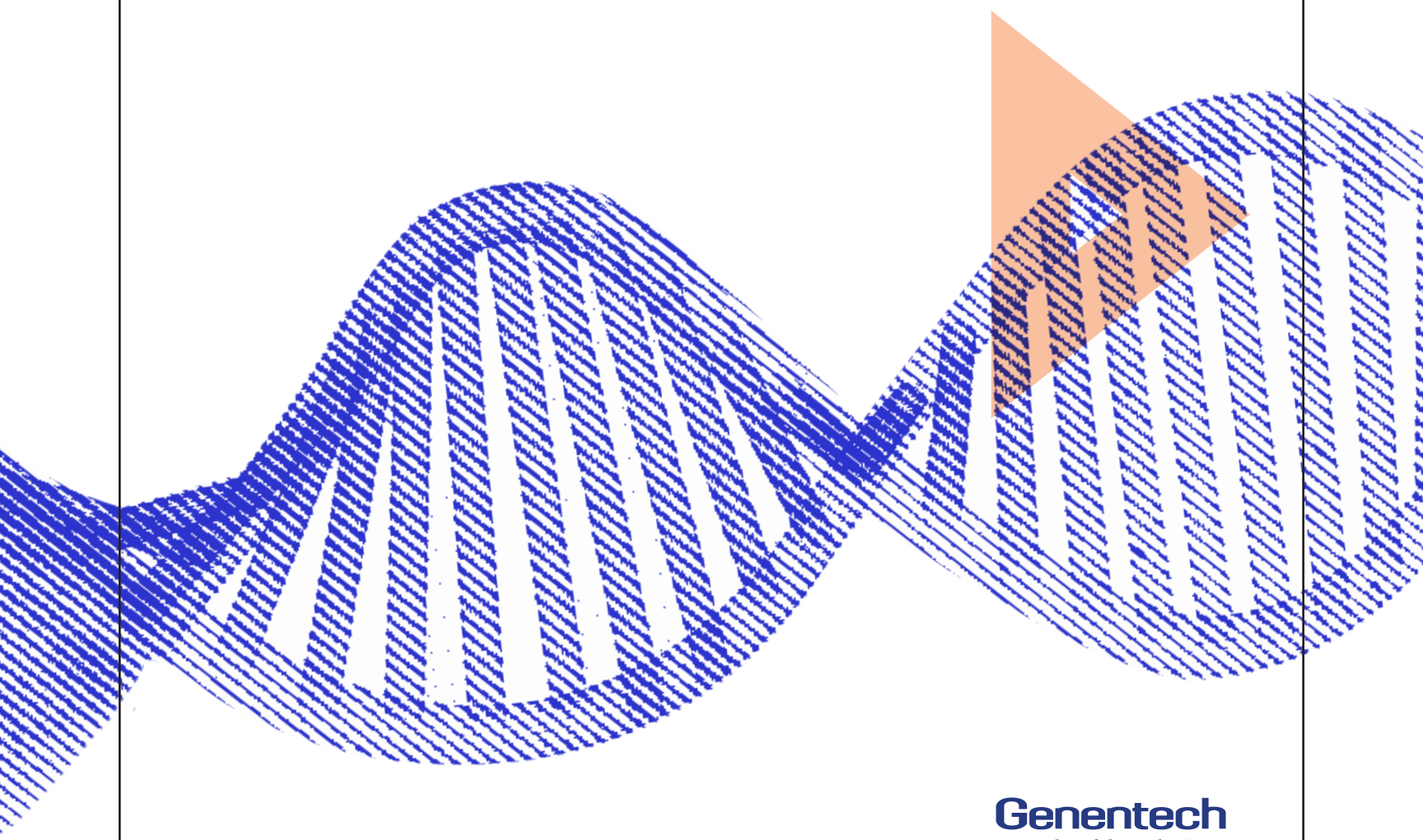
Regardless of the outcome of neoadjuvant treatment, **your patient with HER2+ early breast cancer (EBC) is still at risk of recurrence.**[1-3]

