



For HER2+ metastatic breast cancer,

KADCYLA DEMONSTRATED 30.9 MONTHS MEDIAN OVERALL SURVIVAL¹

**vs 25.1 months with lapatinib + capecitabine (HR=0.682; 95% CI: 0.548-0.849; P=0.0006)
in patients previously treated with trastuzumab and a taxane (overall survival was
a co-primary endpoint)¹**

CI=confidence interval; HER2=human epidermal growth factor receptor 2; HR=hazard ratio.

Indication

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

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

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

Important Safety Information

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

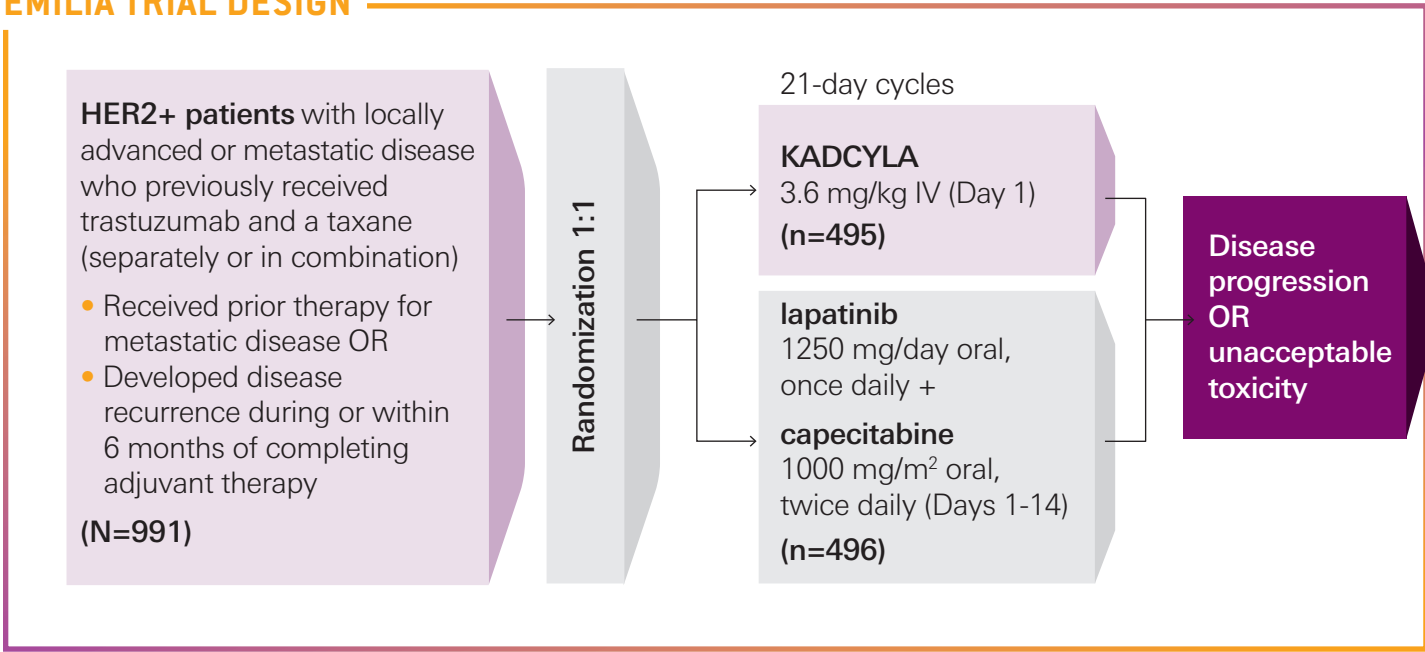
- **Hepatotoxicity:** Serious hepatotoxicity has been reported, including liver failure and death in patients treated with KADCYLA. Monitor serum transaminases and bilirubin prior to initiation of KADCYLA treatment and prior to each KADCYLA dose. Reduce dose or discontinue KADCYLA as appropriate in cases of increased serum transaminases or total bilirubin
- **Cardiac Toxicity:** KADCYLA administration may lead to reductions in left ventricular ejection fraction (LVEF). Evaluate left ventricular function in all patients prior to and during treatment with KADCYLA. Withhold treatment for clinically significant decrease in left ventricular function
- **Embryo-Fetal Toxicity:** Exposure to KADCYLA during pregnancy can result in embryo-fetal harm. Advise patients of these risks and the need for effective contraception

Please see additional Important Safety Information throughout, and [click here](#) for full Prescribing Information, including BOXED WARNINGS.

EMILIA clinical trial design

An open-label, randomized, Phase III trial assessing the efficacy and safety of KADCYLA vs lapatinib + capecitabine in patients with HER2+, unresectable, locally advanced or MBC^{1,2}

EMILIA TRIAL DESIGN



EMILIA trial endpoints included PFS, OS, and safety²

Primary endpoints: Progression-free survival (PFS) by independent review committee (IRC), overall survival (OS), safety.

Key secondary endpoints: PFS by investigator review, objective response rate (ORR), duration of response (DoR), and time to symptom progression (TTP).¹

Indication

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

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

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

Patient baseline characteristics were balanced between treatment arms

Most patients (88%) had received one or more lines of systemic therapy in the metastatic setting prior to receiving KADCYLA¹

SELECT PATIENT BASELINE CHARACTERISTICS WERE BALANCED²

	KADCYLA (n=495)	Lapatinib + capecitabine (n=496)
Median age, years (range)	53 (25-84)	53 (24-83)
Race, % (n)		
White	72 (358)	75 (374)
Asian	19 (94)	17 (86)
Black/African American	6 (29)	4 (21)
Other	1 (7)	2 (10)
Not available	1 (7)	1 (5)
ECOG PS, % (n)		
0	60 (299)	63 (312)
1	39 (194)	36 (176)
Measurable disease by IRC, % (n)		
Yes	80 (397)	78 (389)
Metastatic sites, % (n)		
<3	61 (298)	62 (307)
≥3	37 (189)	35 (175)
Unknown	2 (8)	3 (14)
Hormonal status, % (n)		
ER+ and/or PR+	57 (282)	53 (263)
ER- and PR-	41 (202)	45 (224)
Unknown	2 (11)	2 (9)
Prior treatment type, % (n)		
Chemotherapy (anthracycline)	61 (303)	61 (302)
Chemotherapy (other)	78 (385)	77 (382)
Hormonal therapy	41 (205)	41 (204)
Trastuzumab	100 (495)	100 (495)
Prior chemotherapy regimens for locally advanced or metastatic disease, % (n)		
0 or 1	61 (304)	61 (305)
>1	39 (191)	39 (191)
Prior trastuzumab treatment, % (n)		
MBC (±EBC)	100 (495)	100 (496)
EBC only	16 (78)	16 (77)
Duration of prior trastuzumab treatment, % (n)		
<1 year	42 (210)	43 (212)
≥1 year	58 (285)	57 (284)

In the KADCYLA arm (n=495), 12% of patients received KADCYLA in the first-line setting, 38% of patients received KADCYLA in the second-line setting, and 50% received KADCYLA in the third-line or later setting (based on systemic therapy in the metastatic setting).^{1,3}

Patients with a history of symptomatic congestive heart failure (CHF) or serious cardiac arrhythmia requiring treatment were excluded.¹

EBC=early breast cancer; ECOG PS=Eastern Cooperative Oncology Group performance status; ER=estrogen receptor; PR=progesterone receptor.

