Antibody Drug Conjugates(ADC) in HER2+ metastatic Breast Cancer: What to Consider?

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- For additional information, please refer to the Product information.

Contents

ADC, antibody–drug conjugate;; mBC, metastatic breast cancer;

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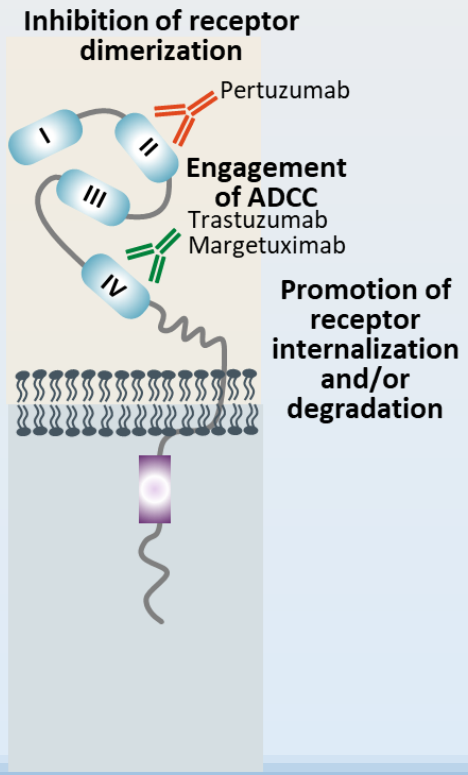
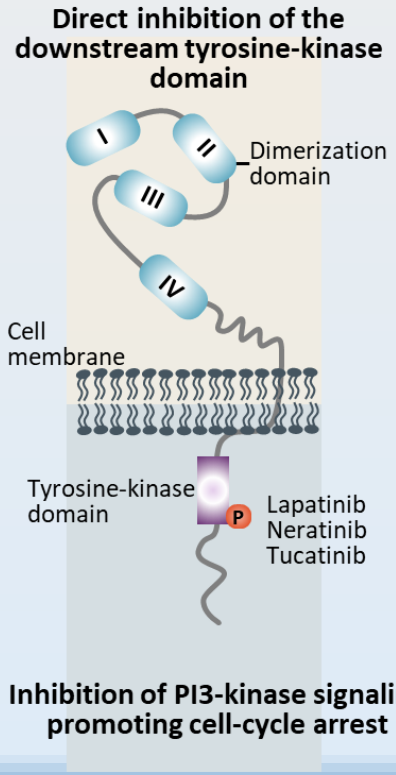
Anti-HER2 therapies