TRASTUZUMAB ALONE IS NOT ENOUGH

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

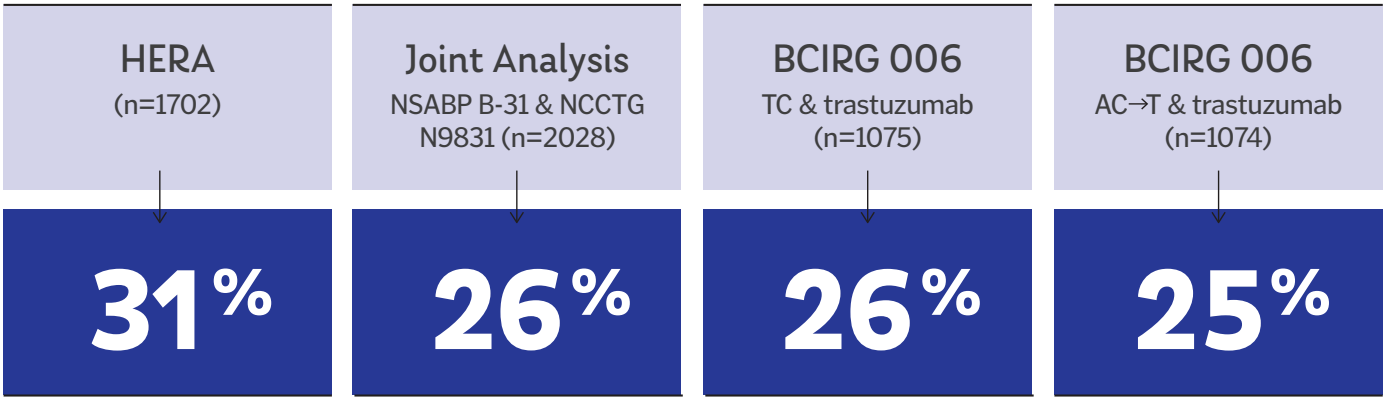


Genentech
A Member of the Roche Group

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).

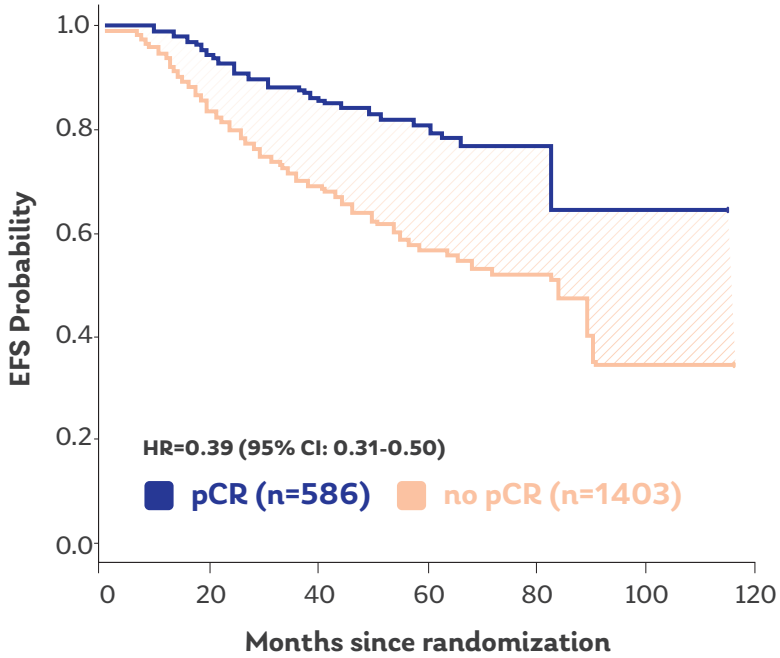
Despite improvement in the early stage treatment setting for HER2+ EBC

~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]

