transient increases in the concentrations of serum transaminases, has been observed in clinical trials with KADCYLA *[see Adverse Reactions (6.1)]*. Serious hepatotoxicity, including 3 fatal cases, has been observed in clinical trials (n=1624) with KADCYLA as single-agent. All fatal cases occurred in MBC clinical trials with KADCYLA, which included severe drug-induced liver injury and associated hepatic encephalopathy. Some of the patients experiencing hepatotoxicity had comorbidities and/or 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 liver disease (such as, hepatitis B virus or hepatitis C virus) were excluded from the EMILIA and KATHERINE studies *[see Clinical Studies (14.1)]*. Reduce the dose or discontinue KADCYLA as appropriate in cases of increased serum transaminases and/or total bilirubin *[see Dosage and Administration (2.2)]*. Permanently discontinue KADCYLA treatment in patients with serum transaminases > 3 x ULN and concomitant total bilirubin > 2 x ULN. KADCYLA has not been studied in patients with serum transaminases > 2.5 x ULN or bilirubin > 1.5 x ULN prior to the initiation of treatment.

In clinical trials of KADCYLA, cases of nodular regenerative hyperplasia (NRH) of the liver have been identified from liver biopsies (5 cases out of 1624 treated patients, one of which was fatal). Two of these five cases of NRH were observed in EMILIA and two were observed in KATHERINE [see Adverse Reactions (6.1)]. NRH is a rare liver condition characterized by widespread benign transformation of hepatic parenchyma into small regenerative nodules; NRH may lead to non-cirrhotic portal hypertension. The diagnosis of NRH can be confirmed only by histopathology. NRH should be considered in all patients with clinical symptoms of portal hypertension and/or cirrhosis-like pattern seen on the computed tomography (CT) scan of the liver but with normal transaminases and no other manifestations of cirrhosis. Upon diagnosis of NRH, KADCYLA treatment must be permanently discontinued.

5.2 Left Ventricular Dysfunction

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. Serious cases of heart failure, with no fatal cases, have been observed in clinical trials 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 lapatinib plus capecitabine-treated group. In KATHERINE, left ventricular dysfunction occurred in 0.4% of patients in the KADCYLA-treated group and 0.6% of patients in the trastuzumab-treated group *[see Adverse Reactions (6.1)]*.

Based on limited data from a retrospective observational study, 22% (7 of 32) of patients with HER2-positive metastatic breast cancer (MBC) with a baseline LVEF of 40-49% treated with KADCYLA developed a congestive heart failure (CHF) or a > 10% reduction in LVEF *[see Adverse Reactions (6.3)]*.

Assess LVEF prior to initiation of KADCYLA and at regular intervals (e.g. every three months) during treatment to ensure the LVEF is within the institution's normal limits. KADCYLA has not been studied in an adequately controlled study in patients with LVEF<50%

For patients with MBC, 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.

For patients with EBC, if, at routine monitoring, LVEF is < 45%, or is 45% to 49% 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 *[see Dosage and Administration (2.2)]*.

Patients with a history of symptomatic CHF, serious cardiac arrhythmia, or history of myocardial infarction or unstable angina within 6 months were excluded from the EMILIA and KATHERINE studies *[see Clinical Studies (14.1)]*.

5.3 Embryo-Fetal Toxicity

KADCYLA can cause fetal harm when administered to a pregnant woman. Cases of oligohydramnios, and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities and neonatal death were observed in the post-marketing setting in patients treated with trastuzumab, the antibody component of KADCYLA. DM1, the cytotoxic component of KADCYLA, can cause embryo-fetal toxicity based on its mechanism of action.

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 *[see Use in Specific Populations (8.1, 8.3)]*.

5.4 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 patients with MBC, pneumonitis was reported at an incidence of 0.8% (7 out of 884 treated patients), with one case of Grade 3 pneumonitis. The overall incidence of pneumonitis was 1.2% in EMILIA. 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 *[see Adverse Reactions (6.1)]*.

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 *[see Dose Modifications (2.2)]*.

Patients with dyspnea at rest due to complications of advanced malignancy, co-morbidities, and receiving concurrent pulmonary radiation therapy may be at increased risk of pulmonary toxicity.

5.5 Infusion-Related Reactions, Hypersensitivity Reactions

Treatment with KADCYLA has not been studied in patients who had trastuzumab permanently discontinued due to infusion-related reactions (IRRs) 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 EMILIA, the overall incidence of IRRs in patients treated with KADCYLA was

1.4%. In KATHERINE, the overall incidence of IRRs in patients treated with KADCYLA was 1.6% *[see Adverse Reactions (6.1)]*. 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. KADCYLA treatment should be permanently discontinued in the event of a life-threatening IRR *[see Dosage and Administration (2.2)]*. Patients should be observed closely for IRR reactions, especially during the first infusion.

One case of a serious, allergic/anaphylactic-like 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.

5.6 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 overall incidence of hemorrhage was 32% in the KADCYLA-treated group and 16% in the lapatinib plus capecitabine-treated group. The incidence of Grade ≥ 3 hemorrhage was 1.8% in the KADCYLA-treated group and 0.8% in the lapatinib plus capecitabine-treated group. In KATHERINE, the overall incidence of hemorrhage was 29% in the KADCYLA-treated group and 10% in the trastuzumab-treated group. The incidence of Grade ≥ 3 hemorrhage was 0.4% in the KADCYLA-treated group, with one fatal case of intracranial hemorrhage, and 0.3% in the trastuzumab-treated group *[see Adverse Reactions (6.1)]*. Although, in some of the observed cases the patients were also receiving anti-coagulation therapy, 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.

5.7 Thrombocytopenia

Thrombocytopenia, or decreased platelet count, was reported in clinical trials of KADCYLA (145 of 1624 treated patients with Grade ≥ 3; 494 of 1624 treated patients with any Grade). 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 overall incidence of thrombocytopenia was 31% in the KADCYLA-treated group and 3.3% in the lapatinib plus capecitabine-treated group *[see Adverse Reactions (6.1)]*. The incidence of Grade ≥ 3 thrombocytopenia was 15% in the KADCYLA-treated group and 0.4% in the lapatinib plus capecitabine-treated group. In Asian patients, the incidence of Grade ≥ 3 thrombocytopenia was 45% in the KADCYLA-treated group and 1.3% in the lapatinib plus capecitabine-treated group.

In KATHERINE, the overall incidence of thrombocytopenia was 29% in the KADCYLA-treated group and 2.4% in the trastuzumab-treated group *[see Adverse Reactions (6.1)]*. The incidence of Grade ≥ 3 thrombocytopenia was 6% in the KADCYLA-treated group and 0.3% in the trastuzumab-treated group. In Asian patients, the incidence of Grade ≥ 3 thrombocytopenia was 19% in the KADCYLA-treated group and 0% in the trastuzumab-treated group. The overall incidence of thrombocytopenia in the KADCYLA-treated group for Asian patients was 50%.

Monitor platelet counts prior to initiation of KADCYLA and prior to each KADCYLA dose *[see Dosage and Administration (2.2)]*. 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 (< 50,000/mm^3) do not administer KADCYLA until platelet counts recover to Grade 1 (≥ 75,000/mm^3) *[see Dosage and Administration (2.2)]*. Closely monitor patients with thrombocytopenia (< 100,000/mm^3) and patients on anti-coagulant treatment during treatment with KADCYLA.

5.8 Neurotoxicity

Peripheral neuropathy, mainly as Grade 1 and predominantly sensory, was reported in clinical trials of KADCYLA (26 of 1624 treated patients with Grade ≥ 3; 435 of 1624 treated patients with any Grade). In EMILIA, the overall incidence of peripheral neuropathy was 21% in the KADCYLA-treated group and 14% in the lapatinib plus capecitabine-treated group *[see Adverse Reactions (6.1)]*. The incidence of Grade ≥ 3 peripheral neuropathy was 2.2% in the KADCYLA-treated group and 0.2% in the lapatinib plus capecitabine-treated group. In KATHERINE, the overall incidence of peripheral neuropathy was 32% in the KADCYLA-treated group and 17% in the trastuzumab-treated group. Peripheral neuropathy, including sensory and motor peripheral neuropathy, for KADCYLA treated patients 30% of cases were not resolved at the time of the primary IDFS analysis for KATHERINE. The incidence of Grade ≥ 3 peripheral neuropathy was 1.6% in the KADCYLA-treated group and 0.1% in the trastuzumab-treated 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 or symptoms of neurotoxicity *[see Nonclinical Toxicology (13.2)]*.