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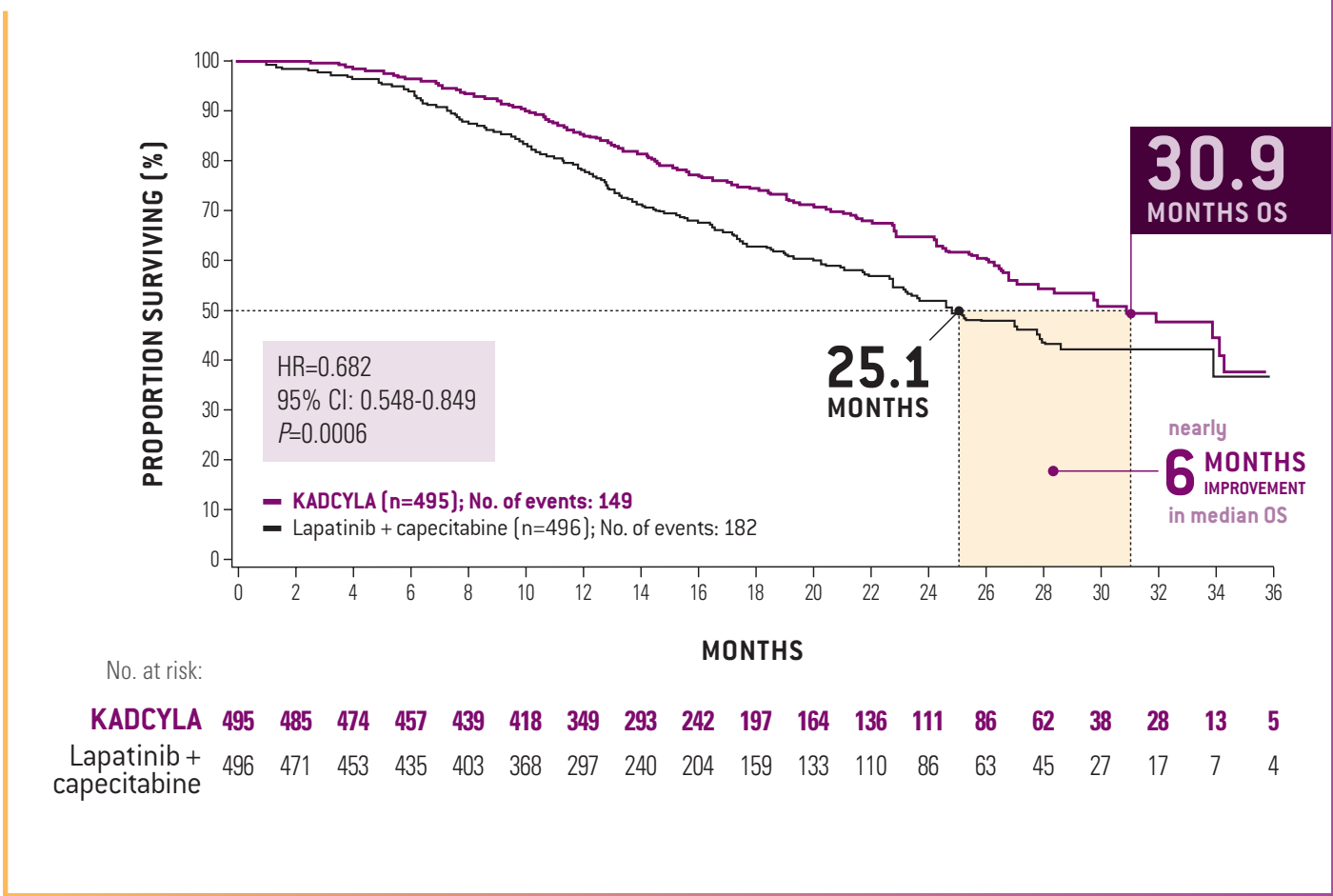


Proven survival benefit

KADCYLA extended median OS by nearly 6 months

30.9 months median OS with KADCYLA vs 25.1 months with lapatinib + capecitabine¹

CO-PRIMARY ENDPOINT: OS¹



Select Important Safety Information

Additional Warnings and Precautions include:

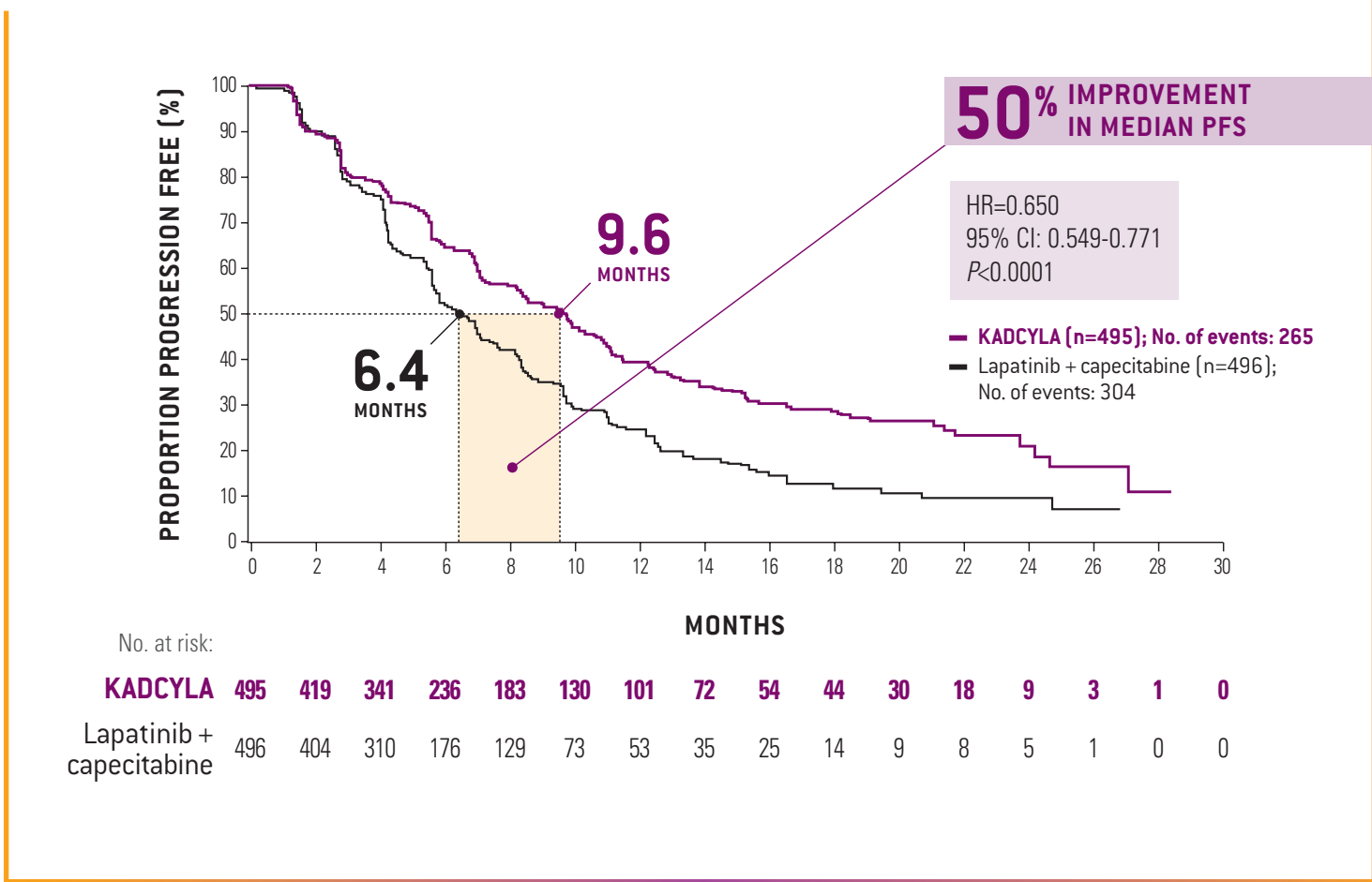
- Pulmonary toxicity (sometimes fatal)
- Infusion-related/hypersensitivity reactions
- Hemorrhage (sometimes fatal)
- Thrombocytopenia
- Neurotoxicity
- Extravasation

More time without disease progression

9.6 months median PFS with KADCYLA

vs 6.4 months with lapatinib + capecitabine¹

CO-PRIMARY ENDPOINT: PFS BY INDEPENDENT REVIEW COMMITTEE*¹



*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).