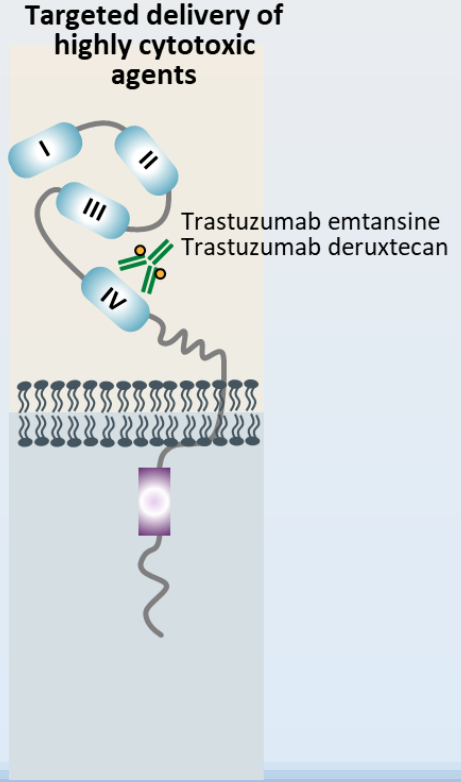
Single-Epitope mAbs



Small-Molecule Inhibitors

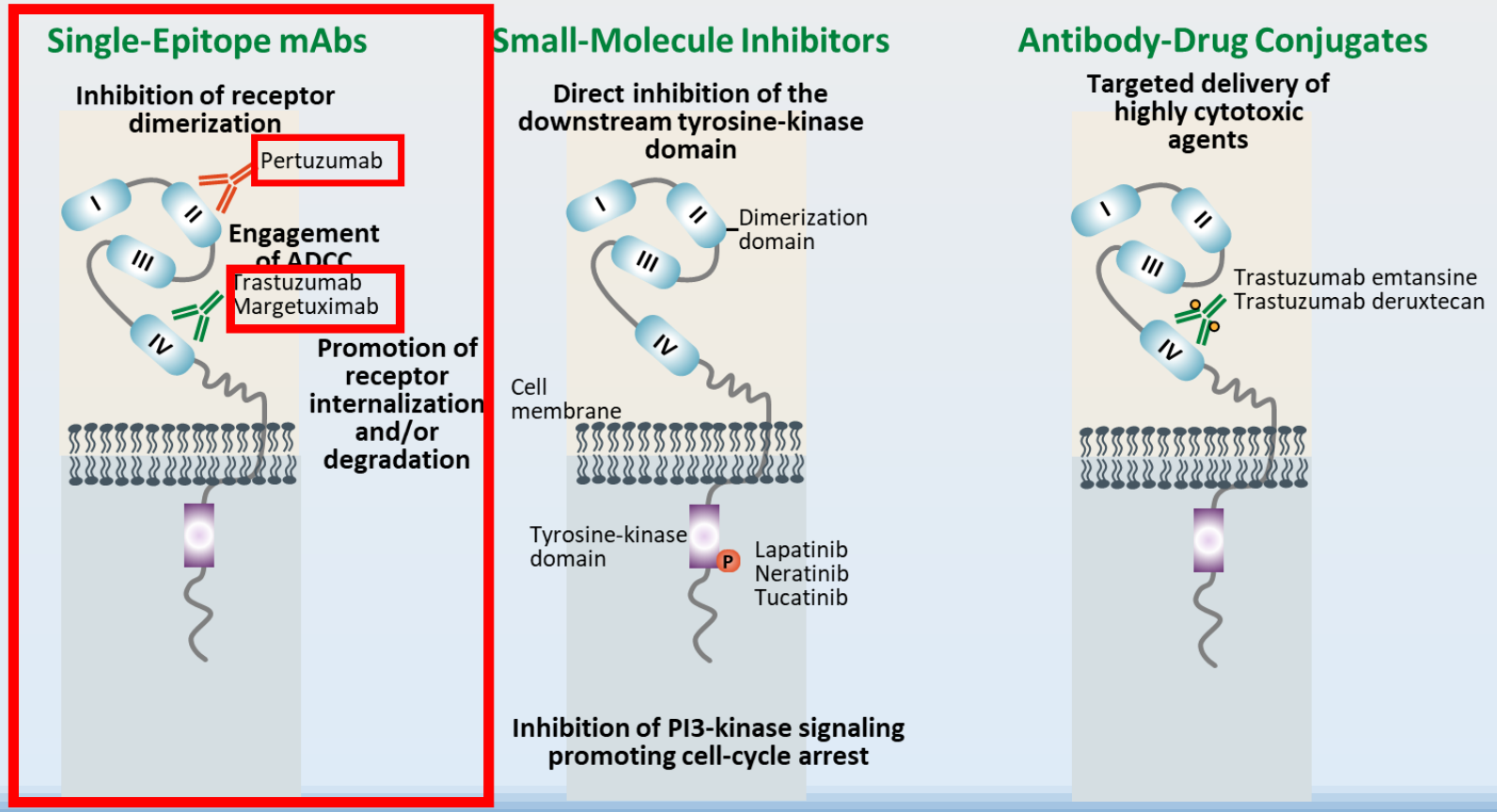


Antibody-Drug Conjugates



DY Oh, et al. Nat Rev Clin Oncol. 2020

Anti-HER2 therapies



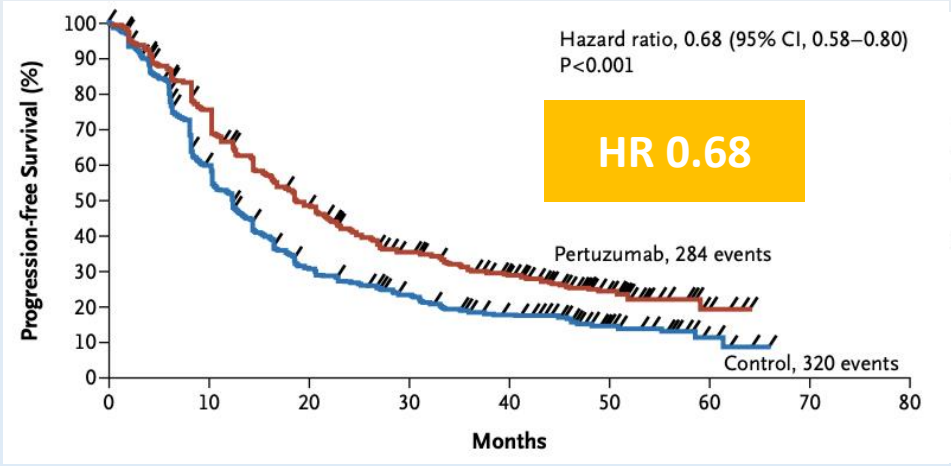
DY Oh, et al. Nat Rev Clin Oncol. 2020

CLEOPATRA trial

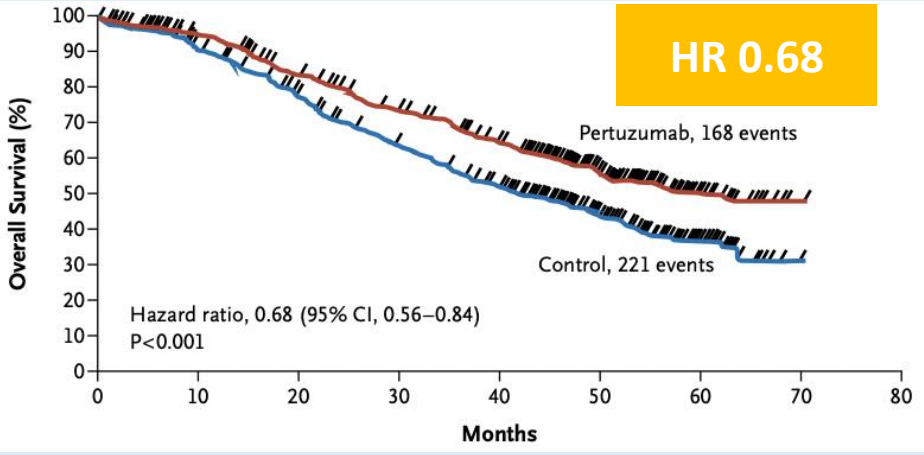
HER2 positive
Metastatic breast cancer, First-line

Pertuzumab + Trastuzumab + chemotherapy vs Trastuzumab + chemotherapy

PFS



OS

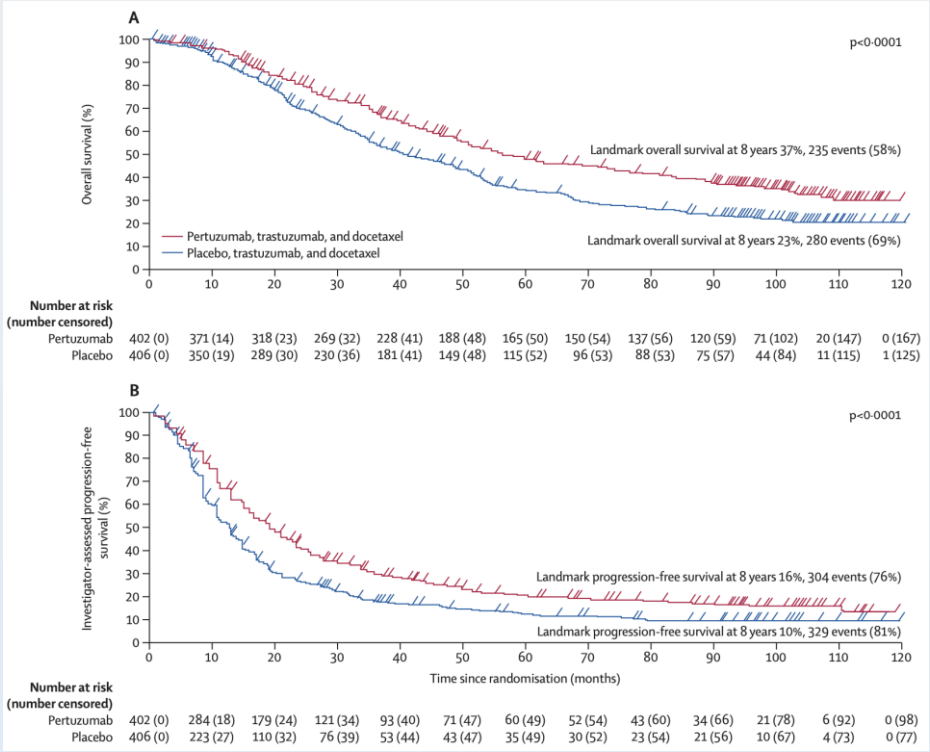


Baselga J, et al., N Engl J Med 2012.
Swain SM, et al., N Engl J Med 2015.

CLEOPATRA trial (99.9mo follow-up)

OS

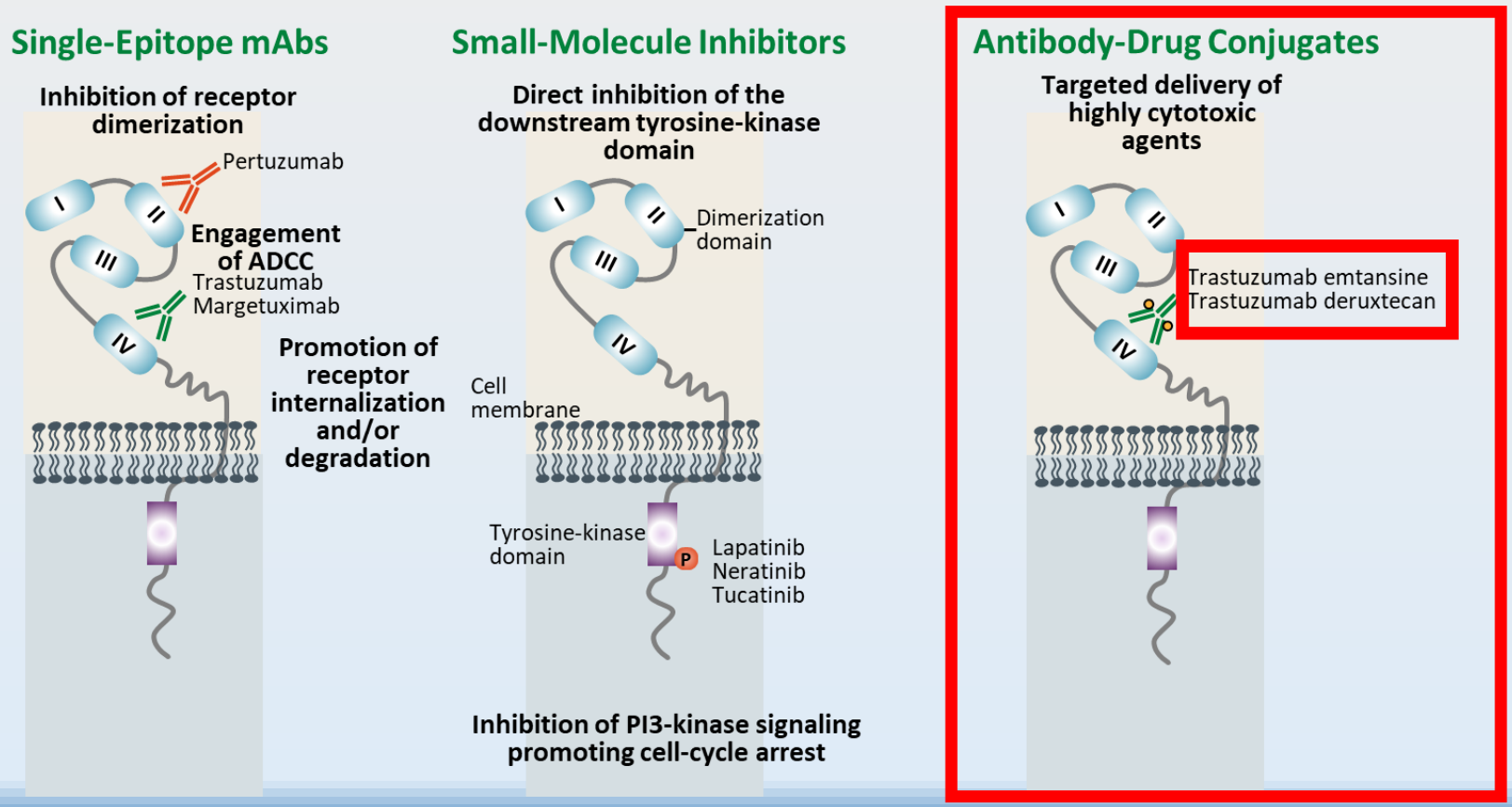
PFS



End of study analysis (10-year follow-up)	PHT (n = 402)	HT (n = 406)
Median OS (mo)	**57.1**	**40.8**
HR (95% CI)	**0.69** (0.58, 0.82)	
8-year OS rate	37%	23%
Median PFS(mo)	**18.7**	**12.4**
HR (95% CI)	**0.69** (0.59, 0.81)	
8-year PFS rates	16%	10%

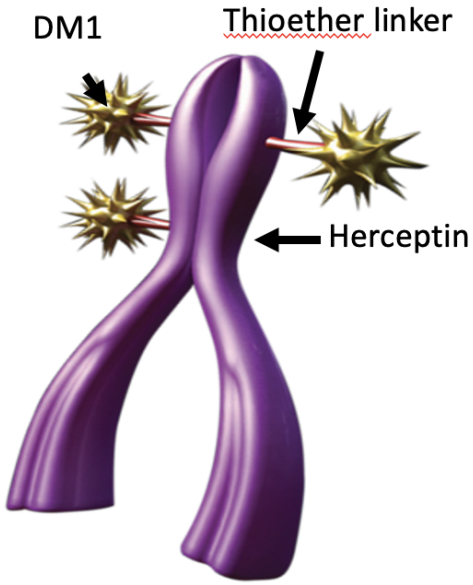
Swain SM, *et al. Lancet Oncol* 2020; **21**:519–530.