5.9 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 erythema, tenderness, skin irritation, pain, or swelling at the infusion site. Specific treatment for KADCYLA extravasation is unknown. The infusion site should be closely monitored for possible subcutaneous infiltration during drug administration.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Hepatotoxicity *[See Warnings and Precautions (5.1)]*
- Left Ventricular Dysfunction *[See Warnings and Precautions (5.2)]*
- Embryo-Fetal Toxicity *[See Warnings and Precautions (5.3)]*
- Pulmonary Toxicity *[See Warnings and Precautions (5.4)]*
- Infusion-Related Reactions, Hypersensitivity Reactions *[See Warnings and Precautions (5.5)]*
- Hemorrhage *[See Warnings and Precautions (5.6)]*
- Thrombocytopenia *[See Warnings and Precautions (5.7)]*
- Neurotoxicity *[See Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in the WARNINGS AND PRECAUTIONS reflect exposure to KADCYLA as a single agent at 3.6 mg/kg given as an intravenous infusion every 3 weeks (21-day cycle) in 1624 patients including 884 patients with HER2-positive metastatic breast cancer and 740 patients with HER2-positive early breast cancer (KATHERINE trial).

Metastatic Breast Cancer

In clinical trials, KADCYLA has been evaluated as single-agent in 884 patients with HER2-positive metastatic breast cancer. The most common (≥ 25%) adverse reactions were fatigue, nausea,

musculoskeletal pain, hemorrhage, thrombocytopenia, headache, increased transaminases, constipation and epistaxis.

The adverse reactions described in Table 3 were identified in patients with HER2-positive metastatic breast cancer treated in the EMILIA trial *[see Clinical Studies (14.1)]*. Patients were randomized to receive KADCYLA or lapatinib plus capecitabine. The median duration of study treatment was 7.6 months for patients in the KADCYLA-treated group and 5.5 months and 5.3 months for patients treated with lapatinib and capecitabine, respectively.

In the EMILIA trial, 43% of patients experienced Grade ≥ 3 adverse reactions in the KADCYLA-treated group compared with 59% of patients in the lapatinib plus capecitabine-treated group.

Dose adjustments for KADCYLA were permitted *[see Dosage and Administration (2.2)]*. Thirty-two patients (7%) discontinued KADCYLA due to an adverse reaction, compared with 41 patients (8%) who discontinued lapatinib, and 51 patients (10%) who discontinued capecitabine due to an adverse reaction. The most common adverse reactions leading to KADCYLA discontinuation were thrombocytopenia and increased transaminases. Eighty patients (16%) treated with KADCYLA had adverse reactions leading to dose reductions. The most frequent adverse reactions leading to dose reduction of KADCYLA (in ≥ 1% of patients) included thrombocytopenia, increased transaminases, and peripheral neuropathy. Adverse reactions that led to dose delays occurred in 116 (24%) of KADCYLA treated patients. The most frequent adverse reactions leading to a dose delay of KADCYLA (in ≥ 1% of patients) were neutropenia, thrombocytopenia, leukopenia, fatigue, increased transaminases and pyrexia.

Table 3 reports the adverse reactions that occurred in patients in the KADCYLA-treated group (n=490) of the EMILIA trial. Selected laboratory abnormalities are shown in Table 4. The most common adverse reactions seen with KADCYLA in the randomized trial (frequency > 25%) were nausea, fatigue, musculoskeletal pain, hemorrhage, thrombocytopenia, increased transaminases, headache, and constipation. The most common NCI–CTCAE (version 3) Grade ≥ 3 adverse reactions (frequency > 2%) were thrombocytopenia, increased transaminases, anemia, hypokalemia, peripheral neuropathy and fatigue.

Table 3 Adverse Reactions Occurring in ≥ 10% of Patients on the KADCYLA Treatment Arm in the EMILIA Trial[1]

Adverse Reactions	**KADCYLA (3.6 mg/kg) n=490**		**Lapatinib (1250 mg) + Capecitabine (2000 mg/m^2) n=488**	
	All Grades (%)	**Grade 3 – 4 (%)**	**All Grades (%)**	**Grade 3 – 4 (%)**
Blood and Lymphatic System Disorders				
Thrombocytopenia	31	15	3.3	0.4
Anemia	14	4.1	11	2.5
Gastrointestinal Disorders				
Nausea	40	0.8	45	2.5
Constipation	27	0.4	11	0

Adverse Reactions	KADCYLA (3.6 mg/kg) n=490		Lapatinib (1250 mg) + Capecitabine (2000 mg/m^2) n=488	
	All Grades (%)	**Grade 3 – 4 (%)**	**All Grades (%)**	**Grade 3 – 4 (%)**
Diarrhea	24	1.6	80	21
Vomiting	19	0.8	30	4.5
Abdominal pain	19	0.8	18	1.6
Dry Mouth	17	0	4.9	0.2
Stomatitis	14	0.2	33	2.5
General Disorders and Administration				
Fatigue	36	2.5	28	3.5
Pyrexia	19	0.2	8	0.4
Asthenia	18	0.4	18	1.6
Investigations				
Transaminases increased	29	8.0	14	2.5
Metabolism and Nutrition Disorders				
Hypokalemia	10	2.7	9	4.7
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain	36	1.8	31	1.4
Arthralgia	19	0.6	8	0
Myalgia	14	0.6	3.7	0
Nervous System Disorders				
Headache	28	0.8	15	0.8
Peripheral neuropathy	21	2.2	14	0.2
Dizziness	10	0.4	11	0.2
Psychiatric Disorders				
Insomnia	12	0.4	9	0.2

Adverse Reactions	KADCYLA (3.6 mg/kg) n=490		Lapatinib (1250 mg) + Capecitabine (2000 mg/m^2) n=488	
	All Grades (%)	**Grade 3 – 4 (%)**	**All Grades (%)**	**Grade 3 – 4 (%)**
Respiratory, Thoracic, and Mediastinal Disorders				
Epistaxis	23	0.2	8	0
Cough	18	0.2	13	0.2
Dyspnea	12	0.8	8	0.4
Skin and Subcutaneous Tissue Disorders				
Rash	12	0	28	1.8
Vascular Disorders				
Hemorrhage	32	1.8	16	0.8

1 Grouped terms were used for the following Adverse Reactions:

Thrombocytopenia: thrombocytopenia, platelet count decreased

Anemia: anemia, hemoglobin decreased

Abdominal pain: abdominal pain, abdominal pain upper

Stomatitis: stomatitis, mucosal inflammation, oropharyngeal pain

Transaminases Increased: transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic enzyme increased, hepatic function abnormal

Hypokalemia: hypokalemia, blood potassium decreased

Musculoskeletal Pain: muscle spasms, musculoskeletal discomfort, musculoskeletal chest pain, back pain, pain in extremity, bone pain, musculoskeletal pain

Peripheral neuropathy: neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy, paresthesia

Hemorrhage: Hemorrhage terms (excl laboratory terms) (SMQ, wide), Hemorrhage laboratory terms (SMQ, narrow).

SMQ=standardized MedDRA queries

The following clinically relevant adverse reactions were reported in < 10% of patients in the KADCYLA-treated group in EMILIA: dyspepsia (9%), urinary tract infection (9%), chills (8%), dysgeusia (8%), neutropenia (7%), peripheral edema (7%), pruritus (6%), hypertension (5%), blood alkaline phosphatase increased (4.7%), vision blurred (4.5%), conjunctivitis (3.9%), dry eye (3.9%), lacrimation increased (3.3%), drug hypersensitivity (2.2%), left ventricular dysfunction (1.8%), infusion-related reaction (1.4%), pneumonitis (1.2%), nodular regenerative hyperplasia (0.4%), portal hypertension (0.4%).

