Kadcyla in HER2+ve Metastatic breast cancer

Speaker:

M-IN-00002764, valid till 28/05/2024

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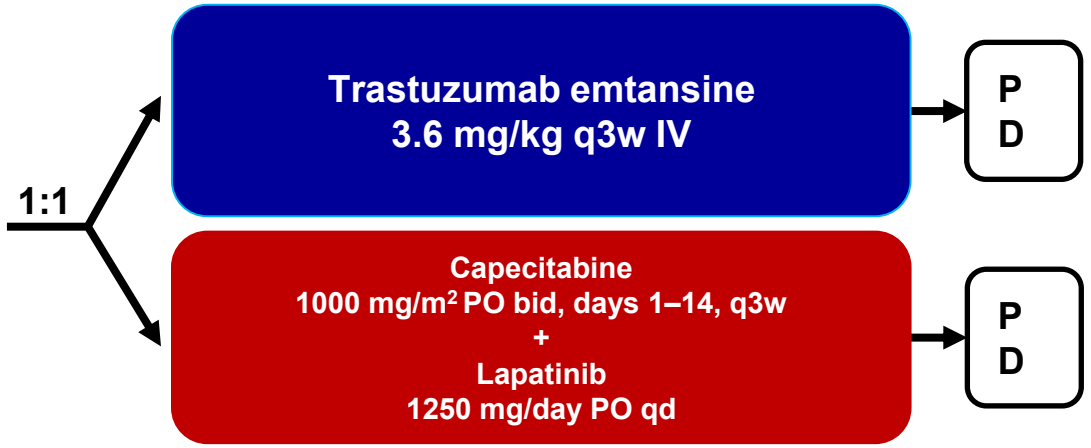
EMILIA: A randomised, Phase III study of Trastuzumab emtansine versus lapatinib plus capecitabine



- **Primary endpoints:** PFS by independent review, OS, and safety
- **Key secondary endpoints:** PFS by investigator, ORR, DOR

Verma S, et al. N Engl J Med. 2012 Nov 8;367(19):1783-91

EMILIA: Patient Demographics and Baseline Characteristics (1)

	Cap + Lap (n=496)	Kadcyla (n=495)
Median age, years (range)	53 (24–83)	53 (25–84)
Race, n (%)		
White	374 (75)	358 (72)
Asian	86 (17)	94 (19)
Black/African American	21 (4)	29 (6)
Other	10 (2)	7 (1)
Not available	5 (1)	7 (1)
World region, n (%)		
United States	136 (27)	134 (27)
Western Europe	160 (32)	157 (32)
Asia	76 (15)	82 (17)
Other	124 (25)	122 (25)
ECOG PS, n (%)		
0	312 (64)	299 (61)
1	176 (36)	194 (39)

Data cutoff: 14JAN2012

Verma S, et al. N Engl J Med. 2012 Nov 8;367(19):1783-91

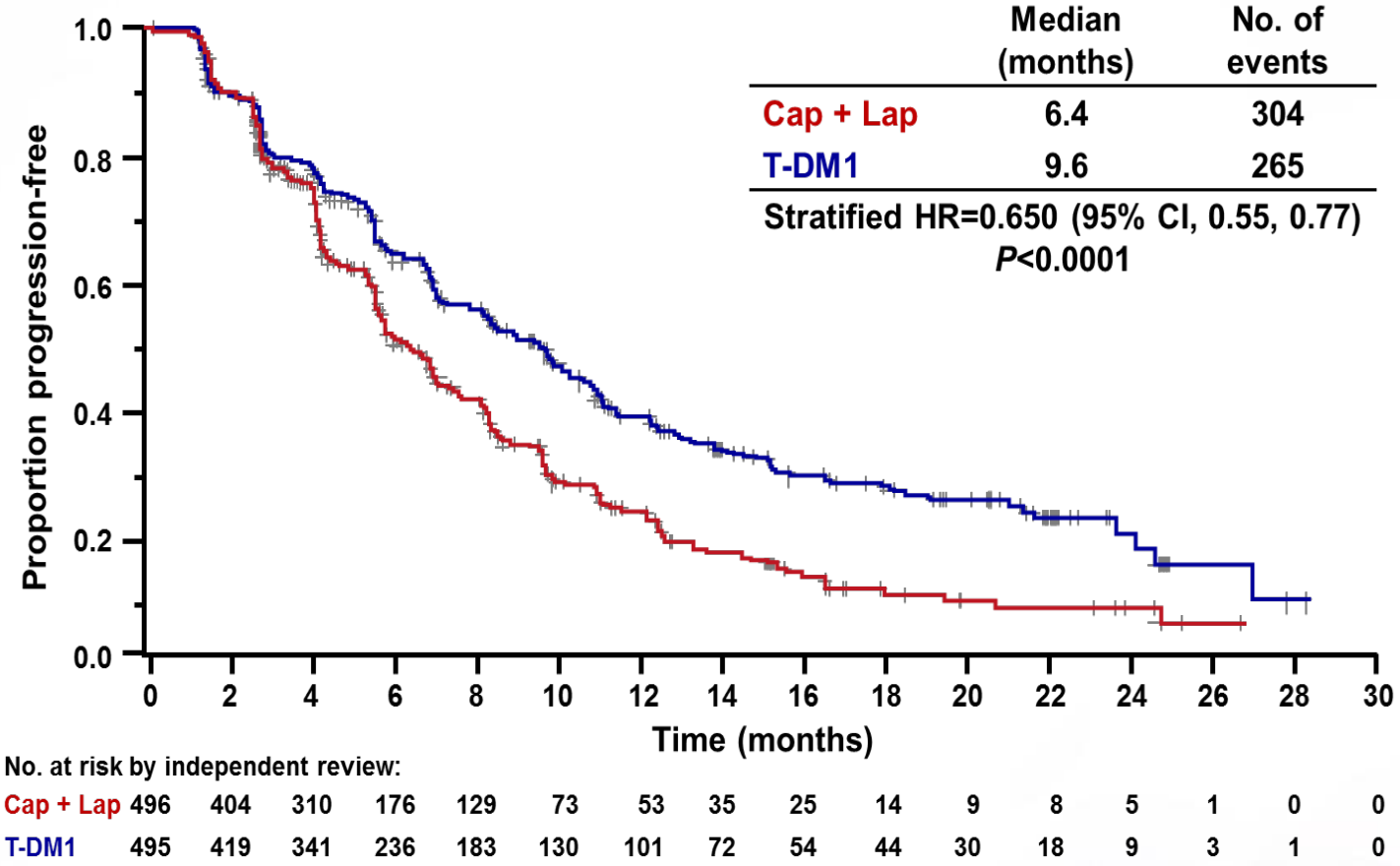
EMILIA: Patient Demographics and Baseline Characteristics (2)