Anti-HER2 therapies



DY Oh, et al. Nat Rev Clin Oncol. 2020

T-DM1 is an ADC specifically designed to target HER2-positive cancer cells, while sparing non-cancer cells



T-DM1 components

Well-understood Herceptin antibody[1,2]

- DM1* is **selectively** targeted to HER2-overexpressing cells
- Herceptin pharmacodynamic properties retained:
  - Prevention of HER2-activated intracellular signalling
  - Antibody-dependent cellular cytotoxicity
  - Prevention of p95HER2 formation

Stable (non-cleavable) thioether linker[1,3]

- Minimises release of DM1, which would otherwise result in systemic toxicities

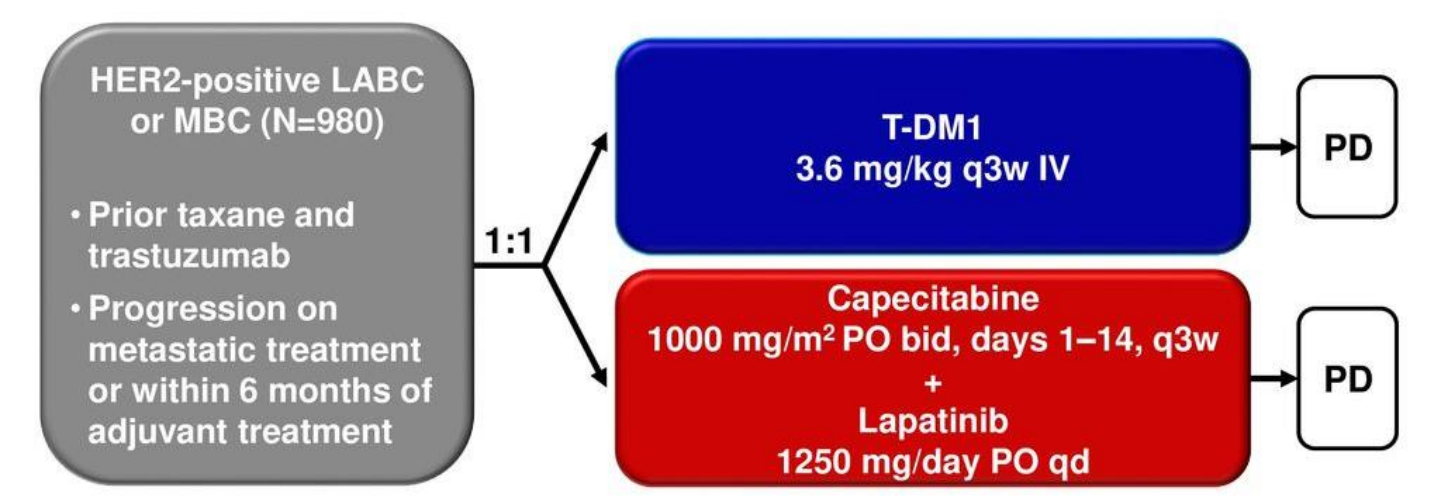
Targeted intracellular delivery of DM1 enhances anti-cancer effect[1,2,4,5]

- DM1 causes apoptosis by inhibiting microtubule assembly
- DM1 is a maytansinoid, which are:
  - 20- to 270-fold more potent than taxanes and vinca alkoids[1,6]
  - 2–3 orders of magnitude more potent than doxorubicin[1]
- Average of 3.0–3.6 DM1 molecules (payload) per 1 Herceptin molecule[4]

* DM1 is a cytotoxic anti-microtubule agent

1. Junttila TT, *et al. Breast Cancer Res Treat* 2011; **128**:347–356; 2. Hudis CA. *N Engl J Med* 2007; **357**:39–51;
3. Burris HA 3rd, *et al. J Clin Oncol* 2011; **29**:398–405; 4. Lewis Phillips GD et al. *Cancer Res* 2008; **68**:9280–9290;
5. Barok M, *et al. Cancer Lett* 2011; **306**:171–179; 6. BPOM Product Information Kadcyla Dec 2021.

EMILIA trial



Co-primary endpoints: PFS (by independent review), OS, safety

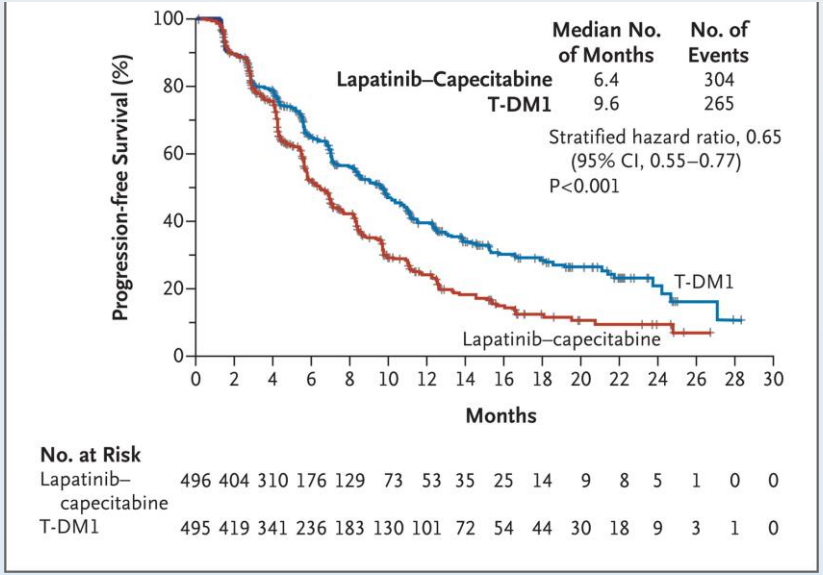
Key secondary objectives: PFS (by investigator), ORR, TTF, CBR