Table 4 Selected Laboratory Abnormalities (EMILIA)

Parameter	KADCYLA (3.6 mg/kg)			Lapatinib (1250 mg) + Capecitabine (2000 mg/m^2)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Chemistry						
Increased AST	98	7	0.5	65	3	0
Increased ALT	82	5	0.2	54	3	0
Decreased potassium	33	3	0	31	6	0.8
Increased bilirubin	17	0.6	0	57	2	0
Hematology						
Decreased platelet count	83	14	3	21	0.4	0.6
Decreased hemoglobin	60	4	1	64	3	0.2
Decreased neutrophils	39	3	0.6	38	6	2

Early Breast Cancer

KADCYLA has been evaluated as a single-agent in 740 patients with HER2-positive early breast cancer.

The adverse reactions described in Table 5 were identified in patients with HER2-positive early breast cancer treated in the KATHERINE trial *[see Clinical Studies (14.2)]*. Patients were randomized to receive KADCYLA or trastuzumab. The median duration of study treatment was 10 months for patients in the KADCYLA-treated group and 10 months for patients treated with trastuzumab.

One hundred and ninety (26%) patients experienced Grade ≥ 3 adverse reactions in the KADCYLA-treated group compared with 111 (15%) patients in the trastuzumab group. One hundred and thirty-three patients (18%) discontinued KADCYLA due to an adverse reaction, compared with 15 patients (2.1%) who discontinued trastuzumab due to an adverse reaction.

The most common adverse reactions leading to KADCYLA discontinuation (in ≥ 1% of patients) were platelet count decreased, blood bilirubin increased, ejection fraction decreased, AST increased, ALT increased, and peripheral neuropathy.

Dose adjustments for KADCYLA were permitted *[see Dosage and Administration (2.2)]*. One hundred and six patients (14%) treated with KADCYLA had dose reductions. The most frequent adverse reactions leading to dose reduction of KADCYLA (in ≥ 1% of patients) included thrombocytopenia, increased transaminases, blood bilirubin and fatigue. Adverse reactions that led to dose delays occurred in 106 (14%) of KADCYLA treated patients. The most frequent adverse reactions leading to a dose delay of KADCYLA (in ≥ 1% of patients) were neutropenia, thrombocytopenia and AST increased.

Selected laboratory abnormalities are shown in Table 6. The most common adverse reactions seen with KADCYLA in the randomized 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 (> 2%) were thrombocytopenia and hypertension.

Table 5 Adverse Reactions Occurring in ≥ 10% of Patients in the KATHERINE Trial[1]

Adverse Reactions	KADCYLA n=740		Trastuzumab n=720	
	All grades (%)	Grade 3 – 4 (%)	All grades (%)	Grade 3 – 4 (%)
Blood and Lymphatic System Disorders				
Thrombocytopenia	29	6	2.4	0.3
Anemia	10	1.1	9	0.1
Gastrointestinal Disorders				
Nausea	42	0.5	13	0.3
Constipation	17	0.1	8	0
Stomatitis	15	0.1	8	0.1
Vomiting	15	0.5	5	0.3
Dry Mouth	14	0.1	1.3	0
Diarrhea	12	0.8	13	0.3
Abdominal pain	11	0.4	7	0.3
General Disorders and Administration				
Fatigue	50	1.1	34	0.1
Pyrexia	10	0	4	0
Infections and Infestations				
Urinary tract infection	10	0.3	6	0.1
Investigations				
Transaminases increased	32	1.5	8	0.4
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain	30	0.7	29	0.7

Adverse Reactions	KADCYLA n=740		Trastuzumab n=720	
	All grades (%)	Grade 3 – 4 (%)	All grades (%)	Grade 3 – 4 (%)
Arthralgia	26	0.1	21	0
Myalgia	15	0.4	11	0
Nervous System Disorders				
Headache	28	0	17	0.1
Peripheral neuropathy	28	1.6	14	0.1
Dizziness	10	0.1	8	0.3
Psychiatric Disorders				
Insomnia	14	0	12	0.1
Respiratory, Thoracic, and Mediastinal Disorders				
Epistaxis	22	0	3.5	0
Cough	14	0.1	12	0
Vascular Disorders				
Hemorrhage	29	0.4*	10	0.3

[1] Grouped terms were used for the following Adverse Reactions:

Thrombocytopenia: thrombocytopenia, platelet count decreased

Anemia: anemia, hemoglobin decreased

Stomatitis: stomatitis, mucosal inflammation, oropharyngeal pain

Abdominal pain: abdominal pain, abdominal pain upper

Urinary Tract Infection: urinary tract infection, cystitis

Transaminases Increased: transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic enzyme increased, hepatic function abnormal

Musculoskeletal Pain: muscle spasms, musculoskeletal discomfort, musculoskeletal chest pain, back pain, pain in extremity, bone pain, musculoskeletal pain

Peripheral neuropathy: neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy, paresthesia

Hemorrhage: Hemorrhage terms (excl laboratory terms) (SMQ, wide), Hemorrhage laboratory terms (SMQ, narrow)

*Included one fatal hemorrhage.

SMQ=standardized MedDRA queries

The following clinically relevant adverse reactions were reported in < 10% of patients in the KADCYLA-treated group in KATHERINE: blood alkaline phosphatase increased (8%), dysgeusia

(8%), dyspnea (8%), neutropenia (8%), blood bilirubin increased (7%), hypokalemia (7%), pruritus (7%), hypertension (6%), lacrimation increased (6%), chills (5%), dry eye (4.5%), dyspepsia (4.3%), peripheral edema (3.9%),vision blurred (3.9%), conjunctivitis (3.5%), left ventricular dysfunction (3.0%), drug hypersensitivity (2.7%), infusion-related reaction (1.6%), radiation pneumonitis (1.5%), pneumonitis (1.1%), rash (1.1%), asthenia (0.4%), nodular regenerative hyperplasia (0.3%).

Table 6 Selected Laboratory Abnormalities (KATHERINE)

Parameter	KADCYLA n=740			Trastuzumab n=720		
	All Grade (%)	**Grade 3 (%)**	**Grade 4 (%)**	**All Grade (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Chemistry						
Increased AST	79	0.8	0	21	0.1	0
Increased ALT	55	0.7	0	21	0.1	0
Decreased potassium	26	2	0.5	9	0.7	0.1
Increased bilirubin	12	0	0	4	0.7	0
Hematology						
Decreased platelet count	51	4	2	13	0.1	0.1
Decreased hemoglobin	31	1	0	29	0.3	0
Decreased neutrophils	24	1	0	19	0.6	0.6

6.2 Immunogenicity

As with all therapeutic proteins, there is the potential for an immune response to KADCYLA. A total of 1243 patients from seven clinical studies were tested at multiple time points for anti-drug antibody (ADA) responses to KADCYLA. Following KADCYLA dosing, 5.1% (63/1243) of patients tested positive for anti-KADCYLA antibodies at one or more post-dose time points. In clinical studies, 6.4% (24/376) of patients tested positive for anti-KADCYLA antibodies. In EMILIA, 5.2% (24/466) of patients tested positive for anti-KADCYLA antibodies, of which 13 were also positive for neutralizing antibodies. In KATHERINE, 3.7% (15/401) of patients tested positive for anti-KADCYLA antibodies, of which 5 were also positive for neutralizing antibodies. Due to the low incidence of ADA, conclusions cannot be made on the impact of anti-KADCYLA antibodies on the pharmacokinetics, safety, and efficacy of KADCYLA. The presence of KADCYLA in patient serum at the time of ADA sampling may interfere with the ability of this assay to detect anti-KADCYLA antibodies. As a result, data may not accurately reflect the true incidence of anti-KADCYLA antibody development.

Immunogenicity data are highly dependent on the sensitivity and specificity of the test methods used. Additionally, the observed incidence of a positive result in a test method may be influenced by several factors, including sample handling, timing of sample collection, drug interference, concomitant medication and the underlying disease. Therefore, comparison of the incidence of antibodies to KADCYLA with the incidence of antibodies to other products may be misleading. Clinical significance of anti-KADCYLA antibodies is not yet known.