	Cap + Lap (n=496)	Kadcyla (n=495)
Measurable disease by independent review, n (%)	389 (78)	397 (80)
Site of disease involvement, n (%)		
Visceral	335 (67)	334 (68)
Non-visceral	161 (32)	161 (33)
Metastatic sites, n (%)		
<3	307 (62)	298 (60)
≥3	175 (35)	189 (38)
Unknown	14 (3)	8 (2)
ER/PR status, n (%)		
ER+ and/or PR+	263 (53)	282 (57)
ER− and PR−	224 (45)	202 (41)
Unknown	9 (2)	11 (2)

Data cutoff: 14JAN2012

Verma S, et al. N Engl J Med. 2012 Nov 8;367(19):1783-91

EMILIA: Progression-Free Survival benefit seen with Kadcyla



Unstratified HR=0.66 (*P*<0.0001).

Data cutoff: 14JAN2012

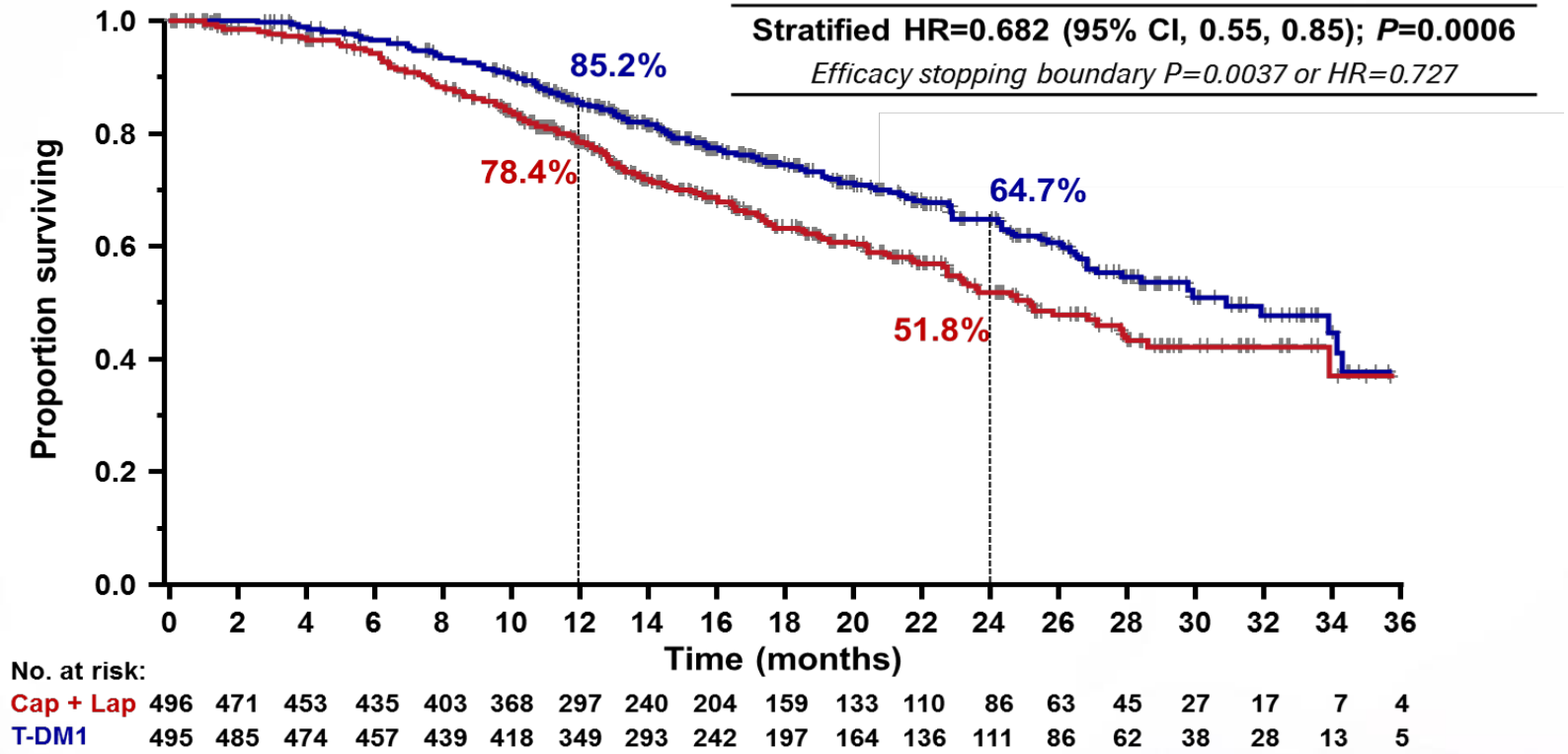
Verma S, et al. N Engl J Med. 2012 Nov 8;367(19):1783-91