Select Important Safety Information

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. Permanently discontinue KADCYLA in patients diagnosed with ILD or pneumonitis.

Please see additional Important Safety Information throughout, and [click here](#) for full Prescribing Information, including BOXED WARNINGS.



KADCYLA demonstrated prolonged survival benefit across select subgroups vs lapatinib + capecitabine

Regardless of hormone-receptor status (ER/PR+ and ER/PR-), KADCYLA provided survival benefit over lapatinib + capecitabine¹

- 28% reduction in the risk of progression or death with KADCYLA in the hormone-positive subgroup (n=545; HR for PFS=0.72; 95% CI: 0.58-0.91)¹
- 38% reduction in the risk of death with KADCYLA in the hormone-positive subgroup (n=545; HR for OS=0.62; 95% CI: 0.46-0.85)¹

PFS AND OS FOR SELECT PATIENT SUBGROUPS/HORMONE RECEPTOR STATUS¹

Category	n	PFS by Independent Review		OS	
		HR estimate	95% CI	HR estimate	95% CI
All patients	991	0.65	0.55-0.77	0.68	0.55-0.85
		P<0.0001		P=0.0006	
Hormone receptor status					
Positive (ER+ and/or PR+)	545	0.72	0.58-0.91	0.62	0.46-0.85
Negative (ER- and PR-)	426	0.56	0.44-0.72	0.75	0.54-1.03

Select Important Safety Information

Infusion-Related/Hypersensitivity Reactions

- Infusion-related reactions, including flushing, chills, pyrexia, dyspnea, hypotension, wheezing, bronchospasm, and tachycardia, have been reported with KADCYLA. Observe patients closely for IRR especially during the first infusion. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. Interrupt KADCYLA in patients with severe IRR and permanently discontinue in the event of a life-threatening IRR

Hemorrhage

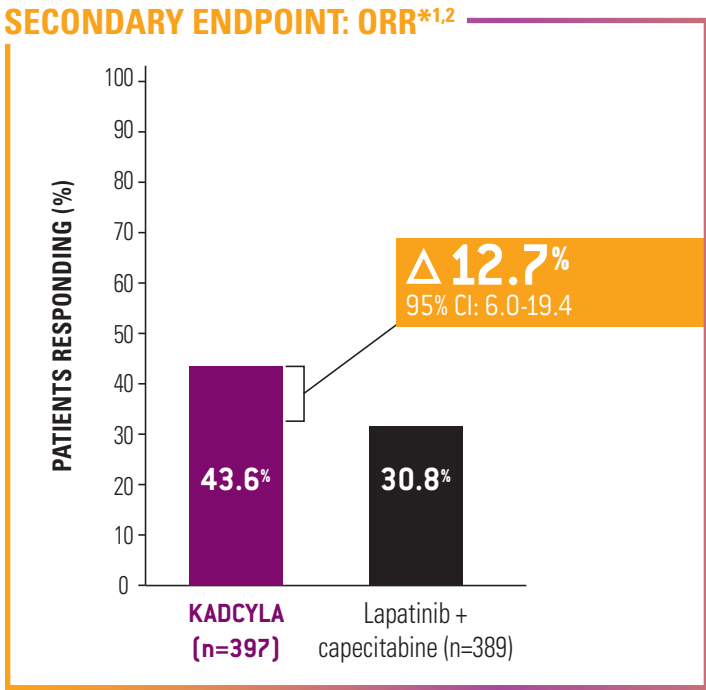
- Fatal cases have been observed in clinical trials. In some of the observed cases, the patients were also receiving anticoagulation therapy or antiplatelet therapy, or had thrombocytopenia; in others, there were no known additional risk factors. Use caution with these agents and consider additional monitoring when concomitant use is medically necessary

Tumor response with KADCYLA surpassed lapatinib + capecitabine

Shown to shrink tumors in more patients^{1,2}

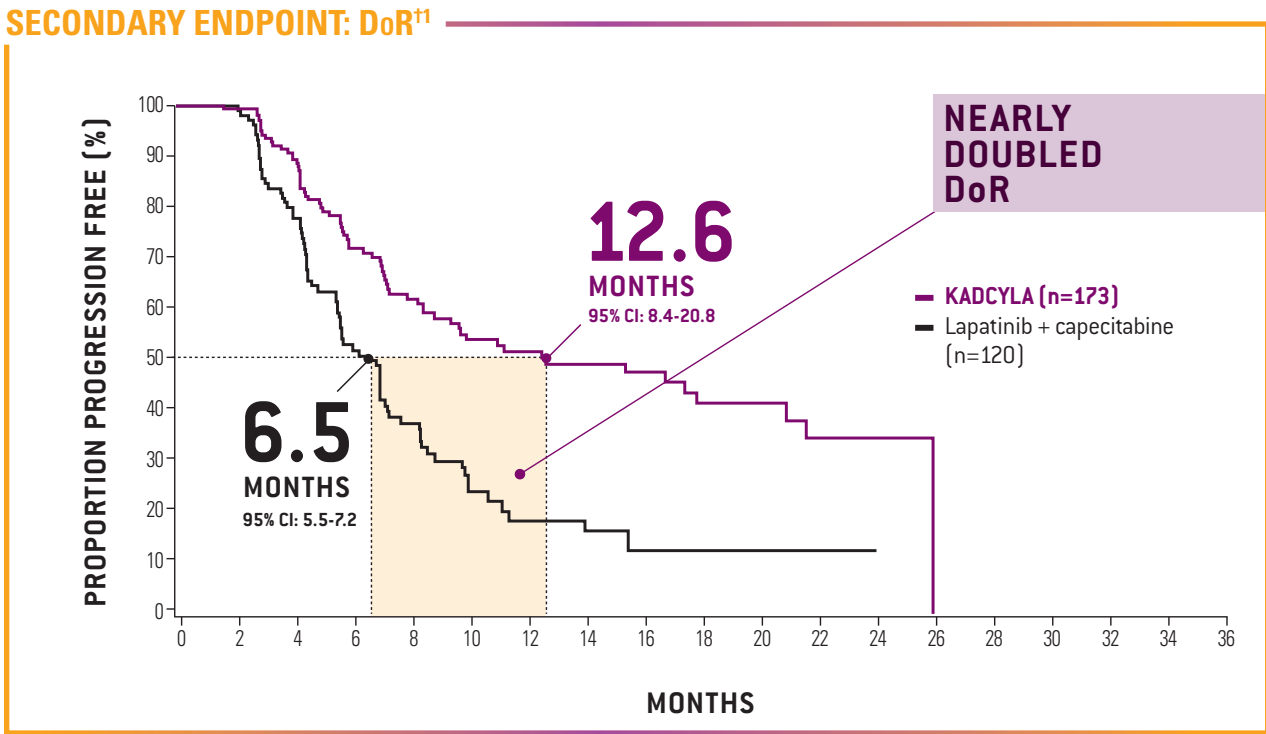
- Patients treated with KADCYLA had a higher partial response (42.6% vs 30.3%) than lapatinib + capecitabine; complete response was 1% and 0.5%, respectively²