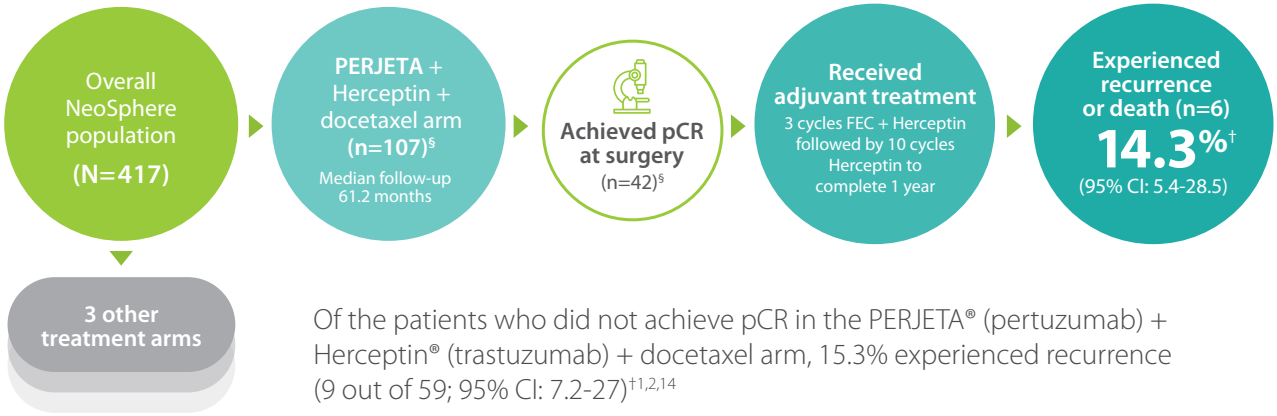
CTNeoBC: HER2+ SUBTYPE[3]

- 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]**

PERJETA® pertuzumab
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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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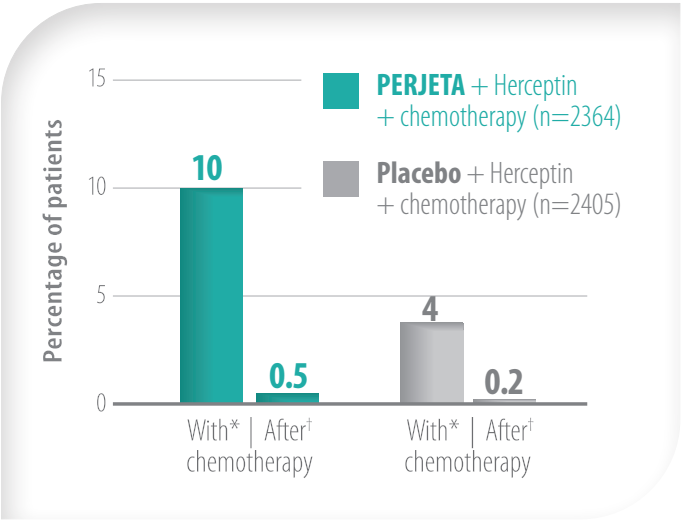
All Grades diarrhea[4]

- 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.