EMILIA: Overall survival benefit seen with Kadcyla

	Median (months)	No. of events
Cap + Lap	25.1	182
T-DM1	30.9	149

Stratified HR=0.682 (95% CI, 0.55, 0.85); *P*=0.0006

Efficacy stopping boundary P=0.0037 or HR=0.727

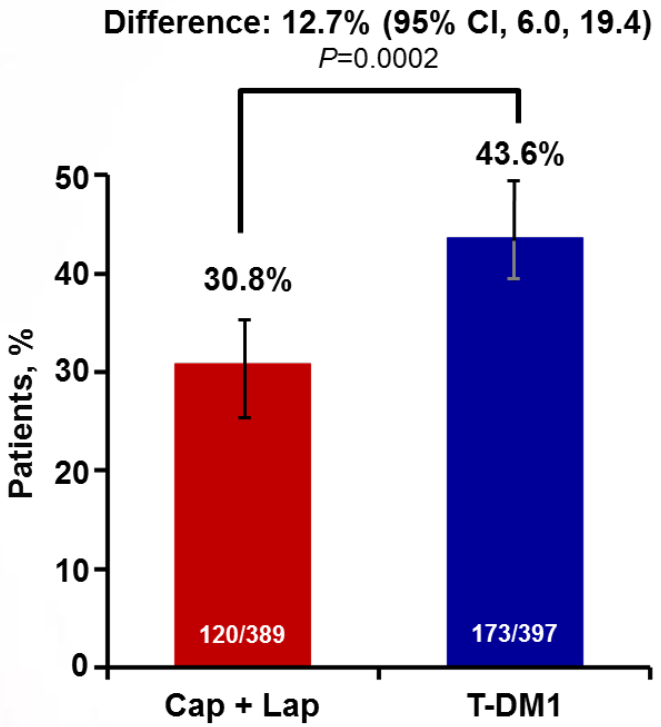


Data cut-off July 31, 2012; Unstratified HR=0.70 (*P*=0.0012).

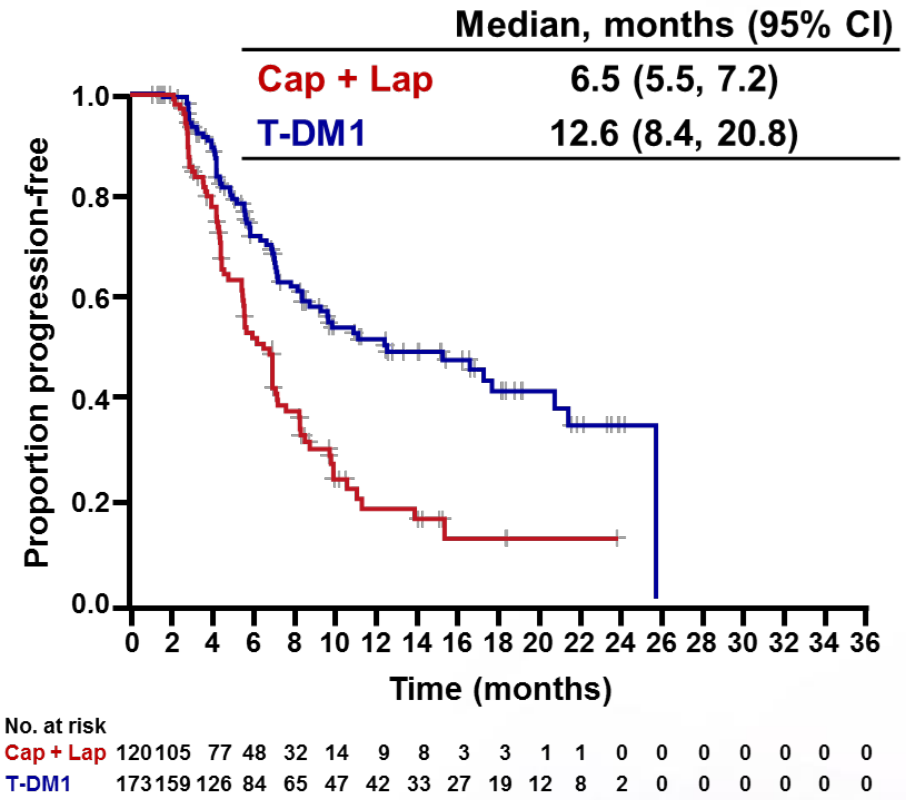
Verma S, et al. N Engl J Med. 2012 Nov 8;367(19):1783-91

EMILIA: Significantly higher ORR and clinically meaningful DOR with Kadcyla

Objective response rate (ORR)



Duration of response (DOR)



Data cutoff: 14JAN2012

Verma S, et al. N Engl J Med. 2012 Nov 8;367(19):1783-91

EMILIA: Patient-reported outcomes *Time to symptom progression*

The FACT-B TOI[1] evaluates

- Physical well-being
- Functional well-being
- Breast cancer-specific symptoms

Symptom progression defined as ≥5-point decrease from baseline

Time to symptom progression[2]	Cap + lap (n = 445)	Trastuzumab emtansine (n = 450)
Median, mo	**4.6**	**7.1**
HR (95% CI) p value	**0.80 (0.67–0.95)** **0.0121**	

CI, confidence interval; FACT-B, Functional Assessment of Cancer Therapy-Breast; HR, hazard ratio; TOI, Trial Outcome Index.

1. Brady MJ, *et al*. *J Clin Oncol* 1997;**15:**974–986;
2. Verma S, et al. N Engl J Med. 2012 Nov 8;367(19):1783-91
3. .