*ORR in patients with measurable disease defined as the proportion of patients who achieved a complete response (disappearance of all target tumors) or a partial response (≥30% decrease in the sum of the longest diameters of target tumors) based on modified Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.²



Nearly doubled the median DoR¹

- 6.1 months improvement in median DoR was demonstrated with KADCYLA¹



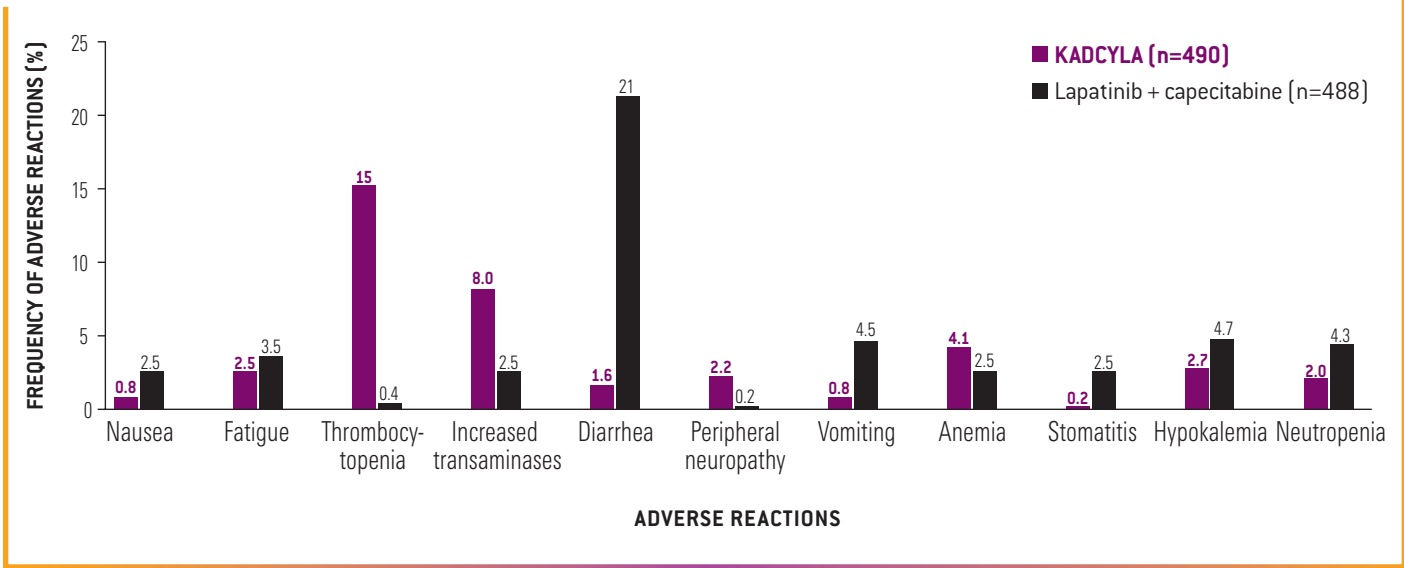
[†]DoR defined as the time from initial documented tumor response until documented disease progression. Only patients who achieved an initial response were evaluated for DoR.³

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Most common severe adverse reactions (ARs)

- In the EMILIA trial, the overall incidence of ARs Grade ≥ 3 was lower with KADCYLA: 43% vs 59% with lapatinib + capecitabine¹

MOST COMMON SEVERE (GRADE ≥ 3) ARs ($>2\%$)*^{1,3}



*ARs categorized according to the National Cancer Institute—Common Terminology Criteria for Adverse Events (NCI-CTCAE) (version 3).

Incidence of interstitial lung disease (ILD) in EMILIA

- Cases of ILD, including pneumonitis, some leading to acute respiratory distress syndrome or fatal outcome have been reported in clinical trials with KADCYLA¹
- 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 pneumonitis¹
- In the EMILIA trial, pneumonitis was reported at an incidence of 1.2% (6 out of 490 KADCYLA-treated patients), with no pneumonitis-related deaths^{1,2}

In the EMILIA trial, incidence of diarrhea was higher in patients treated with lapatinib + capecitabine¹

- Diarrhea (all Grades) was reported at an incidence of 24% in patients treated with KADCYLA compared to 80% in patients treated with lapatinib + capecitabine¹
- The incidence of Grade ≥ 3 diarrhea was 1.6% in patients treated with KADCYLA compared to 21% in patients treated with lapatinib + capecitabine¹

Most common ARs

ARs OCCURRING IN $\geq 10\%$ OF PATIENTS IN THE KADCYLA ARM OF THE EMILIA TRIAL¹

Adverse Reactions	KADCYLA (n=490)		lapatinib + capecitabine (n=488)	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Nausea	40	0.8	45	2.5
Fatigue	36	2.5	28	3.5
Musculoskeletal pain	36	1.8	31	1.4
Hemorrhage	32	1.8	16	0.8
Thrombocytopenia	31	15	3.3	0.4
Transaminases increased	29	8.0	14	2.5
Headache	28	0.8	15	0.8
Constipation	27	0.4	11	0
Diarrhea	24	1.6	80	21
Epistaxis	23	0.2	8	0
Peripheral neuropathy	21	2.2	14	0.2
Vomiting	19	0.8	30	4.5
Arthralgia	19	0.6	8	0
Abdominal pain	19	0.8	18	1.6
Pyrexia	19	0.2	8	0.4
Cough	18	0.2	13	0.2
Asthenia	18	0.4	18	1.6
Dry Mouth	17	0	4.9	0.2
Anemia	14	4.1	11	2.5
Stomatitis	14	0.2	33	2.5
Myalgia	14	0.6	3.7	0
Dyspnea	12	0.8	8	0.4
Insomnia	12	0.4	9	0.2
Rash	12	0	28	1.8
Hypokalemia	10	2.7	9	4.7
Dizziness	10	0.4	11	0.2

More patients were able to stay on treatment with KADCYLA

RATES OF DOSE MODIFICATIONS AND TREATMENT DISCONTINUATION^{1,4}

	KADCYLA (n=490)	lapatinib (n=488)	capecitabine (n=488)
Dose delays	24%	37%	44%
Dose reductions	16%	28%	55%
Treatment discontinuations	7%	8%	10%

- The most frequent ARs leading to a dose delay of KADCYLA (in $\geq 1\%$ of patients) were neutropenia, thrombocytopenia, leukopenia, fatigue, increased transaminases, and pyrexia¹
- The most frequent ARs leading to dose reduction of KADCYLA (in $\geq 1\%$ of patients) included thrombocytopenia, increased transaminases, and peripheral neuropathy¹
- The most common ARs leading to KADCYLA withdrawal were thrombocytopenia and increased transaminases¹