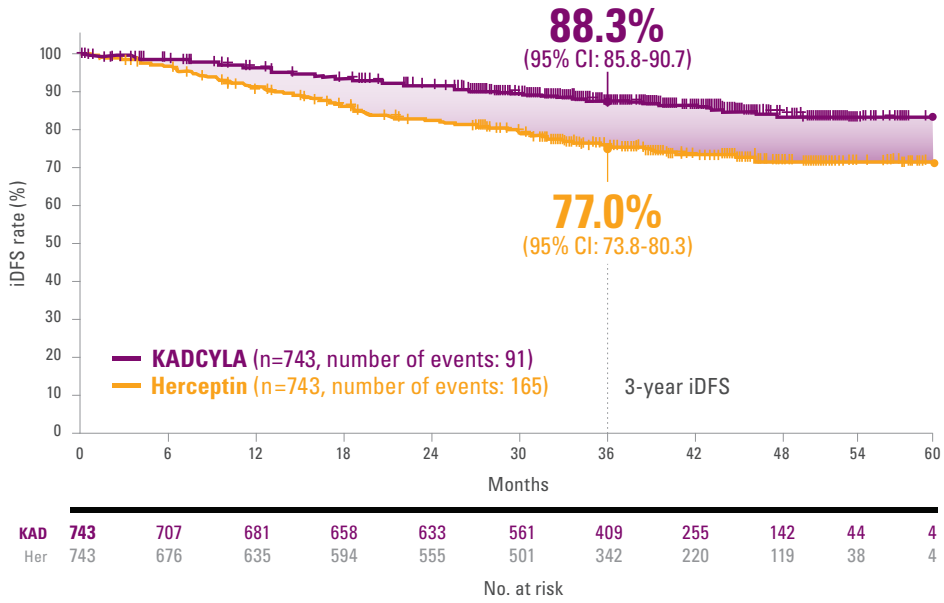
Trastuzumab alone is not enough for your patients with HER2+ EBC who have residual invasive disease[5]

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**

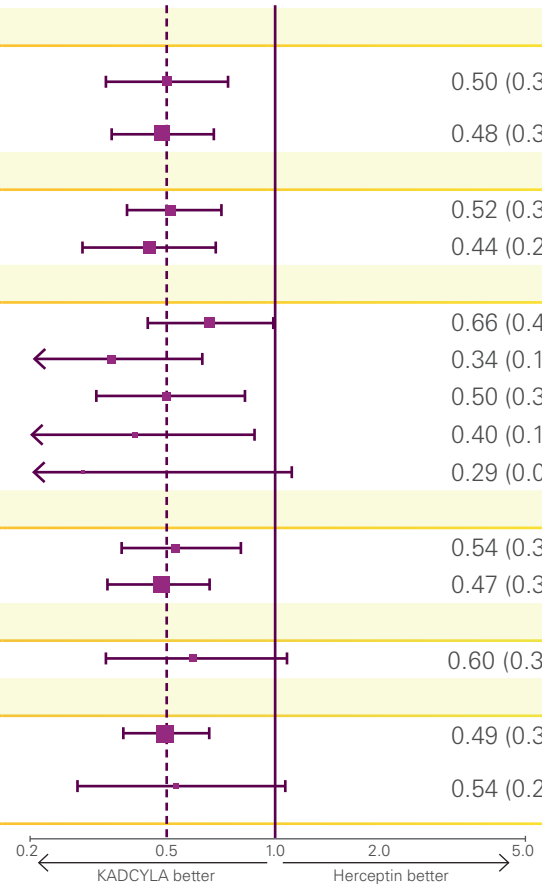
Consistent iDFS benefit was observed with KADCYLA across subgroups[5]