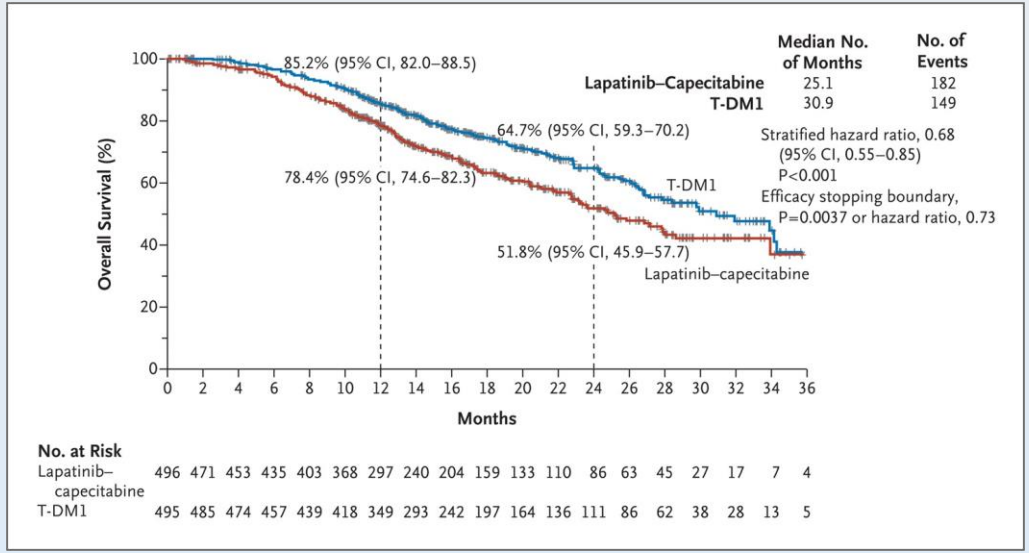
EMILIA trial

ORR L + C: 30.8%
T-DM1: 43.6%

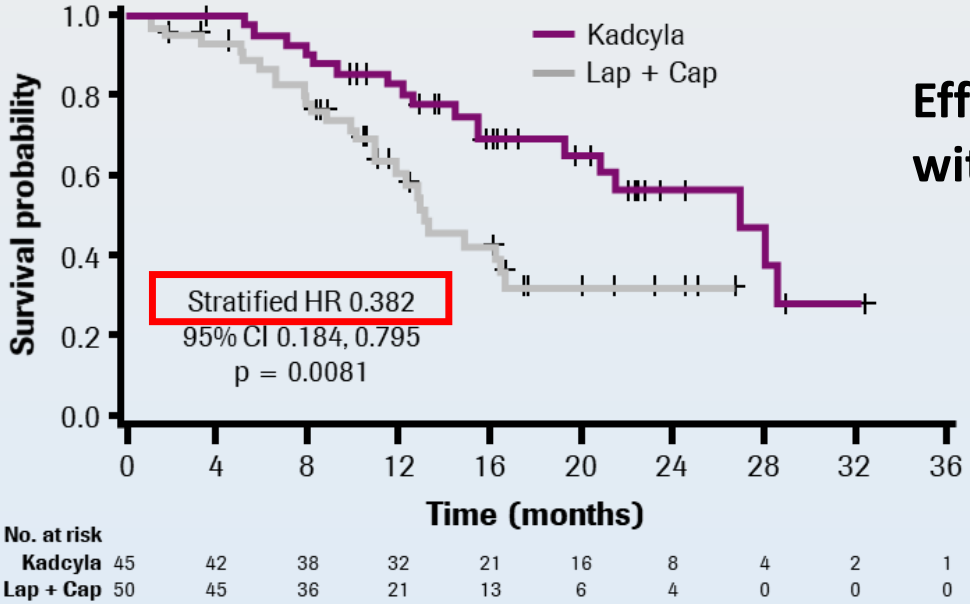
PFS L + C: 6.4m
T-DM1: 9.6m HR: 0.65

OS L + C: 25.1m
T-DM1: 30.9m HR:0.68





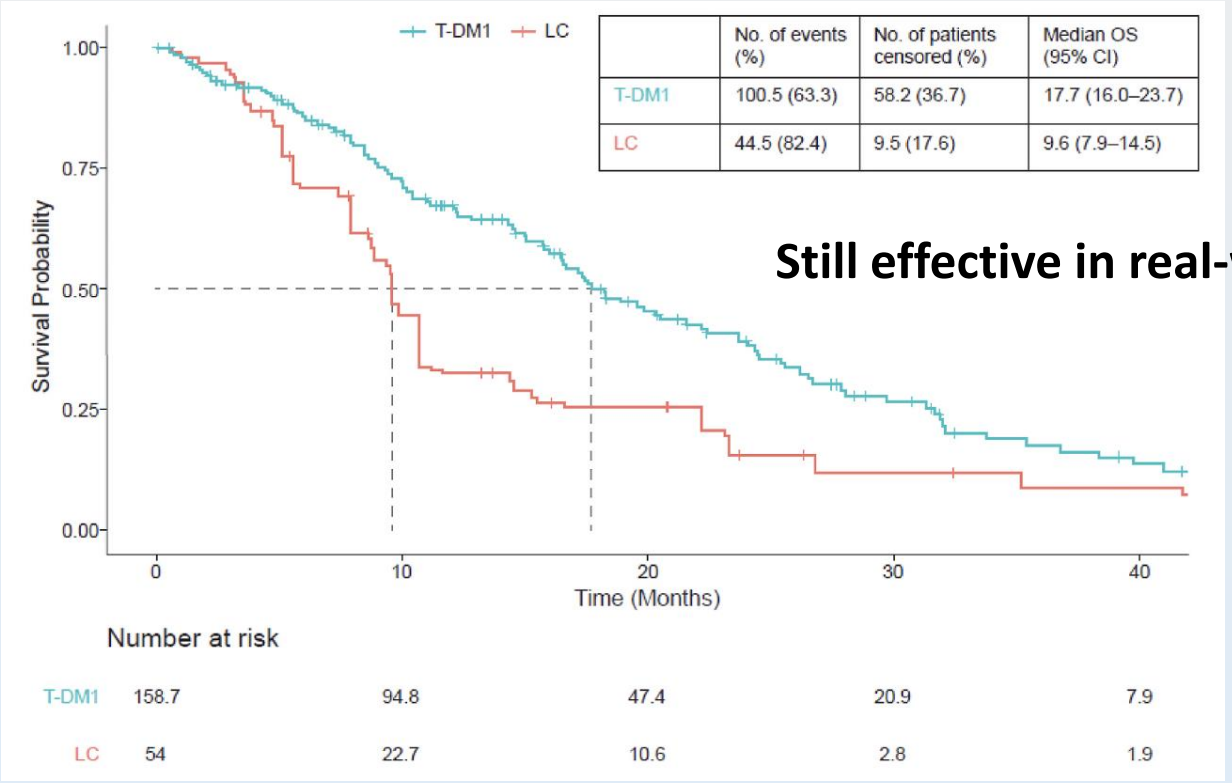
T-DM1 in patients with brain metastasis



Effective in patients with brain metastasis

* Patients with CNS metastases at baseline or who developed CNS metastases on study were identified retrospectively.
Cap, capecitabine; CI, confidence interval; CNS, central nervous system; HR, hazard ratio; Lap, lapatinib; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival.
1. Krop IE, *et al. Ann Oncol* 2015; **26**:113–119; 2. Montemurro F, *et al. Ann Oncol* 2020; **31:**1350–1358.

T-DM1 in patients with brain metastasis(RWE)



	No. of events (%)	No. of patients censored (%)	Median OS (95% CI)
T-DM1	100.5 (63.3)	58.2 (36.7)	17.7 (16.0–23.7)
LC	44.5 (82.4)	9.5 (17.6)	9.6 (7.9–14.5)

Still effective in real-world study

Thibaut Sanglier et al The Breast 69 (2023) 441–45

EMILIA trial - AE

	Kadcyla (n = 490)		Lap + Cap (n = 488)	
	Events of any grade	**Grade ≥3**	**Events of any grade**	**Grade ≥3**
Any event	470 (95.9)	200 (40.8)	477 (97.7)	278 (57.0)
Specific events				
Diarrhoea	114 (23.3)	8 (1.6)	**389 (79.7)**	101 (20.7)
PPE syndrome	6 (1.2)	0 (0)	**283 (58.0)**	80 (16.4)
Vomiting	93 (19.0)	4 (0.8)	143 (29.3)	22 (4.5)
Hypokalaemia	42 (8.6)	11 (2.2)	42 (8.6)	20 (4.1)
Neutropenia	29 (5.9)	10 (2.0)	42 (8.6)	21 (4.3)
Fatigue	172 (35.1)	12 (2.4)	136 (27.9)	17 (3.5)
Nausea	192 (39.2)	4 (0.8)	218 (44.7)	12 (2.5)
Anaemia	51 (10.4)	13 (2.7)	39 (8.0)	8 (1.6)
Mucosal inflammation	33 (6.7)	1 (0.2)	93 (19.1)	11 (2.3)
Elevated ALT	**83 (16.9)**	14 (2.9)	43 (8.8)	7 (1.4)
Elevated AST	**110 (22.4)**	21 (4.3)	46 (9.4)	4 (0.8)
Thrombocytopenia	**137 (28.0)**	63 (12.9)	12 (2.5)	1 (0.2)

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

Management AE

Thrombocytopenia

- For most patients, first occurrence of grade 3-4 thrombocytopenia reported during first **two cycles** of Kadcyla
- With dose modifications, the majority of patients continued treatment

Hepatotoxicity

- Hyperbilirubinemia (any grade) more frequent with lapatinib+capecitabine than with Kadcyla (8.2% vs.1.2%)
- With appropriate dose modifications, most patients with grade 3-4 serum ALT elevations continued treatment

Left ventricular ejection fraction

- LVEF of ≥45% maintained in the majority of patients
- Three patients in each group had a decrease from baseline to <40%

LVEF, left ventricular ejection fraction.
Verma S, *et al. N Engl J Med* 2012; **367**:1783–1791.