Kadcyla was well tolerated with a reduced incidence of grade ≥3 AEs* versus lapatinib plus capecitabine

	Lapatinib + capecitabine (n=488)		Trastuzumab emtansine (n=490)	
AE	**All grades, %**	**Grade ≥3, %**	**All grades, %**	**Grade ≥3, %**
Diarrhoea	79.7	20.7	23.3	1.6
Hand–foot syndrome	58.0	16.4	1.2	0.0
Vomiting	29.3	4.5	19.0	0.8
Neutropenia	8.6	4.3	5.9	2.0
Hypokalaemia	8.6	4.1	8.6	2.2
Fatigue	27.9	3.5	35.1	2.4
Nausea	44.7	2.5	39.2	0.8
Mucosal inflammation	19.1	2.3	6.7	0.2
Thrombocytopenia	2.5	0.2	28.0	12.9
Increased AST	9.4	0.8	22.4	4.3
Increased ALT	8.8	1.4	16.9	2.9
Anaemia	8.0	1.6	10.4	2.7

* Listed are grade ≥3 AEs with an incidence of 2% or higher in either group.

Verma, S *et al*. *N Engl J Med* 2012; **367**:1783–1791.

EMILIA: Fewer patients treated with Trastuzumab Emtansine required a dose reduction vs lapatinib + capecitabine

	Cap (n=487)	Lap (n=488)	Trastuzumab emtansine (n=490)
Median dose intensity, %	77.2	93.4	99.9
Pts with dose reduction, n (%)	**260 (53.4)**	**133 (27.3)**	**80 (16.3)**

Verma S, *et al*. *N Engl J Med* 2012; **367**:1783–1791.

EMILIA: Trastuzumab emtansine was associated with a reduced incidence of grade ≥3 AEs compared with lapatinib + capecitabine

Fewer patients discontinued treatment due to AEs in the Trastuzumab emtansine arm versus the lapatinib plus capecitabine arm

	Lapatinib + capecitabine (n = 488)	Trastuzumab emtansine (n = 490)
All-grade AE, n (%)	477 (97.7)	470 (95.9)
Grade ≥3 AE, n (%)	278 (57.0)	200 (40.8)
AEs leading to treatment discontinuation (for any study drug), n (%)	52 (10.7)	29 (5.9)
AEs leading to death within 30 days of last dose of study drug, n (%)*	4 (0.8)	1 (0.2)

Trastuzumab emtansine demonstrated a lower incidence of AEs commonly associated with chemotherapy

AE, adverse event
* Lapatinib + capecitabine: coronary artery disease, multi-organ failure, coma and hydrocephalus;
Trastuzumab emtansine: metabolic encephalopathy

Verma S, *et al*. *N Engl J Med* 2012; **367**:1783–1791.

EMILIA: Cardiac Dysfunction

	Cap + Lap	Trastuzumab emtansine
Cardiac dysfunction AEs,[a] n (%)	(n=488)	(n=490)
All grades	16 (3.3)	10 (2.0)
Grade 3	2 (0.4)	1 (0.2)
Lowest post-baseline LVEF value, n (%)	(n=462)	(n=482)
≥45%	455 (98.5)	476 (98.8)
≥40 to <45%	4 (0.9)	3 (0.6)
<40%	3 (0.6)	3 (0.6)
LVEF <50% and ≥15-point decrease from baseline, n (%)	(n=446) 8 (1.8)	(n=481) 8 (1.7)

[a]Includes preferred terms 'decreased ejection fraction' and 'left ventricular dysfunction'; Does not include cardiac AEs (e.g. myocardial infarction, atrial fibrillation).

Data cutoff: 31JUL2012

Verma S, et al. N Engl J Med. 2012 Nov 8;367(19):1783-91

EMILIA: Superior efficacy and a favourable safety profile for Kadcyla versus lapatinib + capecitabine

Efficacy

Significant improvement in OS for Trastuzumab emtansine vs. lapatinib + capecitabine[1]
Almost 6-month increase
(30.9 months vs. 25.1 months;
HR = 0.68, p < 0.001)

Significant improvement in PFS (IRF) for Trastuzumab emtansine vs. lapatinib + capecitabine[1]
A greater than 3-month increase in PFS
(9.6 months vs. 6.4 months;
HR = 0.65; p < 0.001)

Key secondary efficacy outcomes, including ORR, were also significantly improved with Trastuzumab emtansine[1]

Safety

The safety profile of Trastuzumab emtansine was favourable compared with that of lapatinib + capecitabine[1]

Patient-reported outcomes

Time to symptom progression was significantly delayed with Trastuzumab emtansine compared with lapatinib + capecitabine[2]

HR, hazard ratio; IRF, independent review facility; ORR, objective response rate; OS, overall survival;
PFS, progression-free survival

1. Verma S, *et al*. *N Engl J Med* 2012; **367**:1783–1791 and Erratum *N Engl J Med* 2013; **368**:2442;
2. Welslau M, *et al. Cancer* 2013;**120**:642–651.