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

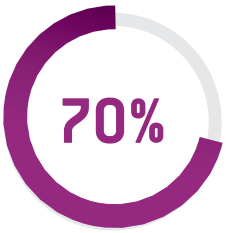
Warnings and Precautions

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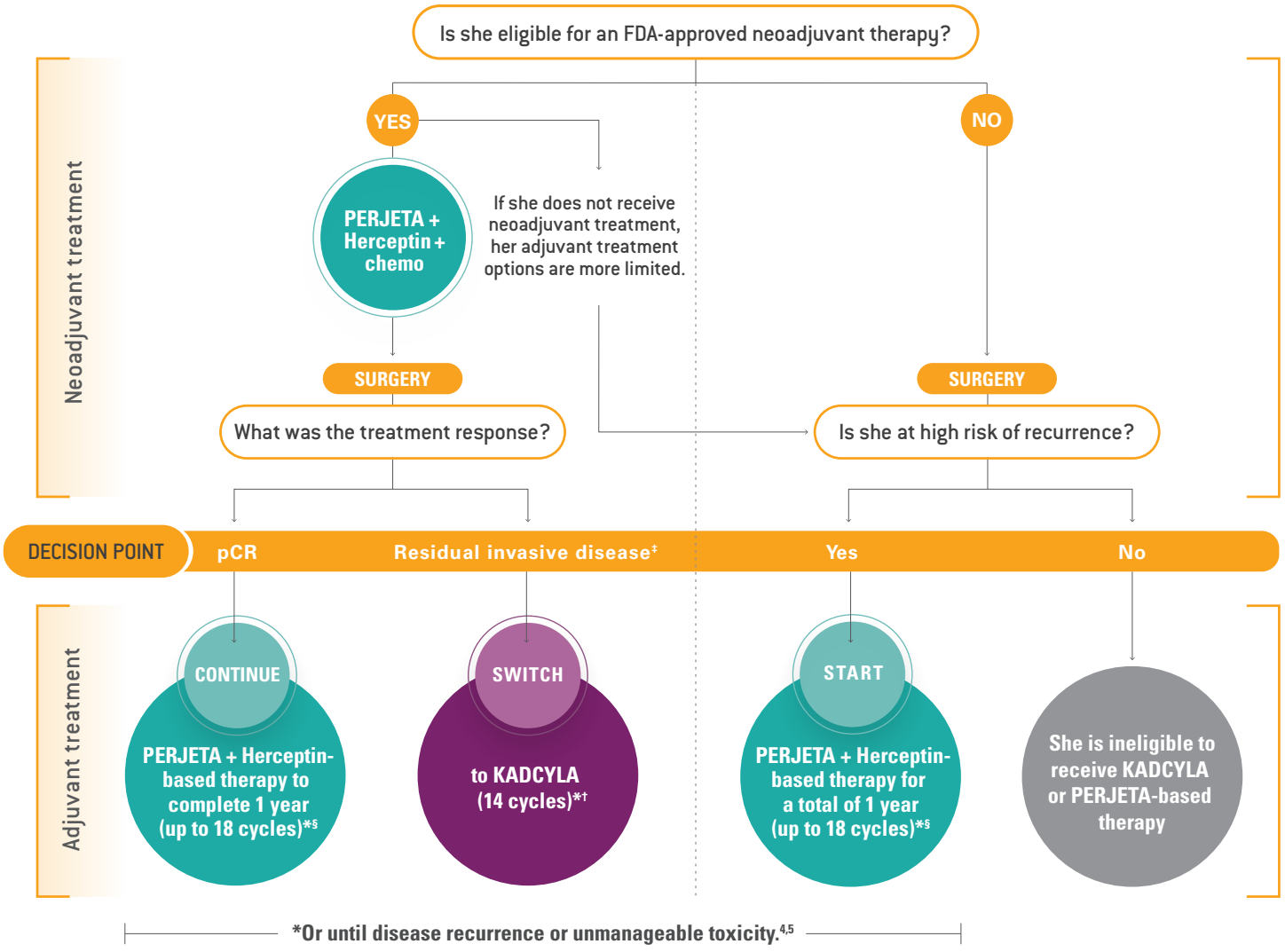
Targeted treatments for HER2+ EBC have advanced in the last 20 years, **but this is still an aggressive disease**[19]

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]