6.3 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of KADCYLA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse Reactions from Observational Studies

- CHF and > 10% reduction in LVEF in patients with HER2-positive metastatic breast cancer with a baseline LVEF of 40-49% treated with KADCYLA *[see Warnings and Precautions (5.2)]*.

Adverse Reactions from Postmarketing Spontaneous Reports

- Tumor lysis syndrome (TLS): Cases of possible TLS have been reported in patients treated with KADCYLA. Patients with significant tumor burden (e.g., bulky metastases) may be at a higher risk. Patients could present with hyperuricemia, hyperphosphatemia, and acute renal failure which may represent possible TLS. Providers should consider additional monitoring and/or treatment as clinically indicated.

7 DRUG INTERACTIONS

No formal drug-drug interaction studies with KADCYLA have been conducted. *In vitro* studies indicate that DM1, the cytotoxic component of KADCYLA, is metabolized mainly by CYP3A4 and to a lesser extent by CYP3A5. Concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole) with KADCYLA should be avoided due to the potential for an increase in DM1 exposure and toxicity. Consider an alternate medication with no or minimal potential to inhibit CYP3A4. If concomitant use of strong CYP3A4 inhibitors is unavoidable, consider delaying KADCYLA treatment until the strong CYP3A4 inhibitors have cleared from the circulation (approximately 3 elimination half-lives of the inhibitors) when possible. If a strong CYP3A4 inhibitor is coadministered and KADCYLA treatment cannot be delayed, patients should be closely monitored for adverse reactions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Pharmacovigilance Program

There is a pregnancy pharmacovigilance program for 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, health care providers and patients should immediately report KADCYLA exposure to Genentech at 1-888-835-2555.

Risk Summary

KADCYLA can cause fetal harm when administered to a pregnant woman. There are no available data on the use of KADCYLA in pregnant women. Cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death were observed in the postmarketing setting in patients treated with trastuzumab, the antibody component of KADCYLA *[see Data]*. Based on its mechanism of action, the DM1 component of KADCYLA can also cause embryo-fetal harm when administered to a pregnant woman [*see Data*]. Apprise the patient of the potential risks to a fetus. There are clinical considerations if KADCYLA is used in a pregnant woman, or if a patient becomes pregnant within 7 months following the last dose of KADCYLA *[see Clinical Considerations]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Monitor women who received KADCYLA during pregnancy or within 7 months prior to conception for oligohydramnios. If oligohydramnios occurs, perform fetal testing that is appropriate for gestational age and consistent with community standards of care.

Data

Human Data

There are no available data on the use of KADCYLA in pregnant women. In the post-marketing setting, cases of oligohydramnios, and of oligohydramnios sequence, manifesting in the fetus as pulmonary hypoplasia, skeletal abnormalities and neonatal death were observed after treatment with trastuzumab during pregnancy. These case reports described oligohydramnios in pregnant women who received trastuzumab either alone or in combination with chemotherapy. In some case reports, amniotic fluid index increased after trastuzumab was stopped. In one case, trastuzumab therapy resumed after amniotic index improved, and oligohydramnios recurred.

Animal Data

There were no reproductive and developmental toxicology studies conducted with ado-trastuzumab emtansine. DM1, the cytotoxic component of KADCYLA, disrupts microtubule function. DM1 is toxic to rapidly dividing cells in animals and is genotoxic, suggesting it has the potential to cause embryotoxicity and teratogenicity. In studies where trastuzumab was administered to pregnant cynomolgus monkeys during the period of organogenesis at doses up to 25 mg/kg given twice weekly (about 7 times the clinical dose), trastuzumab crossed the placental barrier during the early (Gestation Days 20 to 50) and late (Gestation Days 120 to 150) phases of gestation. The resulting concentrations of trastuzumab in fetal serum and amniotic fluid were approximately 33% and 25%, respectively, of those present in the maternal serum but were not associated with adverse developmental effects.

8.2 Lactation

Risk Summary

There is no information regarding the presence of ado-trastuzumab emtansine in human milk, the effects on the breastfed infant, or the effects on milk production. DM1, the cytotoxic component of KADCYLA, may cause serious adverse reactions in breastfed infants based on its mechanism of action *[see Data]*. Advise women not to breastfeed during treatment and for 7 months following the last dose of KADCYLA.

Data

There were no animal lactation studies conducted with ado-trastuzumab emtansine or the cytotoxic component of KADCYLA (DM1). In lactating cynomolgus monkeys, trastuzumab was present in breast milk at about 0.3% of maternal serum concentrations after pre- (beginning Gestation Day 120) and post-partum (through Post-partum Day 28) doses of 25 mg/kg administered twice weekly (about 7 times the clinical dose of KADCYLA). Infant monkeys with detectable serum levels of trastuzumab did not exhibit any adverse effects on growth or development from birth to 1 month of age.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to the initiation of KADCYLA.

Contraception

Females

KADCYLA can cause embryo-fetal harm when administered during pregnancy. Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of KADCYLA [*see Use in Specific Populations (8.1)*].

Males

Because of the potential for genotoxicity, advise male patients with female partners of reproductive potential to use effective contraception during treatment with KADCYLA and for 4 months following the last dose.

Infertility

Based on results from animal toxicity studies, KADCYLA may impair fertility in females and males of reproductive potential. It is not known if the effects are reversible *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness of KADCYLA have not been established in pediatric patients.

8.5 Geriatric Use

Of the 495 patients who were randomized to KADCYLA in EMILIA *[see Clinical Studies (14.1)]*, 65 patients (13%) were ≥ 65 years of age and 11 patients (2%) were ≥ 75 years of age. In patients ≥ 65 years old (n=138 across both treatment arms) the hazard ratios for progression-free survival (PFS) and overall survival (OS) were 1.06 (95% CI: 0.68, 1.66) and 1.05 (95% CI: 0.58, 1.91), respectively. No overall differences in the safety of KADCYLA were observed in patients aged ≥ 65 compared to patients < 65 years of age. EMILIA did not include sufficient numbers of patients aged ≥ 75 years to draw conclusions on the safety or effectiveness of KADCYLA in this age group.

Of the 743 patients who were randomized to KADCYLA in KATHERINE *[see Clinical Studies (14.2)]*, 58 patients (8%) were ≥ 65 years of age and 2 patients (0.3%) were ≥ 75 years of age. No overall differences in the safety or effectiveness of KADCYLA were observed in patients aged ≥ 65 compared to patients < 65 years of age. KATHERINE did not include sufficient numbers of patients aged ≥ 75 years to draw conclusions on the safety or effectiveness of KADCYLA in this age group.

Population pharmacokinetic analysis indicates that age does not have a clinically meaningful effect on the pharmacokinetics of ado-trastuzumab emtansine *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

No dedicated renal impairment trial for KADCYLA has been conducted. Based on the population pharmacokinetics, as well as analysis of Grade 3 or greater adverse reactions and dose modifications, dose adjustments of KADCYLA are not needed in patients with mild (creatinine clearance [CLcr] 60 to 89 mL/min) or moderate (CLcr 30 to 59 mL/min) renal impairment. No dose adjustment can be recommended for patients with severe renal impairment (CLcr less than 30 mL/min) because of the limited data available *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No adjustment to the starting dose is required for patients with mild or moderate hepatic impairment *[see Clinical Pharmacology (12.3)]*. KADCYLA was not studied in patients with severe hepatic impairment. Closely monitor patients with hepatic impairment due to known hepatotoxicity observed with KADCYLA [*see Warnings and Precautions, Hepatotoxicity (5.1)*].