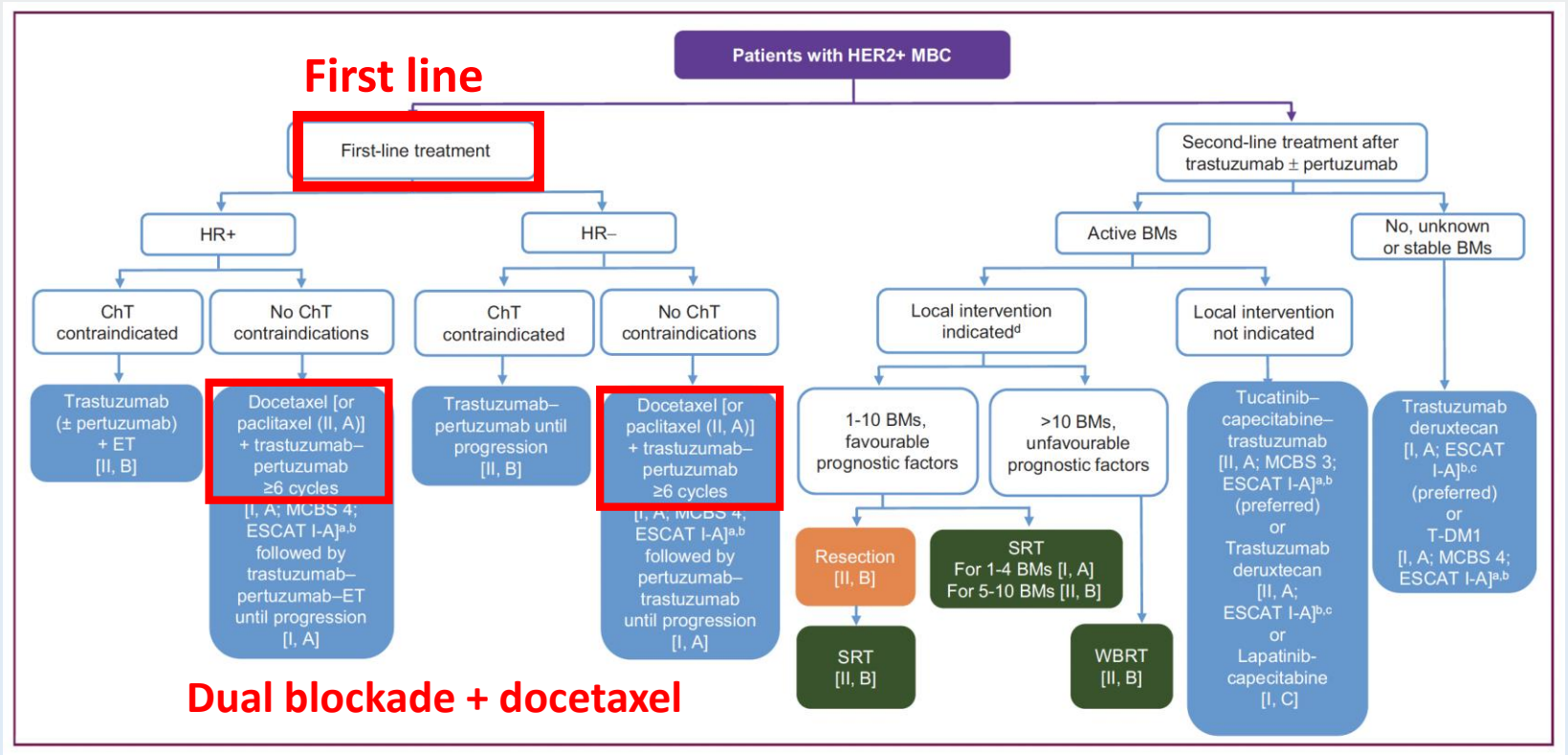
Management of AE

Dose Modifications for Patients with MBC		
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.

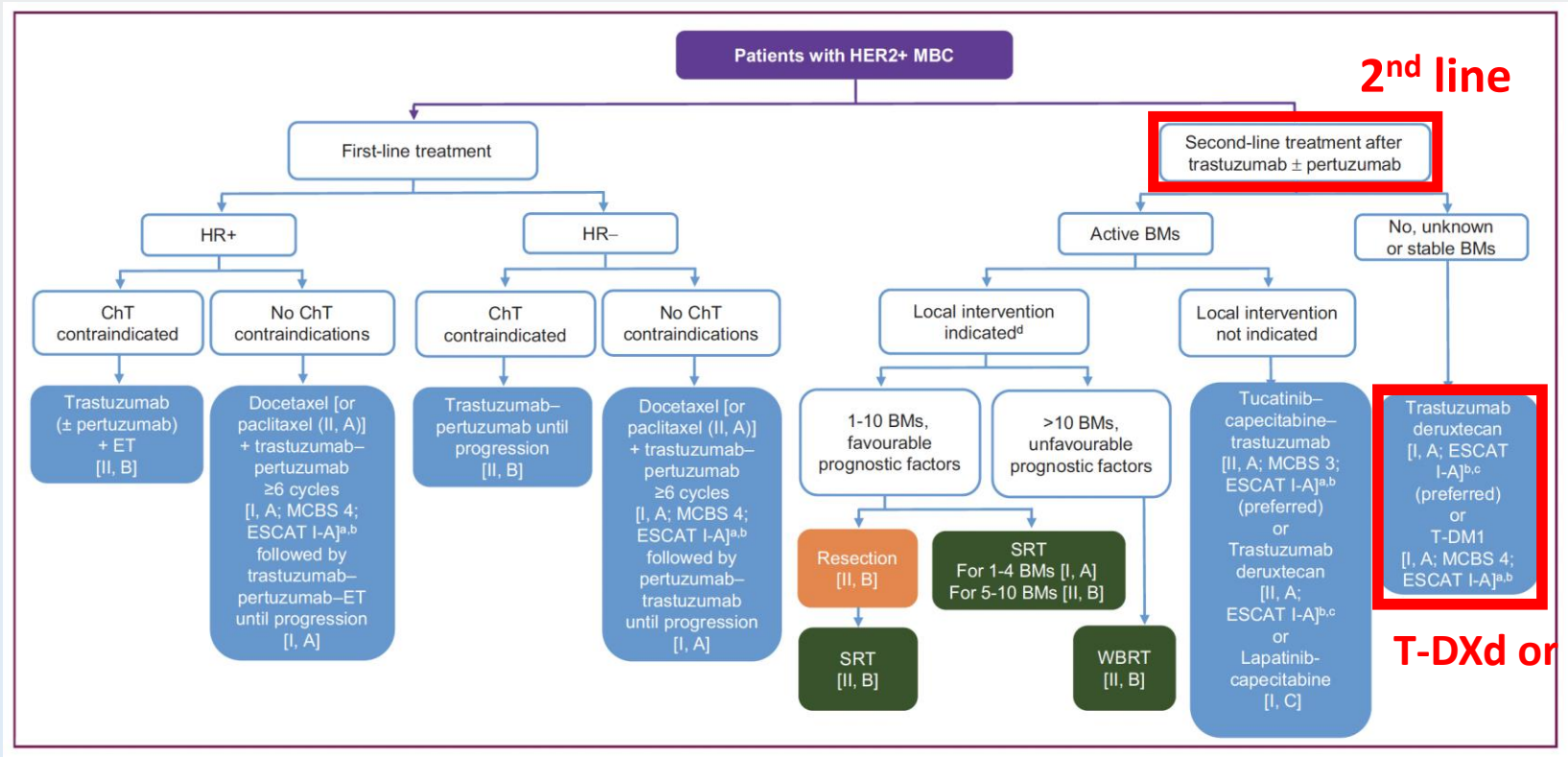
Contents

ADC, antibody–drug conjugate;; mBC, metastatic breast cancer;

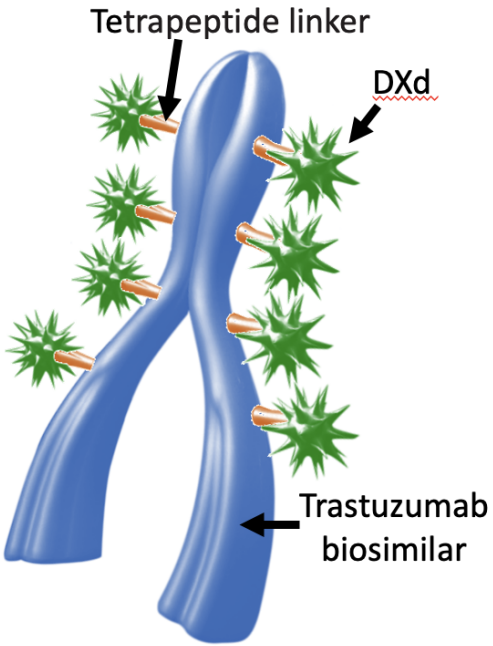
Pan-Asian adapted ESMO guideline for HER2+ MBC