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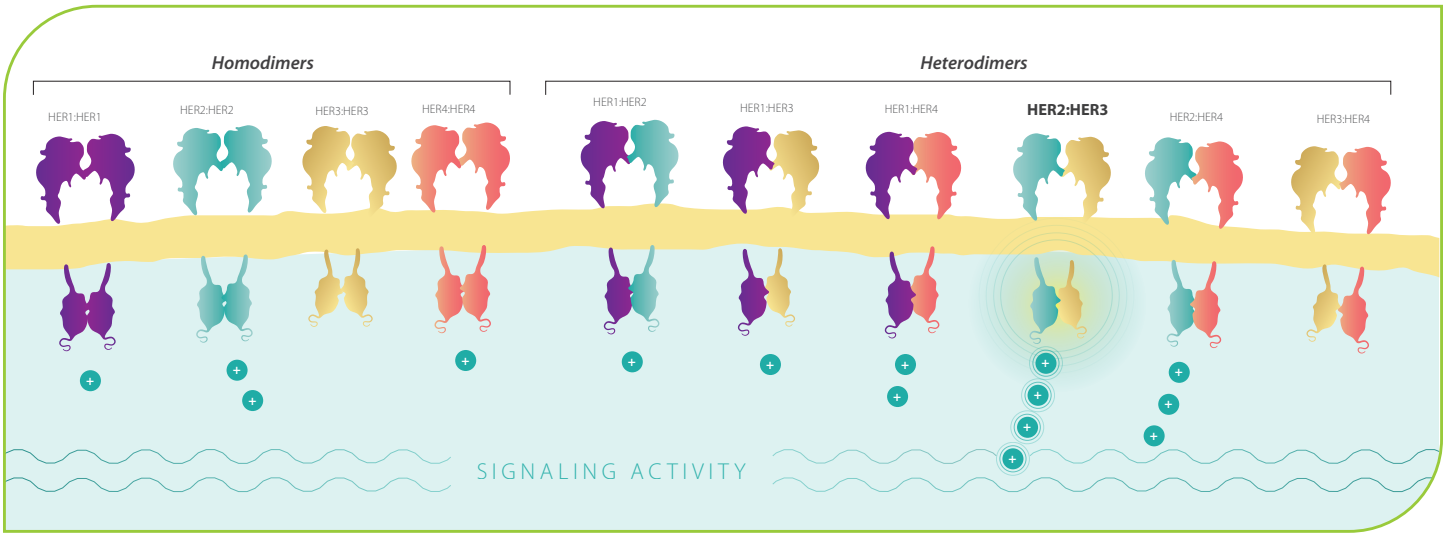
PERJETA is designed to work with Herceptin **for a dual-HER2 blockade**[4,20]

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]

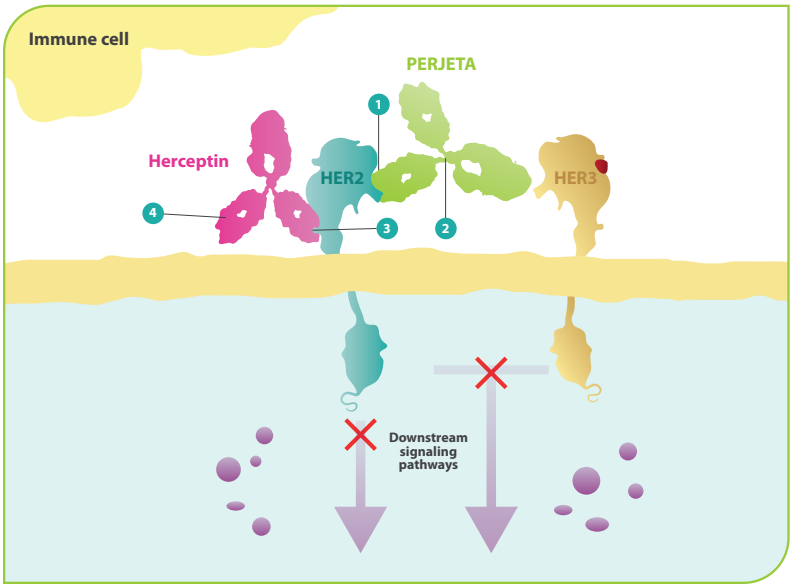
HER2:HER3 dimerization[22-24]



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)

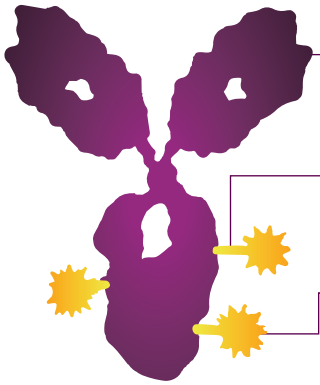
Herceptin activities[20,21,30]