Annals of Oncology 26: 113–119, 2015

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†

I. E. Krop[1*], N. U. Lin[1], K. Blackwell[2], E. Guardino[3], J. Huober[4,‡], M. Lu[3], D. Miles[5], M. Samant[6], M. Welslau[7] & V. Diéras[8]

CNS metastases

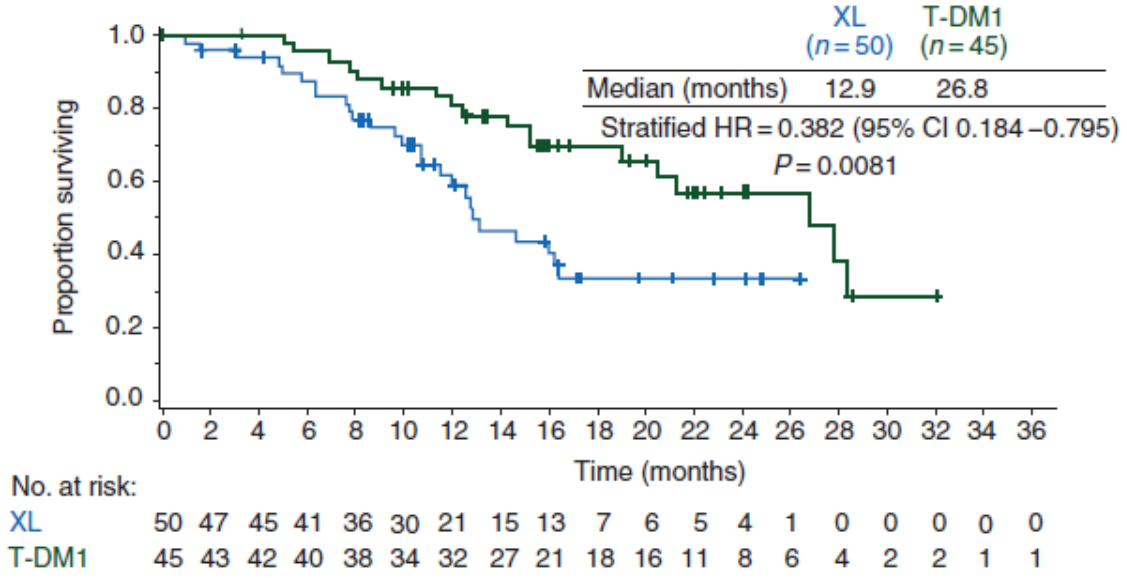
All patients underwent brain MRI or CT at screening. Follow-up scans were carried out as clinically indicated, but were not mandated. Patients with CNS metastases that were untreated, were symptomatic, or required therapy to control symptoms ≤2 months before randomization were excluded, as were patients with CNS-only disease. Patients with asymptomatic CNS metastases previously treated with radiotherapy were eligible to enroll 14 days after last radiotherapy treatment.

CNS metastases at baseline. Among those patients without CNS metastases at baseline, 2.0% (9/450) and 0.7% (3/446) developed CNS progression on study in the T-DM1 and XL arms, respectively. Among the 95 patients with CNS metastases at baseline, 22.2% (10/45) and 16.0% (8/50), respectively, developed CNS progression on study.

Krop IE, et al. Annals of Oncology. 2015;26:113–119.

EMILIA: Clinical outcome in patients who had stable CNS disease at baseline

Overall Survival



In conclusion, our analysis suggests that T-DM1 may confer a survival advantage over XL in patients with treated, asymptomatic CNS metastases and previously treated HER2-positive MBC, without increasing the risk for CNS progression. These findings challenge the concept that patients with stable CNS disease should be switched to lapatinib-based therapy after localized treatment to prevent further CNS progression or to improve clinical outcomes. We acknowledge that these data are hypothesis-generating; however, we believe they warrant prospective study into the activity of HER2-directed therapies in patients with CNS metastases stemming from HER2-positive MBC.

Krop IE, et al. Annals of Oncology. 2015;26:113–119.

How to administer Kadcyla

Dosing for Trastuzumab emtansine is **weight-based**; it is important to verify the correct dose and volume for Trastuzumab emtansine using dose calculation guides

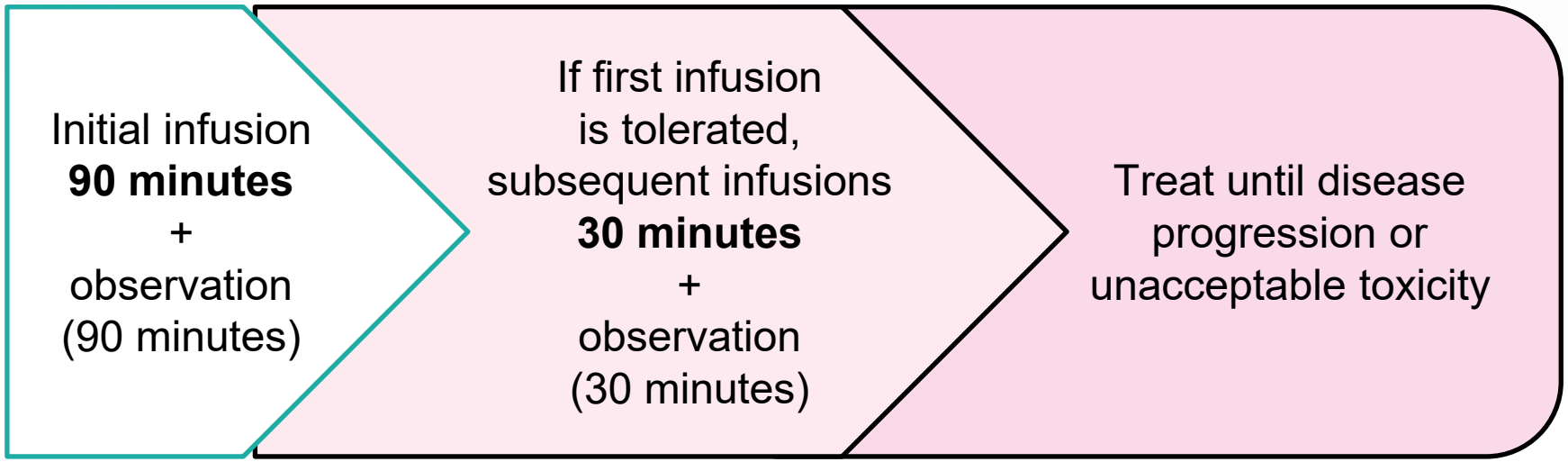
Trastuzumab emtansine is given as a single IV infusion every 3 weeks