Pan-Asian adapted ESMO guideline for HER2+ MBC



T-DXd: An ADC based on a trastuzumab biosimilar linked to a topoisomerase I inhibitor



* Irinotecan is a topoisomerase I inhibitor
Visual for illustration purposes only

T-DXd components

Humanised trastuzumab biosimilar[1–4]

- Trastuzumab biosimilar targets HER2-expressing tumours, in a similar manner to the trastuzumab antibody in Kadcyla

Stable tetrapeptide linker[1–4]

- Cleavable linker prevents premature release of DXd-conjugated cytotoxic agent

DXd (exatecan derivative) is a different class of cytotoxic agent (topoisomerase I inhibitor) from DM1 in Kadcyla[1–4]

- DXd causes DNA damage and apoptotic cell death[5]
- Membrane-permeable DXd can elicit a bystander effect in neighbouring cells, unlike the DM1 payload in Kadcyla[6]
- DXd is 10-fold more potent than irinotecan (a topoisomerase I inhibitor used to treat several solid tumours)[6,7,*]
- Drug–antibody ratio of ~8:1[1–3,8] is higher than Kadcyla (~3.5:1)[9,10]

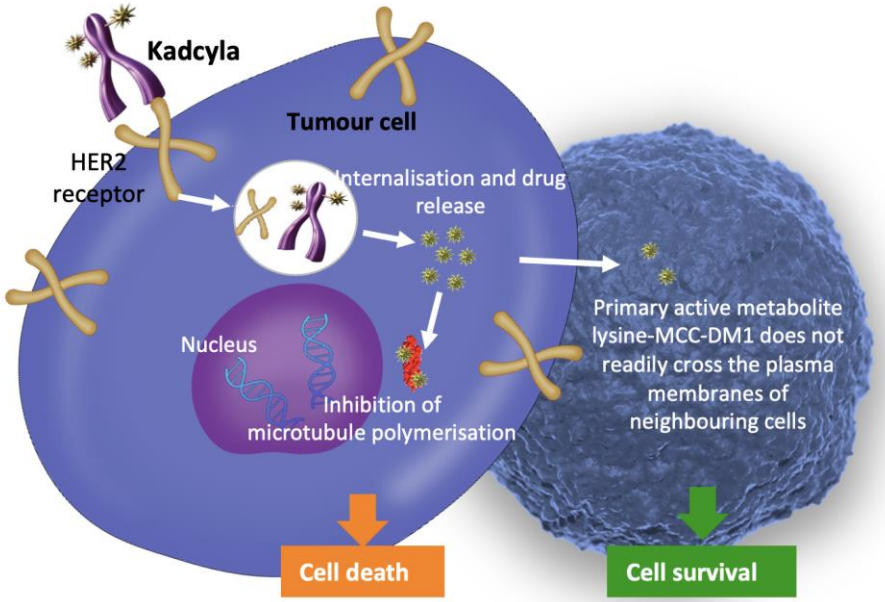
Pharmacological differences between Kadcyla and T-DXd may lead to distinct efficacy and safety profiles between Kadcyla and T-DXd

1. Enhertu PI 2021; 2. Enhertu SmPC 2021; 3. Modi S, et al. N Engl J Med 2020; 382:610–621 (incl. supplemental information); 4. Doi T, et al. Lancet Oncol 2017; 18:1512–1522; 5. Ogitani Y, et al. Clin Cancer Res 2016; 22:5097–5108; 6. Ogitani Y, et al. Cancer Sci 2016; 107:1039–1046; 7. Nakada T, et al. Chem Pharm Bull 2019; 67:173–185; 8. Cortés J, et al. ESMO 2021 (Abstract LBA1; presidential symposium); 9. Lewis Phillips GD, et al. Cancer Res 2008; 68:9280–9290; 10. Barok M, et al. Breast Cancer Res 2014; 16:209.

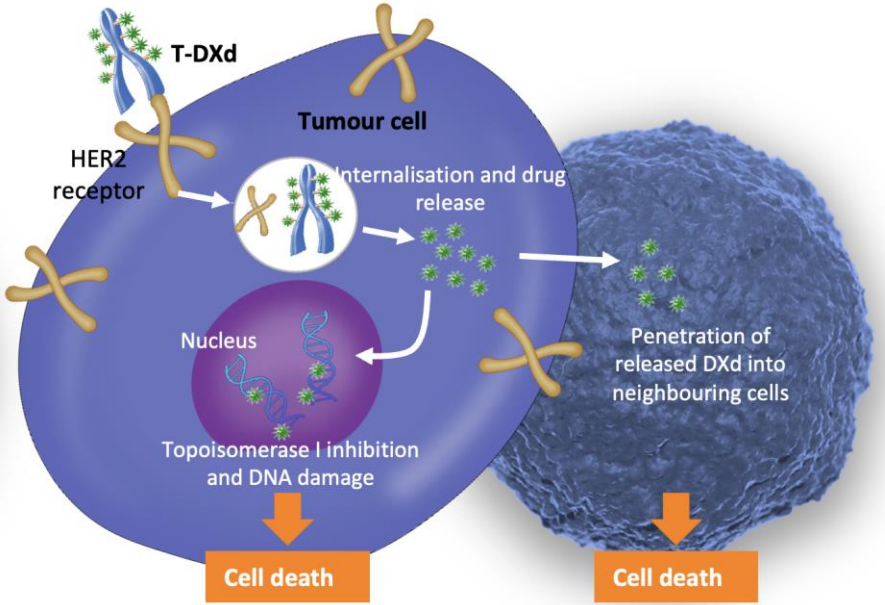
The cytotoxic payload from an ADC may target neighbouring cancer cells (bystander killing effect)

Roche

No bystander effect has been observed with Kadcyla[1–3]



T-DXd has a potent bystander effect due to a highly membrane-permeable cytotoxic agent[4,5]



The long-term impact of the T-DXd bystander killing effect remains to be determined

1. Lewis Phillips GD, et al. Cancer Res 2008; 68:9280–9290; 2. Kovtun YV, et al. Cancer Res 2006; 66:3214–3221; 3. LoRusso PM, et al. Clin Cancer Res 2011; 17:6437–6447; 4. Ogitani Y, et al. Cancer Sci 2016; 107:1039–1046; 5. Nakada T, et al. Chem Pharm Bull 2019; 67:173-185.

	T-DXd (Enhertu)	T-DM1 (Kadcyla)
Drug-antibody ratio (DAR)	**8:1**	3.5:1
Payload	Deruxtecan (topoisomerase I inhibitor)	Emtansine (anti-microtubule agent)
Membrane permeability	**High**	Low
Linker	**Cleavable**	Non-cleavable
Bystander killing effect	**Strong**	Minimal

Nakada. Chem Pharm Bull (Tokyo). 2019. Trail. Pharmacol Ther. 2018.
Ogitani. Cancer Sci. 2016.

Destiny Breast 03

DESTINY-Breast03: First Randomized Ph3 Study of T-DXd

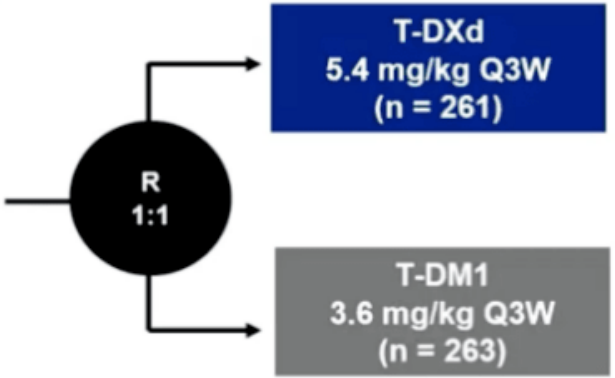
An open-label, multicenter study (NCT03529110)

Patients

- Unresectable or metastatic HER2-positive[a] breast cancer
- Previously treated with trastuzumab and taxane in advanced/metastatic setting[b]
- Could have clinically stable, treated brain metastases

Stratification factors

- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease



Primary endpoint

- PFS (BICR)