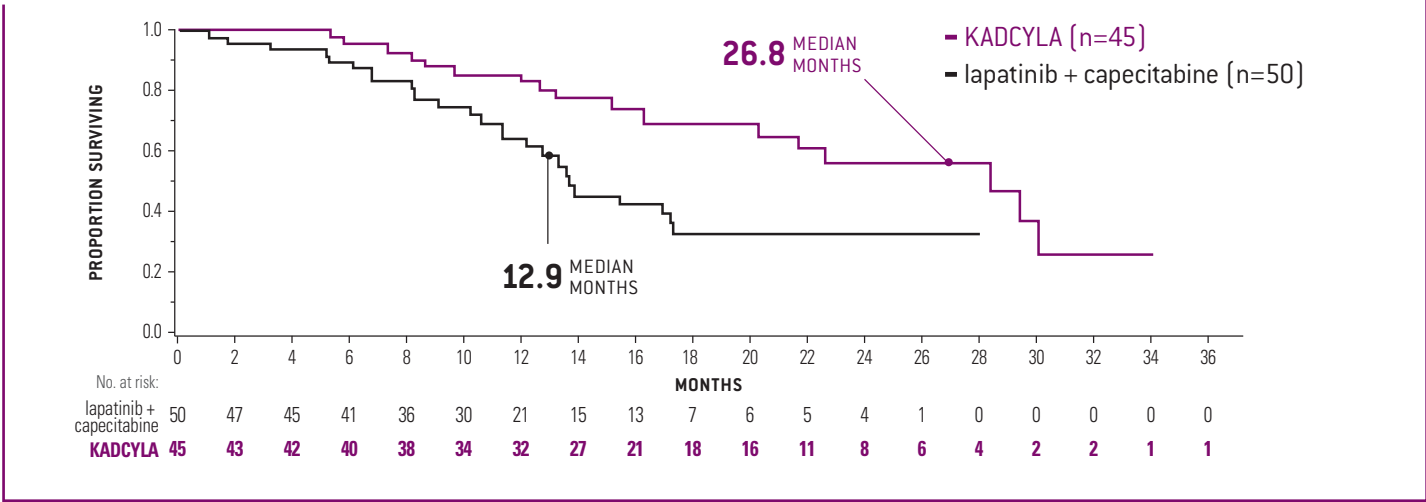
A retrospective exploratory analysis of patients with central nervous system (CNS) metastases at baseline

- Of the 991 patients enrolled in EMILIA, 45/495 in the KADCYLA arm and 50/496 in the lapatinib + capecitabine arm had previously treated and stable CNS metastases at baseline⁵
- Stable CNS metastases** were defined in EMILIA as asymptomatic and previously treated with radiotherapy. Patients with stable CNS metastases were eligible to enroll 14 days after their last radiotherapy treatment⁵
- Patients with CNS metastases that were untreated, were symptomatic, or required therapy to control symptoms ≤2 months before randomization, were excluded, as were patients with CNS-only disease⁵

Limitations of the analysis:

- This exploratory analysis was not powered to detect differences between subgroups; therefore, the results are descriptive. Caution should be exercised when interpreting the results⁵
- The sample size for this analysis is limited (n=95)⁵
- Patients in the KADCYLA arm were more likely than patients in the lapatinib + capecitabine arm to have received brain and non-brain radiation, chemotherapy, HER2-targeted therapy, or other therapy after discontinuation of study treatment⁵
- Baseline characteristics were similar between arms, except there was a higher proportion of Asian patients (both race and region) in the KADCYLA arm (33% vs 16%), and differences in the types of prior radiation therapy for CNS metastases in each arm⁵

OS IN PATIENTS WITH CNS METASTASES AT BASELINE⁵



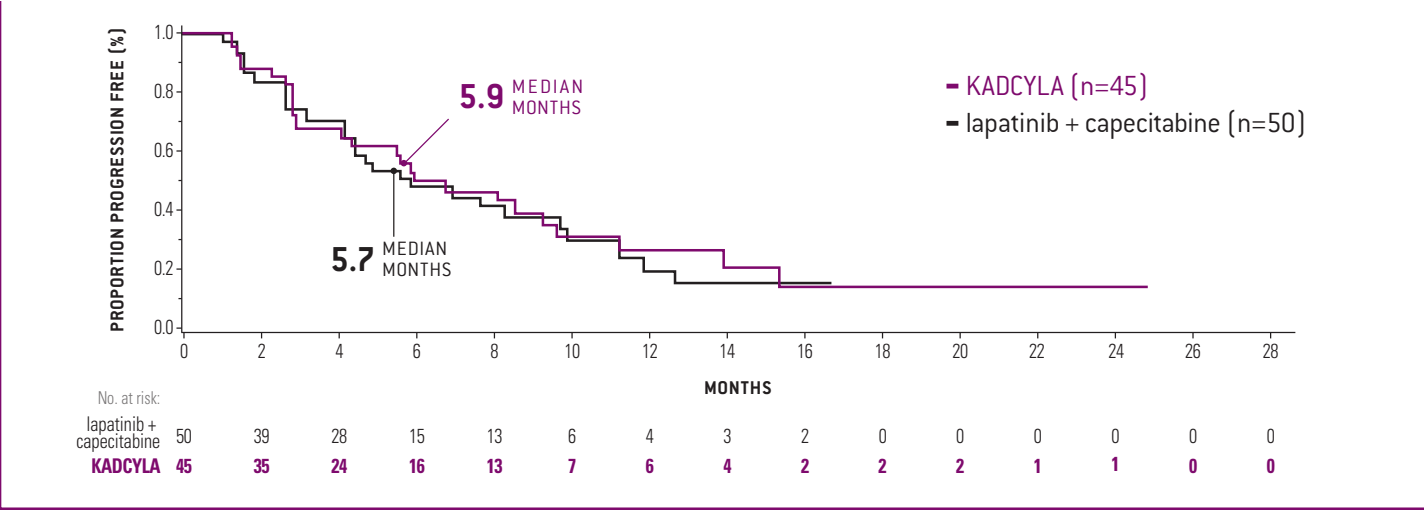
	KADCYLA			Lapatinib + capecitabine			Unstratified HR for OS event (95% CI)
	No. of patients	No. of patients with an OS event/total no.	Median OS (months)	No. of patients with an OS event/total no.	Median OS (months)		
All patients (ITT)	991	149/495	30.9	182/496	25.1		0.70 (0.56-0.87)
CNS metastases at baseline ³							
Yes	95	18/45	26.8	26/50	12.9		0.43 (0.23-0.82)
No	874	129/442	31.9	155/432	25.2		0.71 (0.56-0.90)

This analysis was based on a data cutoff of July 2012. There were 22 patients (14 in the lapatinib + capecitabine group and 8 in the KADCYLA group) whose CNS metastases were unknown.^{3,5}

A retrospective exploratory analysis of patients with central nervous system (CNS) metastases at baseline

See left side of this spread (page 10) for limitations of the analysis.

PFS (BY IRC) IN PATIENTS WITH CNS METASTASES AT BASELINE⁵



	KADCYLA			Lapatinib + capecitabine			Unstratified HR for PFS event (95% CI)
	No. of patients	No. of patients with a PFS event/total no.	Median PFS (months)	No. of patients with a PFS event/total no.	Median PFS (months)		
All patients (ITT)	991	265/495	9.6	304/496	6.4		0.66 (0.56-0.78)
CNS metastases at baseline ³							
Yes	95	27/45	5.9	30/50	5.7		0.94 (0.56-1.58)
No	874	236/442	9.8	270/432	6.4		0.65 (0.54-0.77)

This analysis was based on a data cutoff of January 2012. There were 22 patients (14 in the lapatinib + capecitabine group and 8 in the KADCYLA group) whose CNS metastases were unknown.^{3,5}