- Administer at a dose of 3.6 mg/kg via IV infusion
  - **Do not administer Trastuzumab emtansine as an intravenous push or bolus**
- To be either diluted in 250 ml of sodium chloride 4.5 mg/ml (0.45%) or sodium chloride 9 mg/ml (0.9%) solution for infusion
  - An in-line PES filter (0.22 micron) is required for the 0.9% dilution
- No loading dose

IV, intravenous; PES, polyethersulfone

Kadcyla (Trastuzumab Emtansine) Prescribing information, India 2022

Administration schedule for Kadcyla



Missed doses

- If a planned dose is missed, administer as soon as possible
  - Do not wait until the next planned cycle
- Following a delayed or missed dose, adjust administration schedule to maintain a 3-week dosing interval

Kadcyla (Trastuzumab Emtansine) Prescribing information, India 2022

Dose modifications and reductions

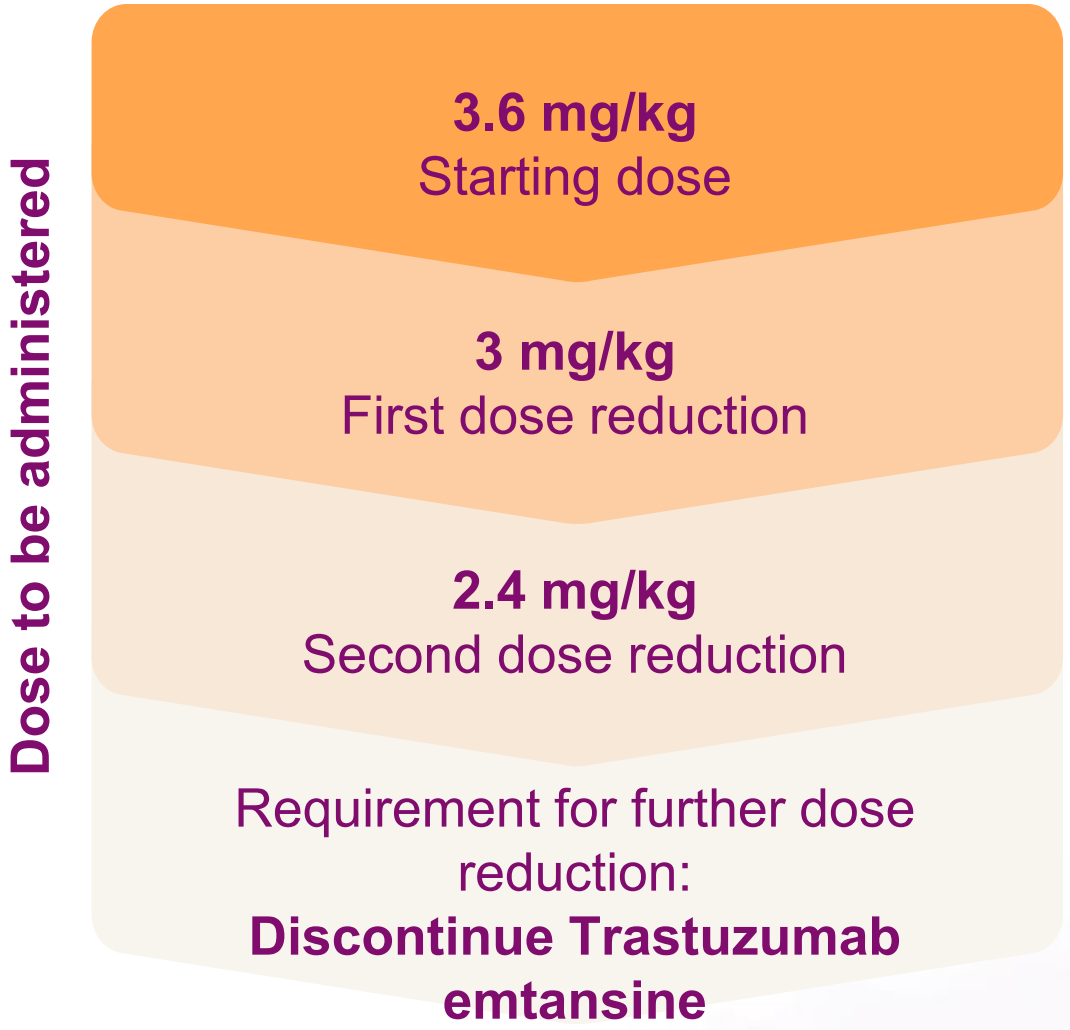
Despite the favourable safety profile for Kadcyla, management of adverse reactions may require temporary interruption, dose reduction or treatment discontinuation

Dose reduction guidelines for Trastuzumab emtansine:

- Dose reductions should be made in decrements of 0.6 mg/kg
- A maximum of two dose reductions are allowed to occur before discontinuation
- **Trastuzumab emtansine dose should not be re-escalated after a dose reduction has been made**