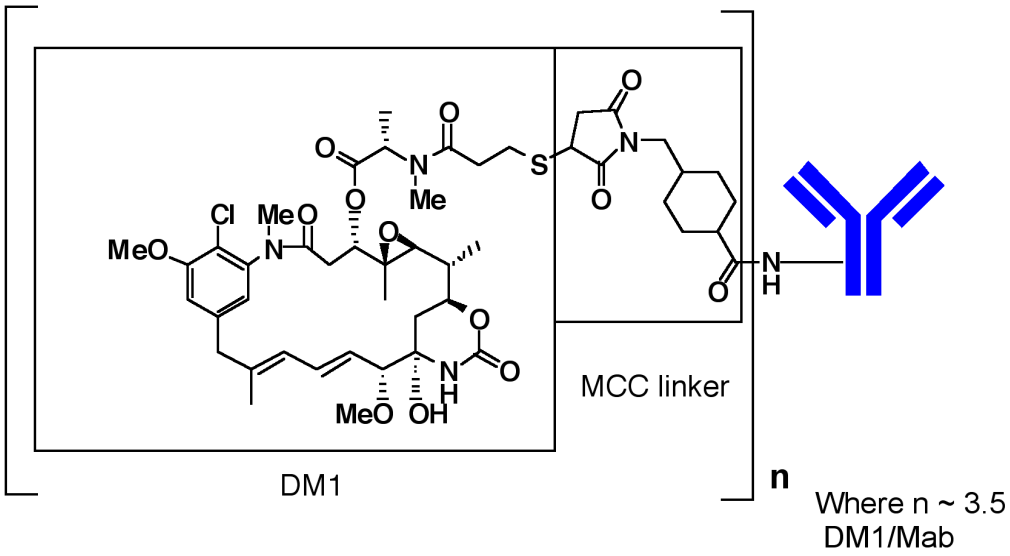
10 OVERDOSAGE

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

11 DESCRIPTION

KADCYLA (ado-trastuzumab emtansine) is a HER2-targeted antibody-drug conjugate (ADC) which contains the humanized anti-HER2 IgG1, trastuzumab, covalently linked to the microtubule inhibitory drug DM1 (a maytansine derivative) via the stable thioether linker MCC (4-[N-maleimidomethyl] cyclohexane-1-carboxylate). Emtansine refers to the MCC-DM1 complex.

The antibody trastuzumab, is a well characterized recombinant monoclonal antibody product produced by mammalian (Chinese hamster ovary) cells, and the small molecule components (DM1 and MCC) are produced by chemical synthesis. Ado-trastuzumab emtansine contains an average of 3.5 DM1 molecules per antibody. Ado-trastuzumab emtansine has the following chemical structure:



Note: The bracketed structure is DM1 plus MCC which represents the emtansine component. The n is, on average, 3.5 DM1 molecules per trastuzumab (Mab) molecule.

KADCYLA (ado-trastuzumab emtansine) is a sterile, white to off-white preservative free lyophilized powder in single-dose vials. Each vial contains 100 mg or 160 mg ado-trastuzumab emtansine. Following reconstitution, each single-dose vial contains ado-trastuzumab emtansine (20 mg/mL), polysorbate 20 [0.02% (w/v)], sodium succinate (10 mM), and sucrose [6% (w/v)] with a pH of 5.0. The resulting solution containing 20 mg/mL ado-trastuzumab emtansine is administered by intravenous infusion following dilution.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ado-trastuzumab emtansine is a HER2-targeted antibody-drug conjugate. The antibody is the humanized anti-HER2 IgG1, trastuzumab. The small molecule cytotoxin, DM1, is a microtubule inhibitor. Upon binding to sub-domain IV of the HER2 receptor, ado-trastuzumab emtansine undergoes receptor-mediated internalization and subsequent lysosomal degradation, resulting in intracellular release of DM1-containing

cytotoxic catabolites. Binding of DM1 to tubulin disrupts microtubule networks in the cell, which results in cell cycle arrest and apoptotic cell death. In addition, *in vitro* studies have shown that similar to trastuzumab, ado-trastuzumab emtansine inhibits HER2 receptor signaling, mediates antibody-dependent cell-mediated cytotoxicity and inhibits shedding of the HER2 extracellular domain in human breast cancer cells that overexpress HER2.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of multiple doses of KADCYLA (3.6 mg/kg every 3 weeks) on the QTc interval was evaluated in an open label, single arm study in 51 patients with HER2-positive metastatic breast cancer. No large changes in the mean QT interval (i.e., > 20 ms) were detected in the study.

12.3 Pharmacokinetics

The pharmacokinetics of KADCYLA was evaluated in a phase 1 study and in a population pharmacokinetic analysis for the ado-trastuzumab emtansine conjugate (ADC) using pooled data from 5 trials in patients with breast cancer. A linear two-compartment model with first-order elimination from the central compartment adequately describes the ADC concentration-time profile. In addition to ADC, the pharmacokinetics of total antibody (conjugated and unconjugated trastuzumab), DM1 were also determined. The population pharmacokinetic analysis of ADC suggested no difference in KADCYLA exposure based on disease status (adjuvant vs. metastatic setting). The pharmacokinetics of KADCYLA are summarized below.

Distribution

Maximum concentrations (C_{max}) of ADC and DM1 were observed close to the end of infusion. In EMILIA, mean (SD) ADC and DM1 Cycle 1 C_{max} following KADCYLA administration was 83.4 (16.5) μg/mL and 4.61 (1.61) ng/mL, respectively. In KATHERINE, mean (SD) ADC and DM1 Cycle 1 C_{max} following KADCYLA administration was 72.6 (24.3) μg/mL and 4.71 (2.25) ng/mL, respectively.

In vitro, the mean binding of DM1 to human plasma proteins was 93%. *In vitro,* DM1 was a substrate of P-glycoprotein (P-gp).

Based on population pharmacokinetic analysis, the central volume of distribution of ADC was 3.13 L.

Metabolism

In vitro studies indicate that DM1, the small molecule component of KADCYLA, undergoes metabolism by CYP3A4/5. DM1 did not inhibit or induce major CYP450 enzymes *in vitro.* In human plasma, ado-trastuzumab emtansine catabolites MCC-DM1, Lys-MCC-DM1, and DM1 were detected at low levels.

Elimination

Based on population pharmacokinetic analysis, following intravenous infusion of KADCYLA, the clearance of the ADC was 0.68 L/day and the elimination half-life ($t_{1/2}$) was approximately 4 days. No accumulation of KADCYLA was observed after repeated dosing of intravenous infusion every 3 weeks.

Based on population pharmacokinetic analysis (n=671), body weight, sum of longest diameter of target lesions by RECIST, HER2 extracellular domain (ECD) concentrations, AST, albumin, and baseline trastuzumab concentrations were identified as statistically significant covariates for ado-trastuzumab emtansine clearance. However, the magnitude of effect of these covariates on ado-trastuzumab emtansine exposure suggests that, with the exception of body weight, these covariates are unlikely to have a clinically meaningful effect on KADCYLA exposure. Therefore, the body weight based dose of 3.6 mg/kg every 3 weeks without correction for other covariates is considered appropriate.

Effect of Renal Impairment

Based on population pharmacokinetic analysis in 668 patients, including moderate (CLcr 30 - 59 mL/min, n=53) and mild (CLcr 60 - 89 mL/min, n=254) renal impairment, indicate that pharmacokinetics of the ADC is not affected by mild to moderate renal impairment as compared to normal renal function (CLcr ≥ 90 mL/min, n=361). Data from only one patient with severe renal impairment (CLcr < 30 mL/min) is available *[see Use in Specific Populations (8.7)]*.

Effect of Hepatic Impairment

The liver is a primary organ for eliminating DM1 and DM1-containing catabolites. The pharmacokinetics of ado-trastuzumab emtansine and DM1-containing catabolites were evaluated after the administration of 3.6 mg/kg of KADCYLA to metastatic HER2-positive breast cancer patients with normal hepatic function (n=10), mild (Child-Pugh A; n=10) and moderate (Child-Pugh B; n=8) hepatic impairment.

- Plasma concentrations of DM1 and DM1-containing catabolites (Lys-MCC-DM1 and MCC-DM1) were low and comparable between patients with and without hepatic impairment.
- Systemic exposures (AUC) of ado-trastuzumab emtansine at Cycle 1 in patients with mild and moderate hepatic impairment were approximately 38% and 67% lower than that of patients with normal hepatic function, respectively. Ado-trastuzumab emtansine exposure (AUC) at Cycle 3 after repeated dosing in patients with mild or moderate hepatic dysfunction was within the range observed in patients with normal hepatic function.

KADCYLA has not been studied in patients with severe hepatic impairment (Child-Pugh class C).