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

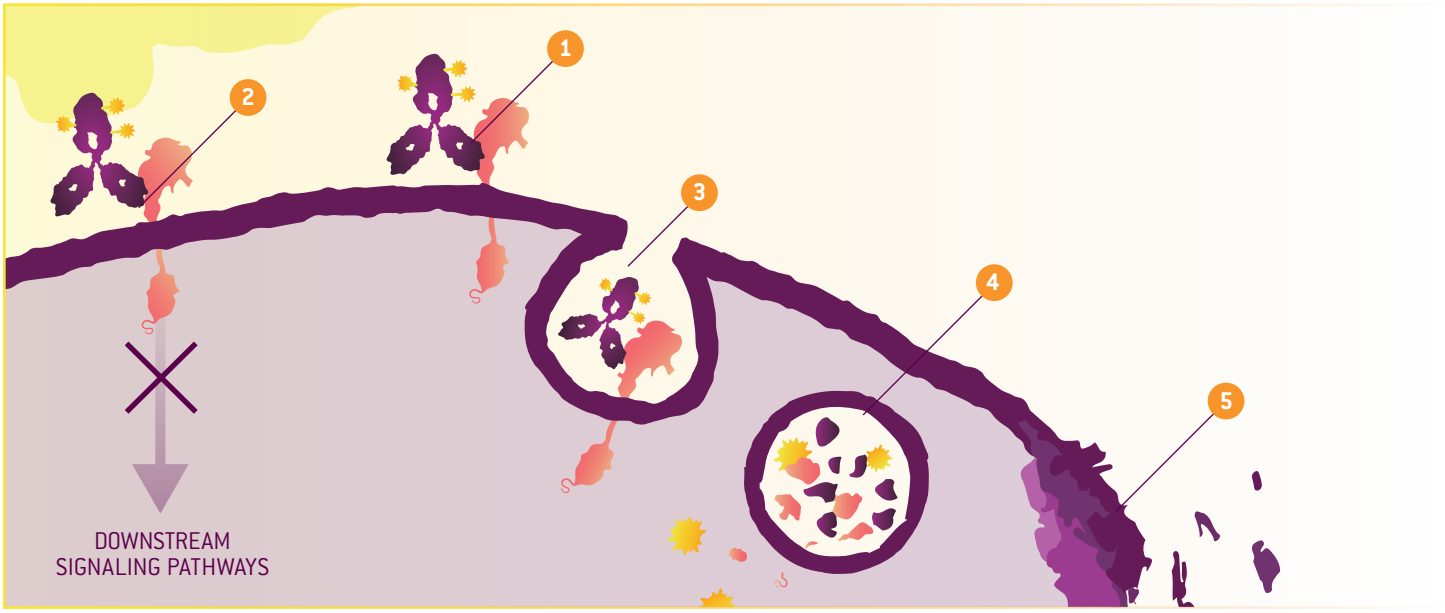
MCC*–stable linker[5,31]