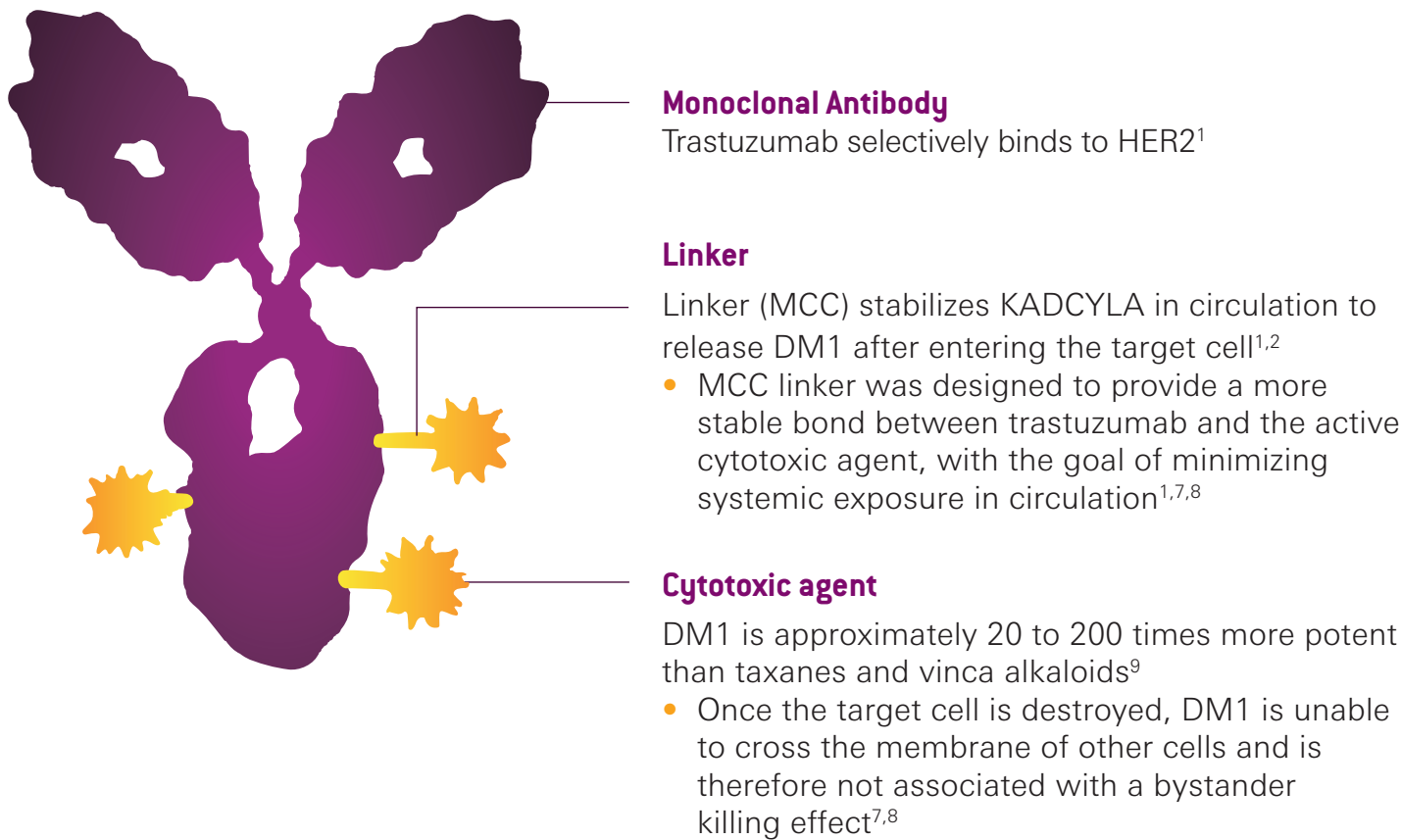
ARs occurring in patients with CNS metastases at baseline⁵

	KADCYLA (n=43)	Lapatinib + capecitabine (n=49)
Any grade ARs	93.0%	95.9%
Grade ≥3 ARs	48.8%	63.3%
Serious ARs	18.6%	26.5%
Selected ARs, any grade		
Thrombocytopenia	32.6%	4.1%
Hemorrhage	27.9%	12.2%
Hepatotoxicity	25.6%	14.3%
Peripheral neuropathy	20.9%	18.4%
Diarrhea	18.6%	79.6%
Eye disorder	9.3%	4.1%
Renal disorder	9.3%	10.2%
Hypokalemia	7.0%	12.2%
Infusion reaction or hypersensitivity	4.7%	0%
PPE syndrome	2.3%	46.9%

The first HER2-targeted antibody-drug conjugate with Herceptin® (trastuzumab)^{1,6}

In preclinical studies

KADCYLA maintained the HER2 suppression and anticancer activities of trastuzumab while delivering cytotoxic DM1 to HER2-expressing cells¹



Emtansine is the combination of DM1, a cytotoxic maytansinoid, and the stable MCC linker.¹

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

Indication

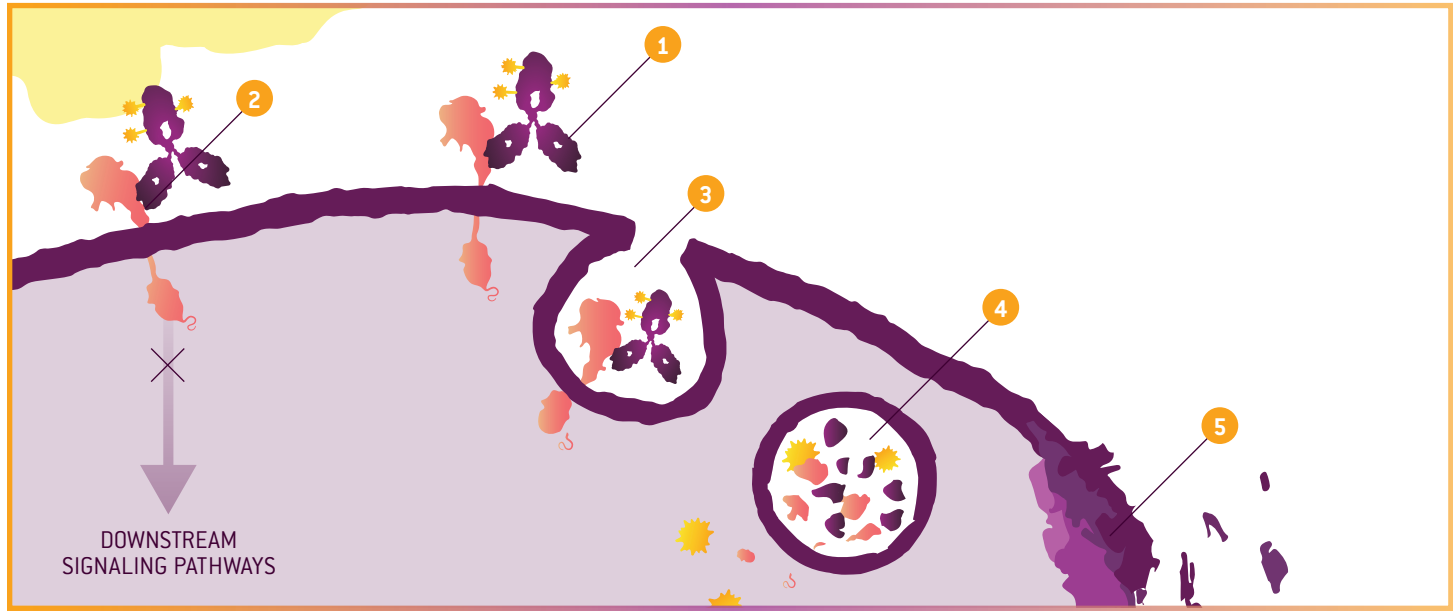
KADCYLA® (ado-trastuzumab emtansine), as a single agent, is indicated for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either:

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

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

KADCYLA is designed to be stable in circulation, reducing systemic exposure and preserving activation until the antibody reaches the HER2+ cell^{7,8}

Proposed mechanism of action for KADCYLA, based on preclinical models



Trastuzumab antibody activities^{1,10}

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

DM1[†] cytotoxic activity¹

- Internalization:** Once bound, the KADCYLA/HER2-receptor complex is internalized via endocytosis.
- DM1 release:** KADCYLA undergoes proteolytic degradation inside the target cell and releases the active chemotherapy, DM1.
- DM1 cytotoxicity:** DM1 binds to microtubules and inhibits their polymerization, causing cell-cycle arrest and cell death.