Effects of Age and Race

Based on population pharmacokinetic analysis, age (< 65 [n=577]; 65 - 75 (n=78); > 75 [n=16]) and race (Asian [n=73]; non-Asian [n=598]) do not have a clinically meaningful effect on the pharmacokinetics of ado-trastuzumab emtansine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with ado-trastuzumab emtansine.

DM1 was aneugenic or clastogenic in an *in vivo* single-dose rat bone marrow micronucleus assay at exposures that were comparable to mean maximum concentrations of DM1 measured in humans administered KADCYLA. DM1 was not mutagenic in an *in vitro* bacterial reverse mutation (Ames) assay.

Based on results from animal toxicity studies, KADCYLA may impair fertility in humans. In a single-dose toxicity study of ado-trastuzumab emtansine in rats, degeneration of seminiferous tubules with hemorrhage in the testes associated with increased weights of testes and epididymides at a severely toxic dose level (60 mg/kg; about 4 times the clinical exposure based on AUC) were observed. The same dose in female rats resulted in signs of hemorrhage and necrosis of the corpus luteum in ovaries. In monkeys dosed with ado-trastuzumab emtansine once every three weeks for 12 weeks (four doses), at up to 30 mg/kg (about 7 times the clinical exposure based on AUC), there were decreases in the weights of epididymides, prostate, testes, seminal vesicles and uterus, although the interpretation of these effects is unclear due to the varied sexual maturity of enrolled animals.

13.2 Animal Toxicology and/or Pharmacology

In monkeys, treatment with doses of ado-trastuzumab emtansine up to 30 mg/kg (about 7 times the clinical exposure based on AUC) caused dose dependent axonal degeneration in the sciatic nerve with hypertrophy or hyperplasia of the Schwann cells, and axonal degeneration of the dorsal funiculus in the spinal cord.

Based on the mechanism of action of the cytotoxic component DM1, there is clinical potential for neurotoxicity *[see Warnings and Precautions (5.8)]*.

14 CLINICAL STUDIES

14.1 Metastatic Breast Cancer

The efficacy of KADCYLA was evaluated in a randomized, multicenter, open-label trial (EMILIA) (NCT00829166) of 991 patients with HER2-positive, unresectable locally advanced or metastatic breast cancer. Prior taxane and trastuzumab-based therapy was required before trial enrollment. Patients with only prior adjuvant therapy were required to have disease recurrence during or within six months of completing adjuvant therapy. Breast tumor samples were required to show HER2 overexpression defined as 3+ IHC or FISH amplification ratio ≥ 2.0 determined at a central laboratory. Patients were randomly allocated (1:1) to receive lapatinib plus capecitabine or KADCYLA. Randomization was stratified by world region (United States, Western Europe, other), number of prior chemotherapy regimens for unresectable locally advanced or metastatic disease (0–1, > 1) and visceral versus non-visceral disease as determined by the investigators.

KADCYLA was given intravenously at 3.6 mg/kg on Day 1 of a 21-day cycle. Lapatinib was administered at 1250 mg/day orally once per day of a 21-day cycle and capecitabine was administered at 1000 mg/m^2 orally twice daily on Days 1−14 of a 21-day cycle. Patients were treated with KADCYLA or lapatinib plus capecitabine until progression of disease, withdrawal of consent, or unacceptable toxicity. At the time of the primary analysis, median time on study drug was 5.7 months (range: 0–28.4) for KADCYLA, 4.9 months (range: 0–30.8) for lapatinib, and 4.8 months (range: 0–30.4) for capecitabine.

The co-primary efficacy outcomes of the study were progression-free survival (PFS) based on tumor response assessments by an independent review committee (IRC), and overall survival (OS). PFS was defined as the time from the date of randomization to the date of disease progression or death from any cause (whichever occurred earlier). Overall survival was defined as the time from the date of randomization to the date of death from any cause. Additional outcomes included PFS (based on investigator tumor response assessments), objective response rate (ORR), duration of response and time to symptom progression.

Patient demographics and baseline tumor characteristics were balanced between treatment arms. All patients had metastatic disease at study entry. The median age was approximately 53 years (range 24-84 years), 74% were White, 18% were Asian and 5% were Black. All but 5 patients were women. Twenty-seven percent of patients were enrolled in United States, 32% in Europe and 16% in Asia. Tumor prognostic characteristics including hormone receptor status (positive: 55%, negative: 43%), presence of visceral disease (68%) and non-visceral disease only (33%) and the number of metastatic sites (< 3: 61%, ≥ 3: 37%) were similar in the study arms.

The majority of patients (88%) had received prior systemic treatment in the metastatic setting. Twelve percent of patients had prior treatment only in the neoadjuvant or adjuvant setting and had disease relapse within 6 months of treatment. All but one patient received trastuzumab prior to study entry; approximately 85% of patients received prior trastuzumab in the metastatic setting. Over 99% percent of patients had received a taxane, and 61% of patients had received an anthracycline prior to study entry. Overall, patients received a median of 3 systemic agents in the metastatic setting. Among patients with hormone receptor-positive tumors, 44.4% received prior adjuvant hormonal therapy and 44.8% received hormonal therapy for locally advanced/metastatic disease.

The randomized trial demonstrated a statistically significant improvement in IRC-assessed PFS in the KADCYLA-treated group compared with the lapatinib plus capecitabine-treated group [hazard ratio (HR) = 0.65, 95% CI: 0.55, 0.77, p < 0.0001], and an increase in median PFS of 3.2 months (median PFS of 9.6

months in the KADCYLA-treated group vs. 6.4 months in the lapatinib plus capecitabine group). See Table 7 and Figure 1. The results for investigator-assessed PFS were similar to those observed for IRC-assessed PFS.

At the time of PFS analysis, 223 patients had died. More deaths occurred in the lapatinib plus capecitabine arm (26%) compared with the KADCYLA arm (19%), however the results of this interim OS analysis did not meet the pre-specified stopping boundary for statistical significance. At the time of the second interim OS analysis, 331 events had occurred. The co-primary endpoint of OS was met; OS was significantly improved in patients receiving KADCYLA (HR = 0.68, 95% CI: 0.55, 0.85, p = 0.0006). This result crossed the pre-specified efficacy stopping boundary (HR = 0.73 or p = 0.0037). The median duration of survival was 30.9 months in the KADCYLA arm vs. 25.1 months in the lapatinib plus capecitabine arm. See Table 7 and Figure 2.

A treatment benefit with KADCYLA in terms of PFS and OS was observed in patient subgroups based on stratification factors, key baseline demographic and disease characteristics, and prior treatments. In the subgroup of patients with hormone receptor-negative disease (n=426), the hazard ratios for PFS and OS were 0.56 (95% CI: 0.44, 0.72) and 0.75 (95% CI: 0.54, 1.03), respectively. In the subgroup of patients with hormone receptor-positive disease (n=545), the hazard ratios for PFS and OS were 0.72 (95% CI: 0.58, 0.91) and 0.62 (95% CI: 0.46, 0.85), respectively. In the subgroup of patients with non-measurable disease (n=205), based on IRC assessments, the hazard ratios for PFS and OS were 0.91 (95% CI: 0.59, 1.42) and 0.96 (95% CI: 0.54, 1.68), respectively; in patients with measurable disease the hazard ratios were 0.62 (95% CI: 0.52, 0.75) and 0.65 (95% CI: 0.51, 0.82), respectively. The PFS and OS hazard ratios in patients who were younger than 65 years old (n=853) were 0.62 (95% CI: 0.52, 0.74) and 0.66 (95% CI: 0.52, 0.83), respectively. In patients ≥ 65 years old (n=138), the hazard ratios for PFS and OS were 1.06 (95% CI: 0.68, 1.66) and 1.05 (95% CI: 0.58, 1.91), respectively.