- 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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   - 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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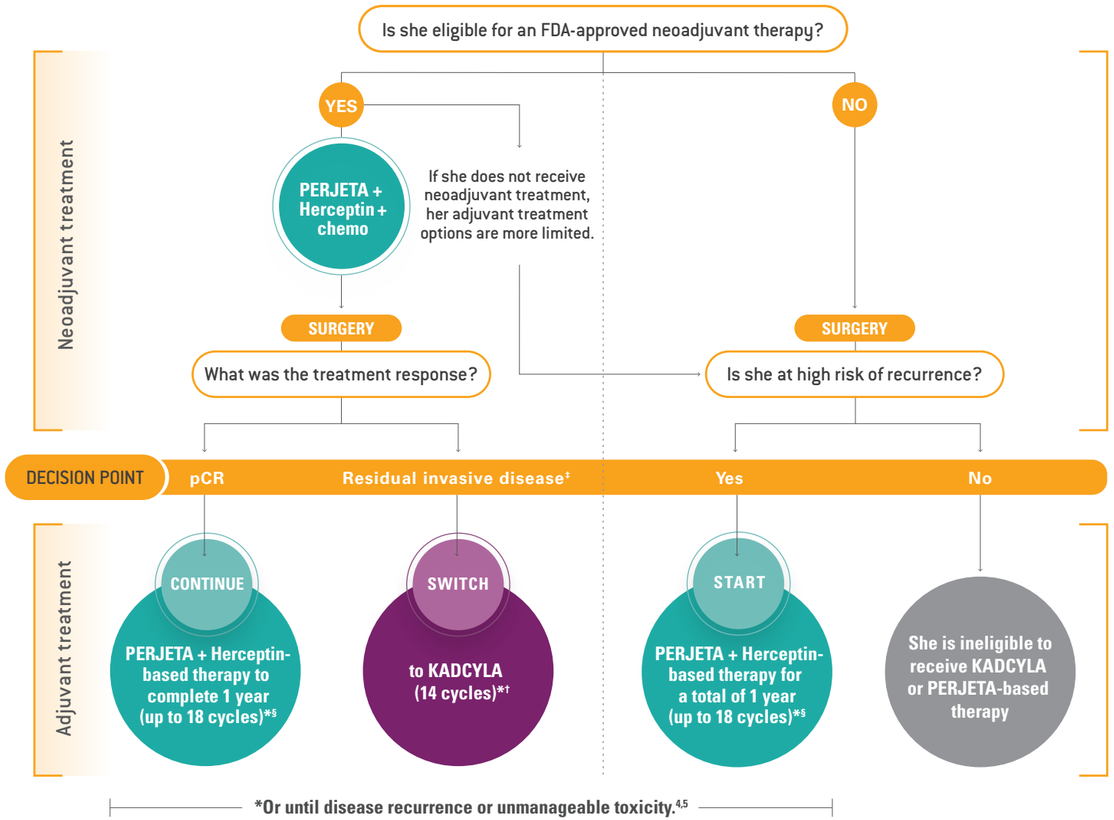

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FLIP OPEN

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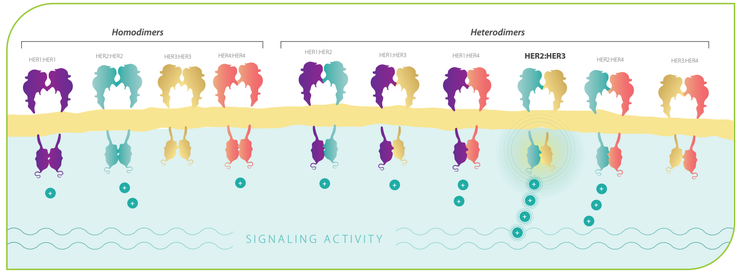

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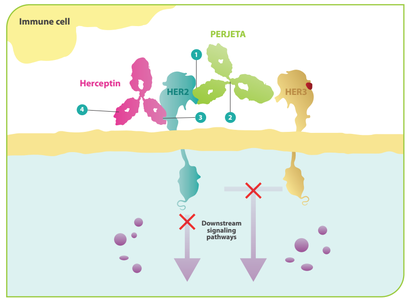

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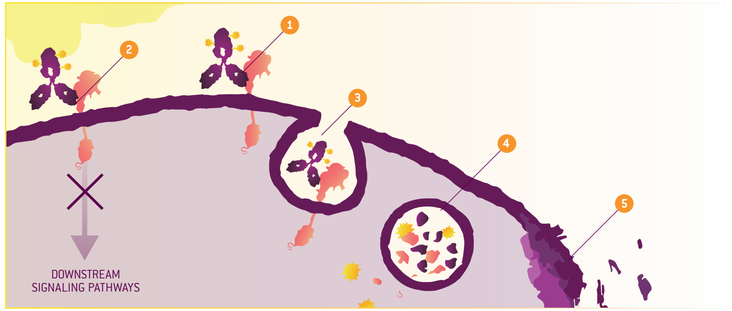

Trastuzumab antibody activities[5,30]

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