Key secondary endpoint

- OS

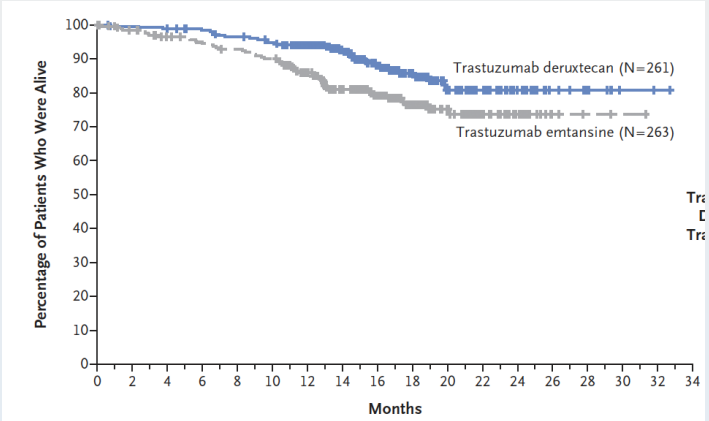
Secondary endpoints

- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

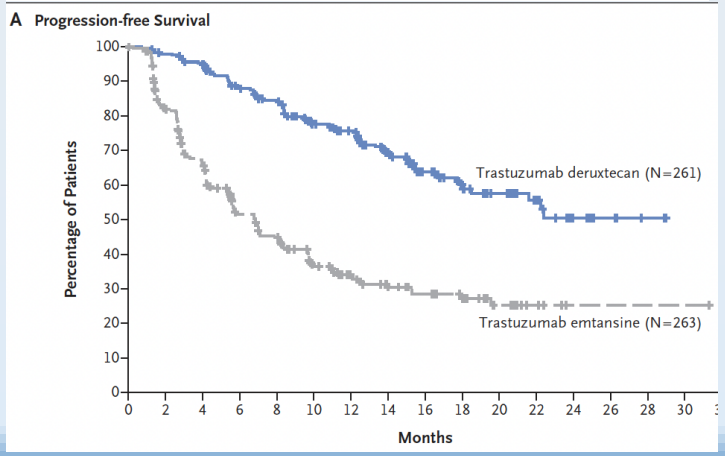
Javier Cortés, et al. N Engl J Med 2022

Destiny Breast 03

OS



PFS

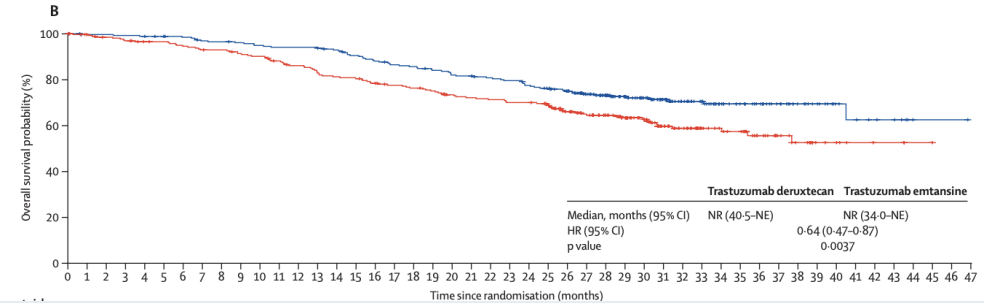


Follow-up 16.2 months (2022)		
	T-DXd	T-DM1
Median OS (mo)	**NR**	**NR**
HR (95% CI)	0.55 (0.36, 0.86)	
Median PFS(mo)	**NR**	**6.8**
HR (95% CI)	0.28 (0.22, 0.37)	

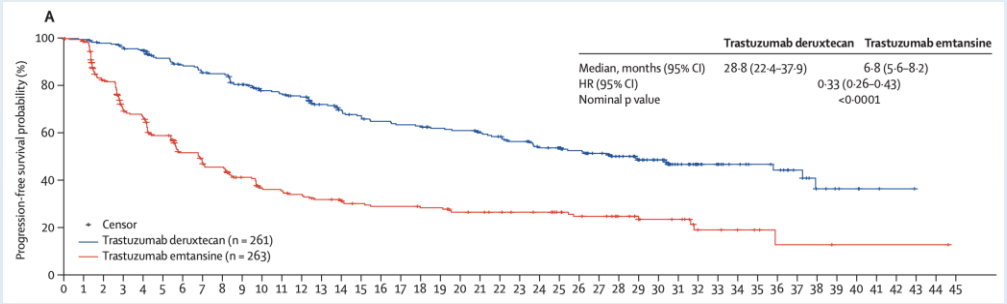
Javier Cortés, et al. N Engl J Med 2022

Destiny Breast 03

OS



PFS



2023 updated result		
	T-DXd	T-DM1
Median OS (mo)	**NR**	**NR**
HR (95% CI)	0.64 (0.47, 0.87)	
Median PFS(mo)	**28.8**	**6.8**
HR (95% CI)	0.33 (0.26, 0.43)	

Sara A Hurvitz et al. Lancet 2023

Destiny Breast 03

	16.2 months follow-up (2022)		28 months follow-up (2023)		43 months follow-up (2024)	
	T-DXd	T-DM1	T-DXd	T-DM1	T-DXd	T-DM1
Median OS (mo)	NR	NR	NR	NR	52.6	42.7
HR (95% CI)	**0.55** (0.36, 0.86)		**0.64** (0.47, 0.87)		**0.73** (0.56, 0.94)	
Median PFS(mo)	NR	6.8	28.8	6.8	29.0	7.2
HR (95% CI)	0.28 (0.22, 0.37)		0.33 (0.26, 0.43)		0.30 (0.24, 0.38)	

The benefit of overall survival persisted, but less significant

Javier Cortés, et al. N Engl J Med 2022; Sara A Hurvitz et al. Lancet 2023; Javier Cortés, et al. Nature Medicine 2024

DB 03 subsequent treatment

n (%)	T-DXd 5.4 mg/kg Q3W *n* = 261	T-DM1 3.6 mg/kg Q3W *n* = 263
Type of post-trial anticancer systemic treatment[c]		
Trastuzumab	57 (39.6)	103 (52.0)
T-DXd	12 (8.3)	64 (32.3)
T-DM1	75 (52.1)	26 (13.1)
Pertuzumab	17 (11.8)	31 (15.7)
Taxane	22 (15.3)	38 (19.2)
Taxane and trastuzumab	12 (8.3)	33 (16.7)
Other HER2-directed therapy	57 (39.6)	102 (51.5)
HER2-directed TKI	52 (36.1)	95 (48.0)
Other HER2-directed antibody or ADC	13 (9.0)	23 (11.6)
Hormone therapy	29 (20.1)	41 (20.7)
Other systemic therapy	100 (69.4)	158 (79.8)

Only 32.3% cross-over

AE in Destiny Breast 03

	Trastuzumab deruxtecan group (n=257)		Trastuzumab emtansine group (n=261)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Blood and lymphatic system disorders				
Anaemia	95 (37%)	24 (9%)	51 (20%)	17 (7%)
Platelet count decreased*	64 (25%)	20 (8%)	114 (44%)	52 (20%)
White blood cell count decreased	60 (23%)	16 (6%)	16 (6%)	2 (<1%)
Gastrointestinal disorders				
Nausea	198 (77%)	18 (7%)	79 (30%)	1 (<1%)
Vomiting	133 (52%)	4 (2%)	28 (11%)	2 (<1%)
Constipation	96 (37%)	0	51 (20%)	0
Diarrhoea	83 (32%)	3 (1%)	21 (8%)	2 (<1%)
General disorders				
Fatigue	79 (31%)	15 (6%)	53 (20%)	2 (<1%)
Headache	61 (24%)	1 (<1%)	40 (15%)	0

T-DXd	T-DM1
More WBC decreased	More PLT decreased
More N/V	

Sara A Hurvitz et al. Lancet 2023

AE in Destiny Breast 03

T-DXd	T-DM1
More WBC decreased	More PLT decreased
More G3/4 neutropenia	
More N/V, **decreased appetite**	More **liver function** abnormality
More **Alopecia**	

	Trastuzumab deruxtecan group (n=257)		Trastuzumab emtansine group (n=261)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Investigations				
Neutrophil count decreased†	79 (31%)	41 (16%)	30 (11%)	8 (3%)
Aspartate aminotransferase increased	72 (28%)	2 (<1%)	108 (41%)	14 (5%)
Alanine aminotransferase increased	59 (23%)	4 (2%)	83 (32%)	12 (5%)
Metabolism and nutrition disorders				
Decreased appetite	78 (30%)	4 (2%)	46 (18%)	1 (<1%)
Bodyweight decreased	58 (23%)	6 (2%)	23 (9%)	2 (<1%)
Skin and subcutaneous disorders				
Alopecia	102 (40%)	1 (<1%)‡	9 (3%)	0