Table 7Summary of Efficacy from EMILIA

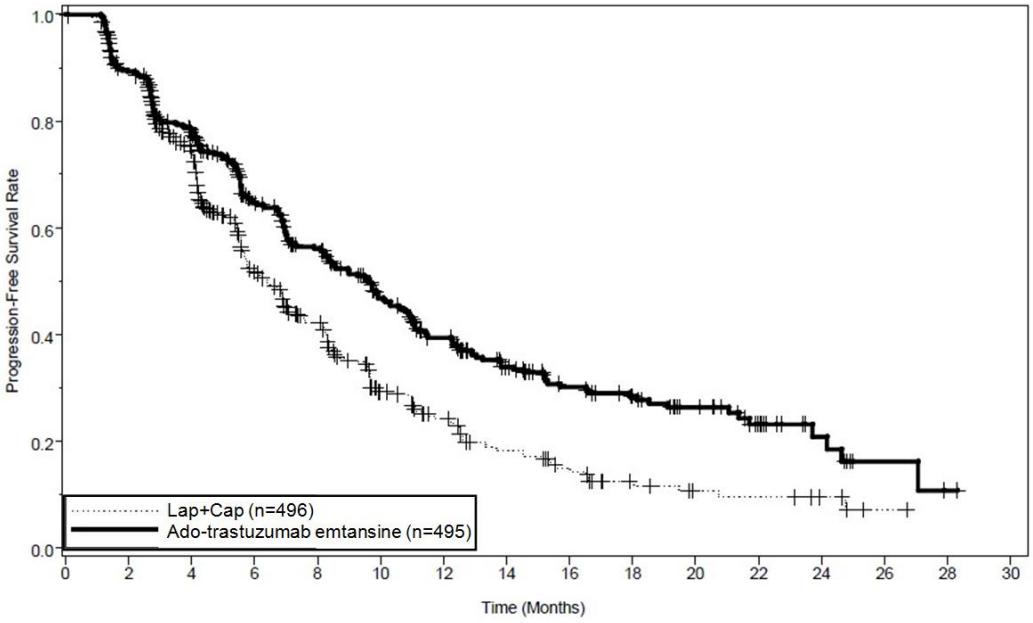
	KADCYLA N=495	Lapatinib+Capecitabine N=496
Progression-Free Survival (independent review)		
Number (%) of patients with event	265 (53.5%)	304 (61.3%)
Median duration of PFS (months)	9.6	6.4
Hazard Ratio (stratified*)	0.650	
95% CI for Hazard Ratio	(0.549, 0.771)	
p-value (Log-Rank test, stratified*)	< 0.0001	
Overall Survival †		
Number (%) of patients who died	149 (30.1%)	182 (36.7%)
Median duration of survival (months)	30.9	25.1
Hazard Ratio (stratified*)	0.682	
95% CI for Hazard Ratio	(0.548, 0.849)	
p-value (Log-Rank test*)	0.0006	
Objective Response Rate (independent review)		
Patients with measurable disease	397	389
Number of patients with OR (%)	173 (43.6%)	120 (30.8%)
Difference (95% CI)	12.7% (6.0, 19.4)	
Duration of Objective Response (months)		
Number of patients with OR	173	120
Median duration (95% CI)	12.6 (8.4, 20.8)	6.5 (5.5, 7.2)

PFS: progression-free survival; OR: objective response

* Stratified by world region (United States, Western Europe, other), number of prior chemotherapeutic regimens for locally advanced or metastatic disease (0-1 vs. > 1), and visceral vs. non-visceral disease.

† The second interim analysis for OS was conducted when 331 events were observed and the results are presented in this table.

Figure 1 Kaplan-Meier Curve of IRC-Assessed Progression-Free Survival for EMILIA

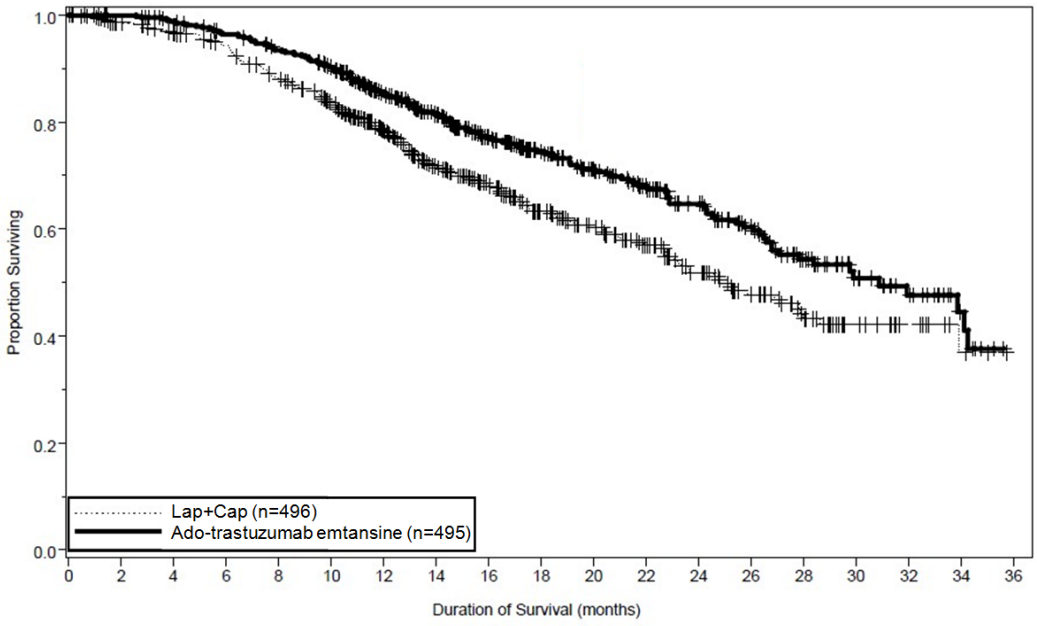


Number at Risk:

Lap+Cap (n=496)	496	404	310	176	129	73	53	35	25	14	9	8	5	1	0	0
Ado-trastuzumab emtansine (n=495)	495	419	341	236	183	130	101	72	54	44	30	18	9	3	1	0

Lap: lapatinib; Cap: capecitabine; IRC: independent review committee.
Hazard ratio is estimated based on a stratified Cox model; p-value is estimated based on a stratified log-rank test.

Figure 2 Kaplan-Meier Curve of Overall Survival for EMILIA



Number at Risk:

Lap+Cap (n=496)	496	471	453	435	403	368	297	240	204	159	133	110	86	63	45	27	17	7	4
Ado-trastuzumab emtansine (n=495)	495	485	474	457	439	418	349	293	242	197	164	136	111	86	62	38	28	13	5

Lap: lapatinib; Cap: capecitabine; IRC: independent review committee.
Hazard ratio is estimated based on a stratified Cox model; p-value is estimated based on a stratified log-rank test.

14.2 Early Breast Cancer

KATHERINE (NCT01772472) was a randomized, multicenter, open-label trial of 1486 patients with HER2-positive, early breast cancer. Patients were required to have had neoadjuvant taxane and trastuzumab-based therapy with residual invasive tumor in the breast and/or axillary lymph nodes. Patients received radiotherapy and/or hormonal therapy concurrent with study treatment as per local guidelines. Breast tumor samples were required to show HER2 overexpression defined as 3+ IHC or ISH amplification ratio ≥ 2.0 determined at a central laboratory using Ventana's PATHWAY anti-HER2-/neu (4B5) Rabbit Monoclonal Primary Antibody or INFORM HER2 Dual ISH DNA Probe Cocktail assays. Patients were randomized (1:1) to receive KADCYLA or trastuzumab. Randomization was stratified by clinical stage at presentation, hormone receptor status, preoperative HER2-directed therapy (trastuzumab, trastuzumab plus additional HER2-directed agent[s]), and pathological nodal status evaluation after preoperative therapy.

KADCYLA was given intravenously at 3.6 mg/kg on Day 1 of a 21-day cycle. Trastuzumab was given intravenously at 6 mg/kg on Day 1 of a 21-day cycle. Patients were treated with KADCYLA or trastuzumab for a total of 14 cycles unless there was recurrence of disease, withdrawal of consent, or unacceptable toxicity. At the time of the major efficacy outcome analysis, median treatment duration was 10 months for both KADCYLA- and trastuzumab-treated patients. Patients who discontinued KADCYLA for reasons other than disease recurrence could complete the remainder of the planned HER2-directed therapy with trastuzumab if appropriate based on toxicity considerations and investigator discretion.