[†]Cytotoxic DM1-containing catabolites (primarily lysine-bound emtansine).¹

ADCC=antibody-dependent cell-mediated cytotoxicity.

Please see additional Important Safety Information throughout, and [click here](#) for full Prescribing Information, including BOXED WARNINGS.

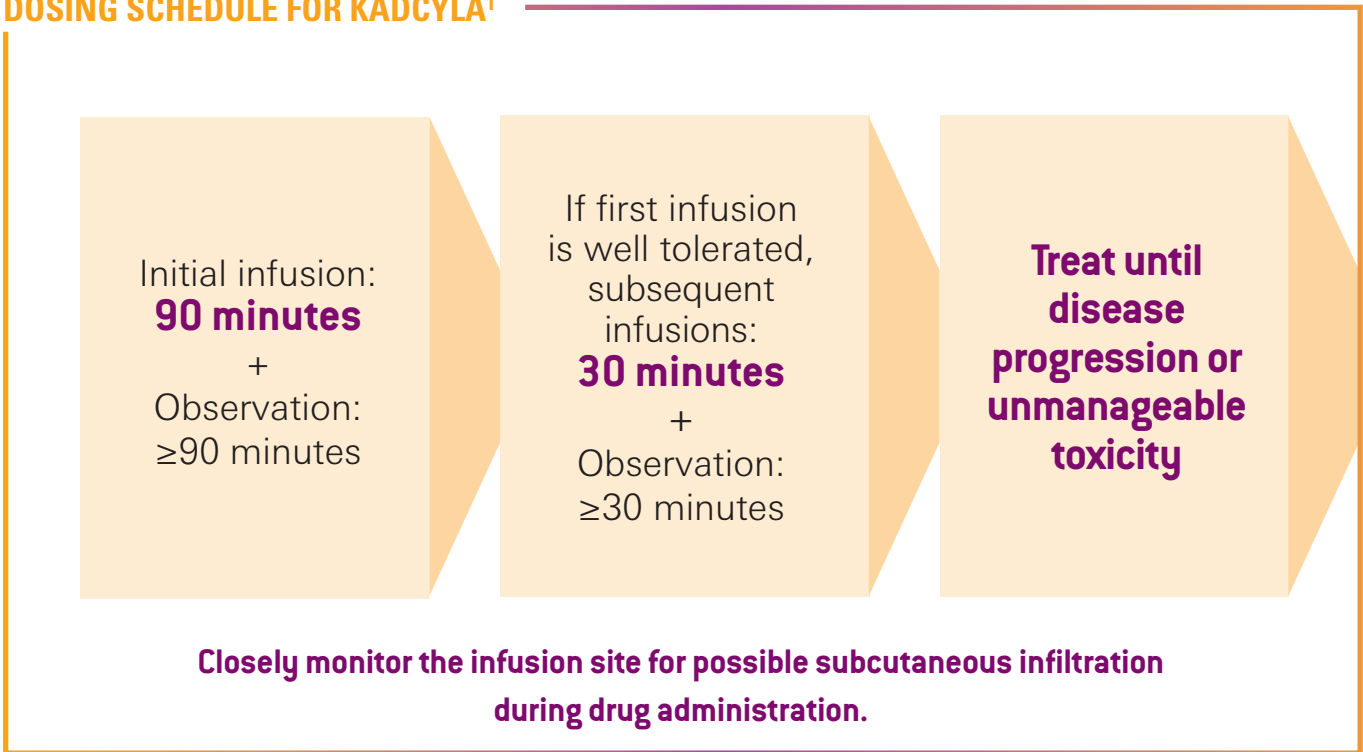

ado-trastuzumab emtansine
20 mg/mL INJECTION FOR INTRAVENOUS USE

Dosing for metastatic breast cancer¹

Patient Selection: 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.

- Do not substitute trastuzumab for or with KADCYLA
- Administer at a dose of 3.6 mg/kg via IV infusion every 3 weeks (21-day cycle) until disease progression or unmanageable toxicity
- Do not administer KADCYLA at doses greater than 3.6 mg/kg
- An in-line PES filter (0.2 or 0.22 micron) is required for administration
- KADCYLA does not require a loading dose

DOSING SCHEDULE FOR KADCYLA¹



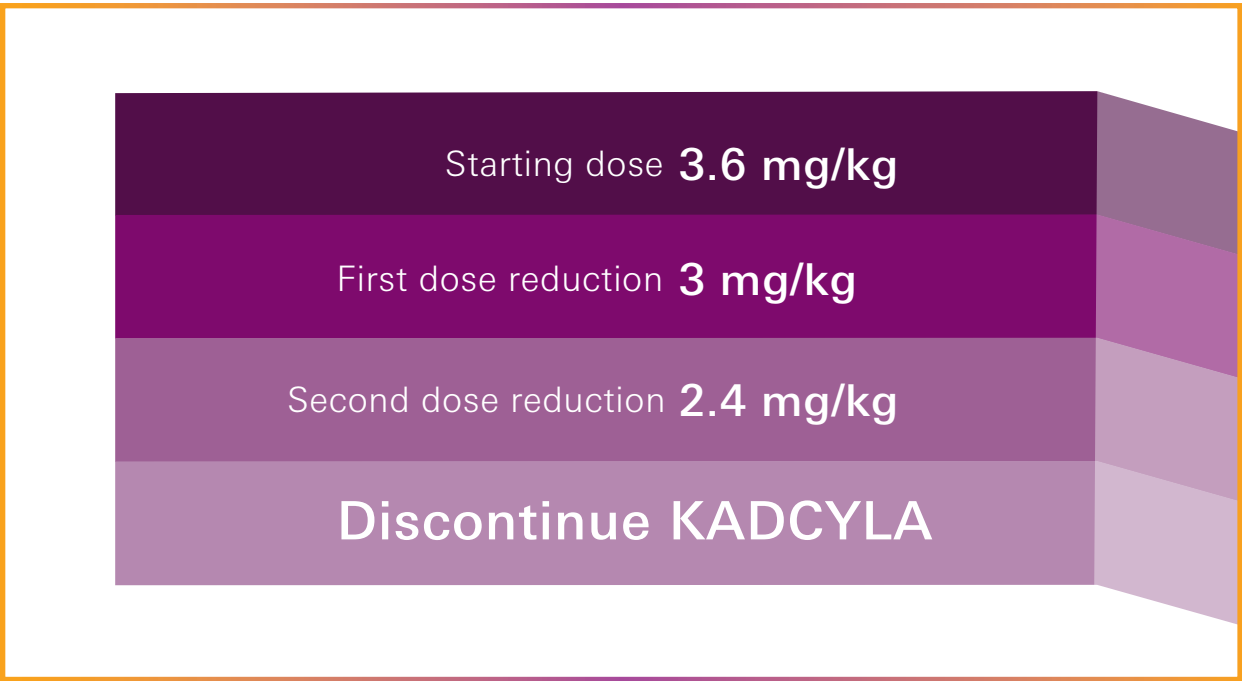
If a planned dose is missed, administer the next dose as soon as possible at the most recently tolerated infusion rate. Do not wait until the next planned cycle.

Following a missed dose, adjust administration schedule to maintain dosing interval (21 days).

Dose reduction guidelines

For patients who experience select ARs with KADCYLA*¹:

- Dose reductions should be made in decrements of 0.6 mg/kg
- A maximum of 2 dose reductions should occur before discontinuation



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

*Dose reduction guidelines based on KADCYLA full Prescribing Information.

Monitoring for infusion-related reactions (IRRs)

IRRs have been reported in clinical trials with KADCYLA. In most patients, these reactions resolved over the course of several hours to a day after completing the infusion.