Kadcyla (Trastuzumab Emtansine) Prescribing information, India 2022

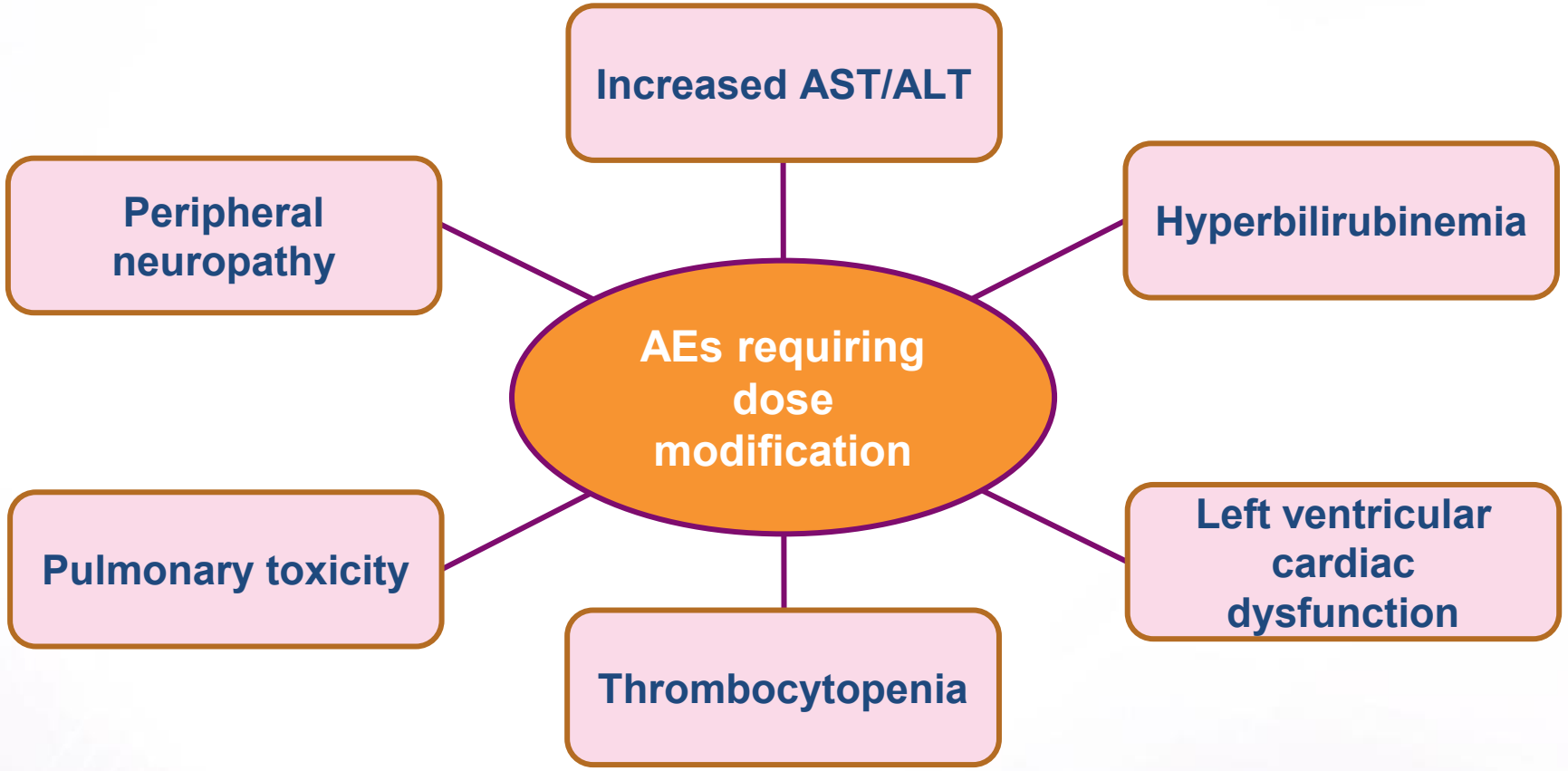
Dose reduction schedule



Kadcyla (Trastuzumab Emtansine) Prescribing information, India 2022

Adverse events associated with Kadcyla requiring dose modifications

Please refer to PI for further details of dose modification guidelines for Trastuzumab emtansine



Kadcyla (Trastuzumab Emtansine) Prescribing information, India 2022

Kadcyla dose modification guidelines: Liver toxicity*

Hepatotoxicity: Increased serum transaminases (AST/ALT)		
>2.5 to ≤5x ULN (grade 2)	>5 to ≤20x ULN (grade 3)	>20x ULN (grade 4)
1. No dose modification required	1. Do not dose until recovery to grade 2 (>2.5 to ≤5x ULN) 2. Then reduce one dose level	1. Discontinue Trastuzumab emtansine

Hyperbilirubinemia		
>1.5 to ≤3x ULN (grade 2)	>3 to ≤10x ULN (grade 3)	>10x ULN (grade 4)
1. Do not dose until total bilirubin level recovers to >ULN to ≤1.5 x ULN 2. No dose modification is required	1. Do not dose until total bilirubin level recovers to grade 1 (>ULN to ≤1.5 x ULN) 2. Then reduce one dose level	1. Discontinue Trastuzumab emtansine.

* Permanently discontinue Trastuzumab emtansine treatment in patients with serum transaminases >3 x ULN and concomitant total bilirubin >2 x ULN, OR diagnosed with nodular regenerative hyperplasia

Kadcyla (Trastuzumab Emtansine) Prescribing information, India 2022

Kadcyla dose modification guidelines: Left ventricular cardiac dysfunction

Left ventricular cardiac dysfunction				
LVEF <40%	LVEF >45%	LVEF 40% to ≤45% & <10% point decline from B/L	LVEF 40% to ≤45% & ≥10% point decline from B/L	Symptomatic congestive heart failure
1. Do not administer Trastuzumab emtansine 2. Repeat LVEF assessment within 3 weeks 3. If LVEF <40% is confirmed, discontinue Trastuzumab emtansine	1. Continue treatment with Trastuzumab emtansine	1. Continue treatment with Trastuzumab emtansine 2. Repeat LVEF assessment within 3 weeks	1. Do not administer Trastuzumab emtansine 2. Repeat LVEF assessment within 3 weeks 3. If LVEF has not recovered to within 10% points of absolute B/L, discontinue Trastuzumab emtansine	1. Discontinue Trastuzumab emtansine