The major efficacy outcome of the study was invasive disease-free survival (IDFS). IDFS was defined as the time from the date of randomization to first occurrence of ipsilateral invasive breast tumor recurrence, ipsilateral local or regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, or death from any cause. Additional efficacy outcomes included IDFS including second primary non-breast cancer, disease free survival (DFS), and overall survival (OS).

Patient demographics and baseline tumor characteristics were generally balanced between treatment arms. The median age was approximately 49 years (range 23-80 years), 73% were White, 9% were Asian, 6% were American Indian or Alaska Native and 3% were Black or African American. Most patients (99.7%) were women. Enrollment by region was as follows: 23% in North America, 54% in Europe and 23% throughout the rest of the world. Tumor prognostic characteristics including hormone receptor status (positive: 72%, negative: 28%), clinical stage at presentation (inoperable: 25%, operable: 75%) and pathological nodal status after preoperative therapy (node positive: 46%, node negative or not evaluated: 54%) were similar across study arms.

The majority of patients (77%) had received an anthracycline-containing neoadjuvant chemotherapy regimen. Twenty percent of patients received another HER2-targeted agent in addition to trastuzumab as a component of neoadjuvant therapy; 94% of these patients received pertuzumab.

After a median follow-up of 40 months, a statistically significant improvement in IDFS was observed in patients who received KADCYLA compared with trastuzumab. The OS data were not mature at the time of the IDFS analysis (98 deaths [6.6%] occurred in 1486 patients). The efficacy results from KATHERINE are summarized in Table 8 and Figure 3.

Consistent results were observed with KADCYLA in terms of IDFS across subgroups based on stratification factors, key baseline demographic and disease characteristics, and prior treatments.

Table 8 Efficacy Results from KATHERINE

	KADCYLA N=743	**Trastuzumab N=743**
Invasive Disease-Free Survival (IDFS)[1,4]		
Number (%) of patients with event	91 (12.2%)	165 (22.2%)
HR [95% CI][2]	0.50 [0.39, 0.64]	
p-value (Log-Rank test, unstratified)	< 0.0001	
3-year event-free rate[3], % [95% CI]	88.3 [85.8, 90.7]	77.0 [73.8, 80.7]
IDFS including second primary non-breast cancer		
Number (%) of patients with event	95 (12.8%)	167 (22.5%)
HR [95% CI][2]	0.51 [0.40, 0.66]	
3-year event-free rate[3], % [95% CI]	87.7 [85.2, 90.2]	76.9 [73.7, 80.1]
Disease-Free Survival (DFS)		
Number (%) of patients with event	98 (13.2%)	167 (22.5%)
HR [95% CI][2]	0.53 [0.41, 0.68]	
3-year event-free rate[3], % [95% CI]	87.4 [84.9, 89.9]	76.9 [73.7, 80.1]

HR: Hazard Ratio; CI: Confidence Intervals,

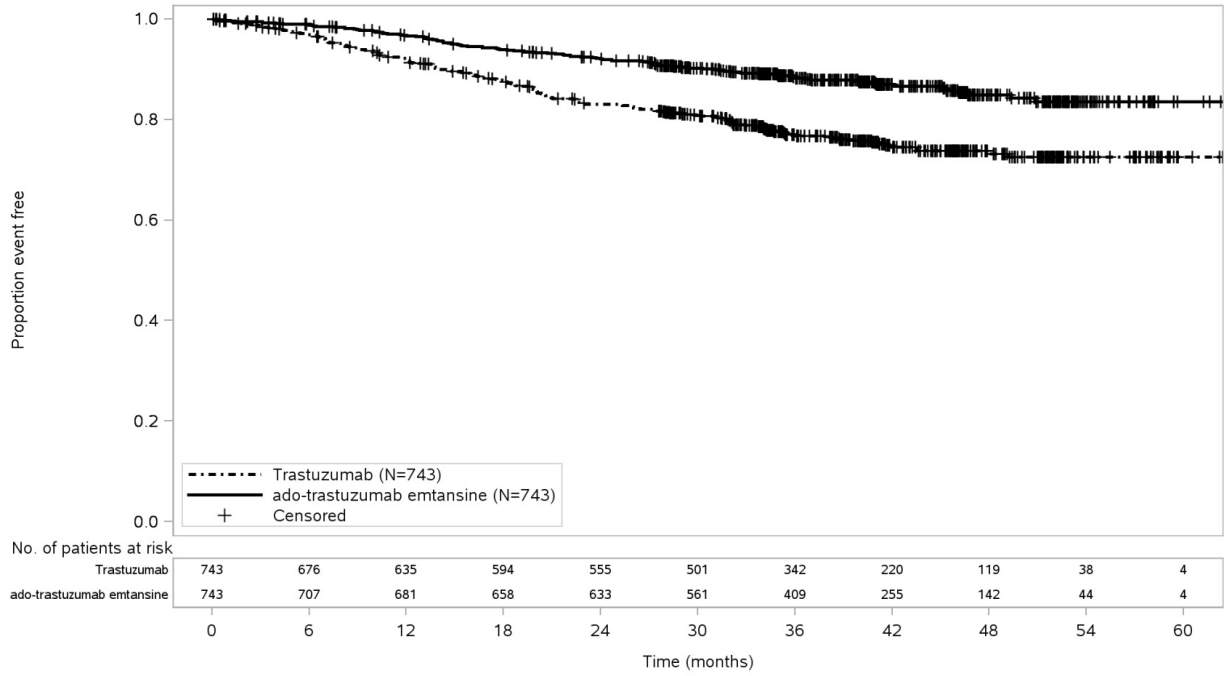
[1] Hierarchical testing applied for IDFS and OS

[2] Unstratified analysis

[3] 3-year event-free rate derived from Kaplan-Meier estimates

[4] Data from the pre-specified interim analysis (67% of the number of events for the planned final analysis) with the p-value compared with the allocated alpha of 0.0124

Figure 3 Kaplan-Meier Curve of Invasive Disease-Free Survival in KATHERINE



15 REFERENCES

1. OSHA Hazardous Drugs. *OSHA.* http://www.osha.gov/SLTC/hazardousdrugs/index.html

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied/Storage

KADCYLA (ado-trastuzumab emtansine) is supplied as:

Carton Contents	NDC
One 100 mg vial, single-dose vial	NDC 50242-088-01
One 160 mg vial, 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.*

16.2 Special Handling

Follow procedures for proper handling and disposal of anticancer drugs.

17 PATIENT COUNSELING INFORMATION

Hepatotoxicity

- Inform patients of the possibility of severe liver injury and advise patients to immediately seek medical attention if they experience symptoms of acute hepatitis such as nausea, vomiting, abdominal pain (especially RUQ abdominal pain), jaundice, dark urine, generalized pruritus, anorexia, etc. *[see Warnings and Precautions (5.1)]*.

Left Ventricular Dysfunction

- Advise patients to contact a health care professional immediately for any of the following: new onset or worsening shortness of breath, cough, swelling of the ankles/legs, palpitations, weight gain of more than 5 pounds in 24 hours, dizziness or loss of consciousness *[see Warnings and Precautions (5.2)]*.

Embryo-Fetal Toxicity

- Advise pregnant women and females of reproductive potential that KADCYLA exposure during pregnancy or within 7 months prior to conception can result in fetal harm. Advise female patients to contact their healthcare provider with a known or suspected pregnancy *[see Use in Specific Populations (8.1, 8.3)]*.
- Advise women who are exposed to KADCYLA during pregnancy or who become pregnant within 7 months following the last dose of KADCYLA that there is a pregnancy pharmacovigilance program that monitors pregnancy outcomes. Encourage these patients to report their pregnancy to Genentech *[see Use in Specific Populations (8.1)]*.
- Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of KADCYLA *[see Use in Specific Populations (8.1, 8.3)]*.
- 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 *[see Use in Specific Populations (8.3)]*.

Lactation

- Advise women not to breastfeed during treatment and for 7 months after the last dose of KADCYLA *[see Use in Specific Populations (8.2)]*.

KADCYLA® [ado-trastuzumab emtansine]

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