- Monitor patients for IRRs, especially during the first infusion
- Slow or interrupt the infusion and administer appropriate medical therapies if IRRs occur
- Permanently discontinue KADCYLA for life-threatening IRRs

Dose modification guidelines for MBC¹

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 >3x ULN and concomitant total bilirubin >2x 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.

Adverse reaction	Severity	Treatment modification
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.

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

Select Important Safety Information

Thrombocytopenia

- Thrombocytopenia was reported in clinical trials of KADCYLA. The incidence and severity was higher in Asian patients. Monitor platelet counts prior to initiation of KADCYLA and prior to each dose. Institute dose modifications as appropriate

Neurotoxicity

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

Important Safety Information

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

- **Hepatotoxicity:** Serious hepatotoxicity has been reported, including liver failure and death in patients treated with KADCYLA. Monitor serum transaminases and bilirubin prior to initiation of KADCYLA treatment and prior to each KADCYLA dose. Reduce dose or discontinue KADCYLA as appropriate in cases of increased serum transaminases or total bilirubin
- **Cardiac Toxicity:** KADCYLA administration may lead to reductions in left ventricular ejection fraction (LVEF). Evaluate left ventricular function in all patients prior to and during treatment with KADCYLA. Withhold treatment for clinically significant decrease in left ventricular function
- **Embryo-Fetal Toxicity:** Exposure to KADCYLA during pregnancy can result in embryo-fetal harm. Advise patients of these risks and the need for effective contraception

Warnings and Precautions

Hepatotoxicity

Hepatotoxicity, predominantly in the form of asymptomatic increases in the concentrations of serum transaminases, has been observed in 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 EMILIA (for patients with metastatic breast cancer [MBC]) 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 $>3 \times$ ULN and concomitant total bilirubin $>2 \times$ 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 EMILIA. 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 EMILIA, left ventricular dysfunction occurred in 1.8% of patients in the KADCYLA group and 3.3% of patients in the lapatinib + capecitabine group.

Based on limited data from a retrospective observational study, 22% (7 of 32) of patients with HER2-positive MBC with a baseline LVEF of 40-49% treated with KADCYLA developed congestive heart failure (CHF) or a $>10\%$ reduction in LVEF.

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. 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 $\geq 10\%$ 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 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.

Permanently discontinue treatment with KADCYLA in patients diagnosed with ILD or pneumonitis.

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 EMILIA, the overall incidence of IRR in patients treated with KADCYLA was 1.4%. 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 EMILIA, the overall incidence of hemorrhage was 32% in the KADCYLA group and 16% in the lapatinib + capecitabine group. The incidence of Grade ≥ 3 hemorrhage was 1.8% in the KADCYLA group and 0.8% in the lapatinib + capecitabine 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 ($< \text{LLN}$ to $\geq 50,000/\text{mm}^3$) with the nadir occurring by day 8 and generally improving to Grade 0 or 1 ($\geq 75,000/\text{mm}^3$) 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 group and 3.3% in the lapatinib + capecitabine group. The incidence of Grade ≥ 3 thrombocytopenia was 15% in the KADCYLA group and 0.4% in the lapatinib + capecitabine group. In Asian patients, the incidence of Grade ≥ 3 thrombocytopenia was 45% and 1.3%, respectively. Monitor platelet counts prior to initiation of KADCYLA and prior to each KADCYLA dose. KADCYLA has not been studied in patients with platelet counts

$<100,000/\text{mm}^3$ prior to initiation of treatment. In the event of decreased platelet count to Grade ≥ 3 ($<50,000/\text{mm}^3$), do not administer KADCYLA until platelet counts recover to Grade 1 ($\geq 75,000/\text{mm}^3$). Closely monitor patients with thrombocytopenia ($< 100,000/\text{mm}^3$) 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 EMILIA, the overall incidence of peripheral neuropathy was 21% in the KADCYLA group and 14% in the lapatinib + capecitabine group. The incidence of Grade ≥ 3 peripheral neuropathy was 2.2% and 0.2%, respectively.

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

Metastatic Breast Cancer

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

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 additional Important Safety Information throughout, and [click here](#) for full Prescribing Information, including BOXED WARNINGS.



More than 7 years ago,
KADCYLA began as the first antibody-drug conjugate (ADC) in HER2+ breast cancer
The first ADC to include Herceptin[®] (trastuzumab)^{1,6}

NCCN
RECOMMENDED OPTION

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) recommend ado-trastuzumab emtansine (KADCYLA) monotherapy as an option for the treatment of all eligible HER2+ patients with metastatic breast cancer (category 2A) following treatment with trastuzumab and a taxane.*¹¹

*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.

Indication

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

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

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

Important Safety Information

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

- **Hepatotoxicity:** Serious hepatotoxicity has been reported, including liver failure and death in patients treated with KADCYLA. Monitor serum transaminases and bilirubin prior to initiation of KADCYLA treatment and prior to each KADCYLA dose. Reduce dose or discontinue KADCYLA as appropriate in cases of increased serum transaminases or total bilirubin
- **Cardiac Toxicity:** KADCYLA administration may lead to reductions in left ventricular ejection fraction (LVEF). Evaluate left ventricular function in all patients prior to and during treatment with KADCYLA. Withhold treatment for clinically significant decrease in left ventricular function
- **Embryo-Fetal Toxicity:** Exposure to KADCYLA during pregnancy can result in embryo-fetal harm. Advise patients of these risks and the need for effective contraception

Please see additional Important Safety Information throughout, and [click here](#) for full Prescribing Information, including BOXED WARNINGS.

References: 1. KADCYLA Prescribing Information. Genentech, Inc. 2019. 2. Verma S, Miles D, Gianni L, et al; EMILIA Study Group. Trastuzumab emtansine for HER2-positive advanced breast cancer [published correction appears in *N Engl J Med*. 2013;368:2442]. *N Engl J Med*. 2012;367:1783-1791 and Supplementary Appendix. 3. Data on file. Genentech, Inc. 4. Center for Drug Evaluation and Research. Clinical review — BLA 125427: Kadcyla (ado-trastuzumab emtansine) for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/125427Orig1s000MedR.pdf. Completed: January 25, 2013. Accessed July 27, 2020. 5. Krop IE, Lin NU, Blackwell K, et al. Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: a retrospective, exploratory analysis in EMILIA. *Ann Oncol*. 2015;26(2):113-119. 6. Roche.com. FDA approves Roche's Kadcyla (trastuzumab emtansine), the first antibody-drug conjugate for treating HER2-positive metastatic breast cancer. <http://www.roche.com/media/releases/med-cor-2013-02-22.htm>. Accessed May 29, 2020. 7. Staudecher AH, Brown MP. Antibody drug conjugates and bystander killing: is antigen-dependent internalisation required? *Br J Cancer*. 2017;117(12):1736-1742. 8. Lewis Phillips GD, Li G, Dugger DL, et al. Targeting HER2-positive breast cancer with trastuzumab-DM1, an antibody-cytotoxic drug conjugate. *Cancer Res*. 2008;68(22):9280-9290. 9. Junttila TT, Li G, Parsons K, Phillips GL, Sliwkowski MX. Trastuzumab-DM1 (T-DM1) retains all the mechanisms of action of trastuzumab and efficiently inhibits growth of lapatinib insensitive breast cancer. *Breast Cancer Res Treat*. 2011;128:347-356. 10. Nahta R, Esteva FJ. Herceptin: mechanisms of action and resistance. *Cancer Lett*. 2006; 232:123-138. 11. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) for Breast Cancer V6.2020. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed September 11, 2020. To view the most recent and complete version of the guideline, go online to NCCN.org.