Kadcyla (Trastuzumab Emtansine) Prescribing information, India 2022

Kadcyla dose modification guidelines: Thrombocytopenia, pulmonary toxicity and peripheral neuropathy

Thrombocytopenia	
25,000 to <50,000 platelets/mm^3 (grade 3)	<25,000 platelets/mm^3 (grade 4)
1. Do not dose until recovered to ≥75,000 platelets/mm^3 2. Then treat at same dose level	1. Do not dose until recovered to ≥75,000 platelets/mm^3 2. Then reduce one dose level

Pulmonary toxicity: Permanently discontinue in patients diagnosed with interstitial lung disease (ILD) or pneumonitis

Peripheral neuropathy: Do not dose in patients with severe to life-threatening peripheral neuropathy (grade 3 or 4) until resolution to grade ≤2

Kadcyla (Trastuzumab Emtansine) Prescribing information, India 2022

Kadcyla is recommended by AGO as highest ranked treatment option for second-line HER2-positive mBC

Treatment regimen	Recommendation†
Trastuzumab emtansine*	Grade A, ++ (A++ highest rank, D-- lowest rank criteria)
Lapatinib + capecitabine	Grade B, +
Trastuzumab + lapatinib	Grade B, +
TBP: Second-line chemotherapy + trastuzumab	Grade D, +
Pertuzumab + trastuzumab + taxane	Grade D, +
Pertuzumab + trastuzumab + other second-line chemotherapy (e.g. vinorelbine; taxane/carboplatin; capecitabine/docetaxel)	Grade D,+/-
Trastuzumab + AI (ER-positive)	Grade B, +
Lapatinib + AI (ER-positive)	Grade B, +

AGO, German Gynaecological Oncology Group; AI, aromatase inhibitor; ER, oestrogen receptor; HR, hormone receptor; TBP, treatment beyond progression

*** The AGO guidelines highlight that Trastuzumab emtansine is recommended more highly than lapatinib + capecitabine;**
Trastuzumab emtansine is also recommended (Grade A++) in further lines of therapy.

† See speaker notes and Appendix for further information on recommendations/gradings; AGO recommendations for second-line therapies apply to patients whose disease has progressed on trastuzumab-based therapy.

Not all treatment combinations recommended by the guidelines are approved by the regulatory authorities.

http://www.ago-online.de/en/guidelines-mamma/march-2014/

Not all treatment combinations recommended by guidelines are approved by regulatory authorities

Kadcyla is recommended by the ESMO as a preferred treatment option for second-line HER2-positive mBC

Treatment regimen	Recommendation†
After 1st line trastuzumab-based therapy, T-DM1 provides superior efficacy relative to other HER-2-based therapies in the 2nd line (vs. lapatinib + capecitabine) and beyond (vs. treatment of physician's choice). T-DM1 should be preferred in patients who have progressed through at least 1 line of trastuzumab-based therapy, since it provides an OS benefit	1A

* **Level 1A:** Strong recommendation based on high quality evidence

Cardoso F, et al. Annals of Oncology. 2018;29: 1634–1657. (ESMO guideline)

Kadcyla approved in India (Therapeutic indication)

- **Metastatic Breast Cancer (MBC):** Kadcyla, as a single agent, is indicated for the treatment of patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who have received prior treatment with trastuzumab and a taxane.
- **Early Breast Cancer (EBC):** Kadcyla, as a single agent, is indicated for the adjuvant treatment of adult patients with HER2-positive early breast cancer who have residual disease, in the breast and/or lymph nodes, after pre-operative systemic treatment that included HER2 targeted therapy.

Kadcyla (Trastuzumab Emtansine) Prescribing information, India 2022

Kadcyla approved in India (Dosage and administration)

- **Trastuzumab emtansine is given as a single IV infusion every 3 weeks**
- Administer at a dose of 3.6 mg/kg via IV infusion
- Initial infusion 90 minutes followed by observation (90 minutes). If first infusion is tolerated, subsequent infusions 30 minutes + observation (30 minutes)
- No loading dose
- Dose reductions for management of adverse effect allowed
- Patients should be treated until disease progression or unmanageable toxicity

Kadcyla (Trastuzumab Emtansine) Prescribing information, India 2022

Enhanced Safety Reporting for Potential Kadcyla -Exposed Pregnancies

- Kadcyla should be avoided during pregnancy. There is limited amount of data from the use of Kadcyla in pregnant women and the safe use of Kadcyla during pregnancy and lactation has not been established.

- Verify pregnancy status prior to the initiation of Kadcyla . Women of child-bearing potential should use effective contraception while receiving Kadcyla and for 6 months following the last dose of Kadcyla .

- Monitor patients who become pregnant during Kadcyla therapy or within 6 months following the last dose of Kadcyla closely for oligohydramnios.

- If Kadcyla is used during pregnancy or if a patient becomes pregnant while being treated with Kadcyla or within 6 months following the last dose of Kadcyla , immediately report exposure to the local Roche Adverse Event Line at **india.drugsafety@roche.com** , Emergency Contact(24 X 7): 98201 63752, Fax No. +91 22 33941054

- Additional information will be requested during a Kadcyla -exposed pregnancy and the first year of the infant's life. This will enable Roche to better understand the safety of Kadcyla and to provide appropriate information to Health Authorities, Healthcare Providers and patients.

Kadcyla (Trastuzumab Emtansine) Prescribing information, India 2022

Overall summary

Kadcyla (Trastuzumab emtansine) is a novel ADC

EMILIA study

- Significant improvement in efficacy and toxicity compared with capecitabine/lapatinib

Approved for treating HER2-postive MBC in patients previously treated with trastuzumab and a taxane

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