Sara A Hurvitz et al. Lancet 2023

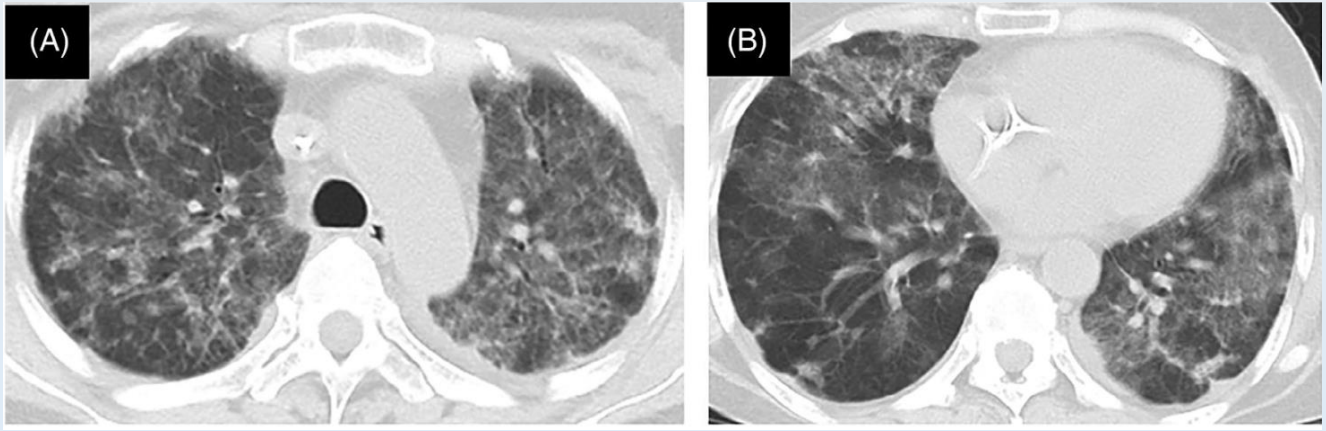
DB 03 ILD 2024 updated

n (%)	T-DXd, 5.4 mg/kg Q3W, *n*=257	T-DM1, 3.6 mg/kg Q3W, *n*=261
Any grade	43 (16.7)	9 (3.4)
Grade 1	11 (4.3)	5 (1.9)
Grade 2	30 (11.7)	3 (1.1)
Grade 3	2 (0.8)	1 (0.4)
Grade 4	0	0
Grade 5	0	0
Grade ≥3	2 (0.8)	1 (0.4)

Interstitial lung disease(ILD) in DB 03

	T-DXd	T-DM1
Incidence (%)	16.7	3.4
Time to ILD (mo)	8.1	11.7

A 57 y/o woman received 4 cycles of T-DXd…



Sara A Hurvitz et al. Lancet 2023; Javier Cortés, et al. Nature Medicine 2024
Kyoko Gocho et al. Respirology Case Reports 2022

AE in Destiny Breast 03

More TEAE with T-DXd

n (%)	T-DXd, 5.4 mg/kg Q3W, *n*=257	T-DM1, 3.6 mg/kg Q3W, *n*=261
Any-grade TEAEs	256 (99.6)	249 (95.4)
Drug-related	252 (98.1)	228 (87.4)
Grade ≥3 TEAEs	149 (58.0)	136 (52.1)
Drug-related	125 (48.6)	111 (42.5)
Serious TEAEs	71 (27.6)	59 (22.6)
Drug-related	35 (13.6)	20 (7.7)

Javier Cortés, et al. Nature Medicine 2024

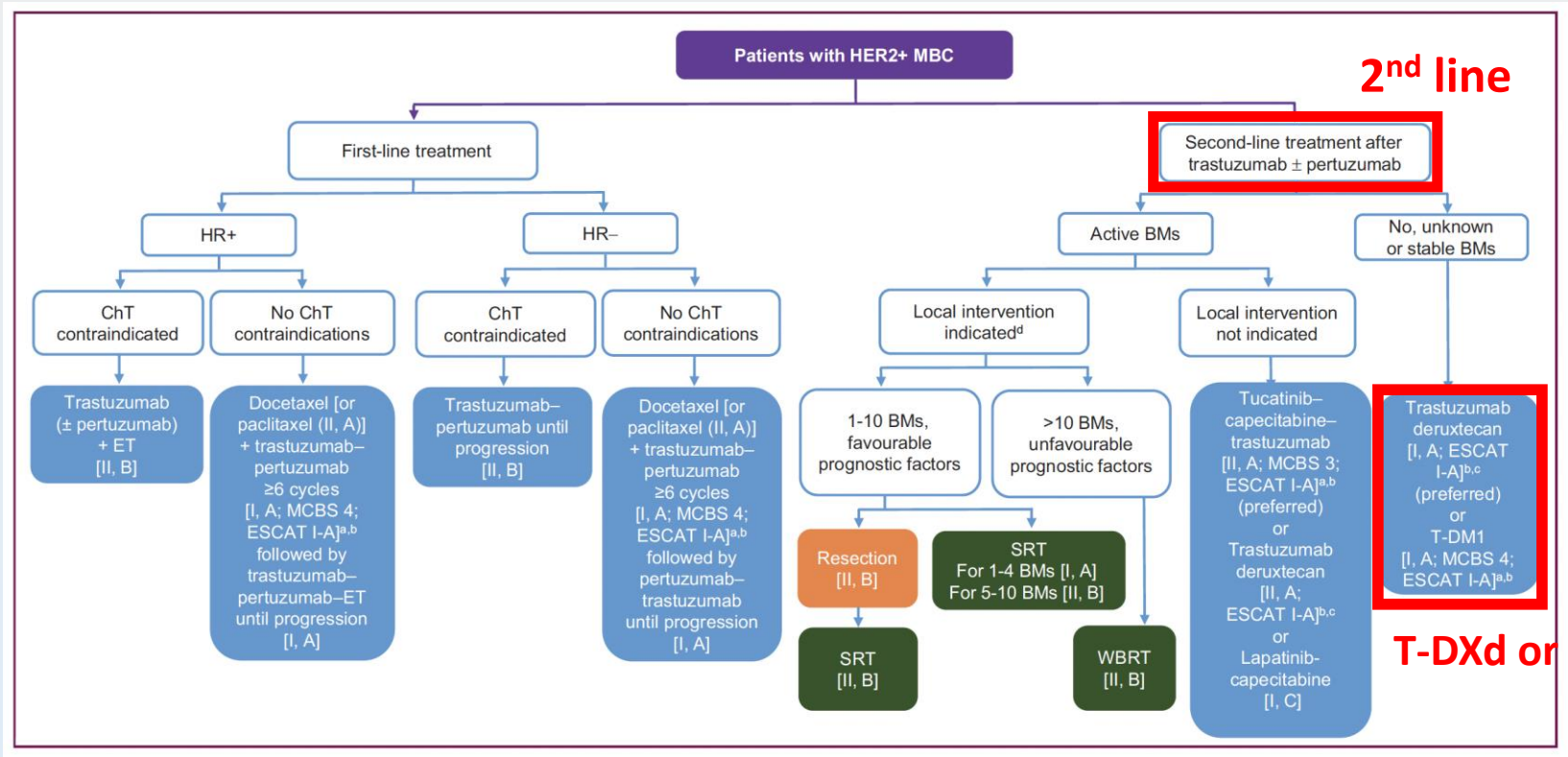
AE in Destiny Breast 03

More drug interruption with T-DXd

n (%)	T-DXd, 5.4 mg/kg Q3W, *n*=257	T-DM1, 3.6 mg/kg Q3W, *n*=261
TEAEs leading to dose reduction	73 (28.4)	40 (15.3)
Drug-related	72 (28.0)	40 (15.3)
TEAEs leading to drug interruption	146 (56.8)	78 (29.9)
Drug-related	113 (44.0)	48 (18.4)
TEAEs associated with death	9 (3.5)	7 (2.7)
Drug-related	0	0

Javier Cortés, et al. Nature Medicine 2024

Pan-Asian adapted ESMO guideline for HER2+ MBC



Guidelines are starting to recommend T-DXd (if available); while T-DM1 remains as a valid option in the 2L setting

	T-DM1	T-DXd
NCCN	2L option if not a candidate for T-DXd; 3L+ option	Preferred 2L option†
ESMO	2L option in cases where T-DXd is unavailable; 3L option for pts who have not received Kadcyla in 2L	Preferred 2L option; may also be used in the 3L+ setting
ASCO	3L+ for pts who have not received Kadcyla in 2L	Preferred regimen in 2L; may also be used in the 3L+ setting

† T-DXd may be considered in 1L for patients who relapse within 6 months of neo/adjuvant therapy (or 12 months for PERJETA-containing regimens).

1L, first-line; 2L, second-line; 3L, third-line; BMs, brain metastases, mBC, metastatic breast cancer; SoC, standard of care; pts, patients.

1. NCCN Breast Cancer Guidelines. Version 4, 202[illegible]; 2. Gennari A, *et al. Ann Oncol* 2021; **32:**1475–1495; 3. AGO BC Guidelines 2023; 4. Giordano S, *et al. J Clin Oncol* 2022

T-DXd is still effective in 3rd line

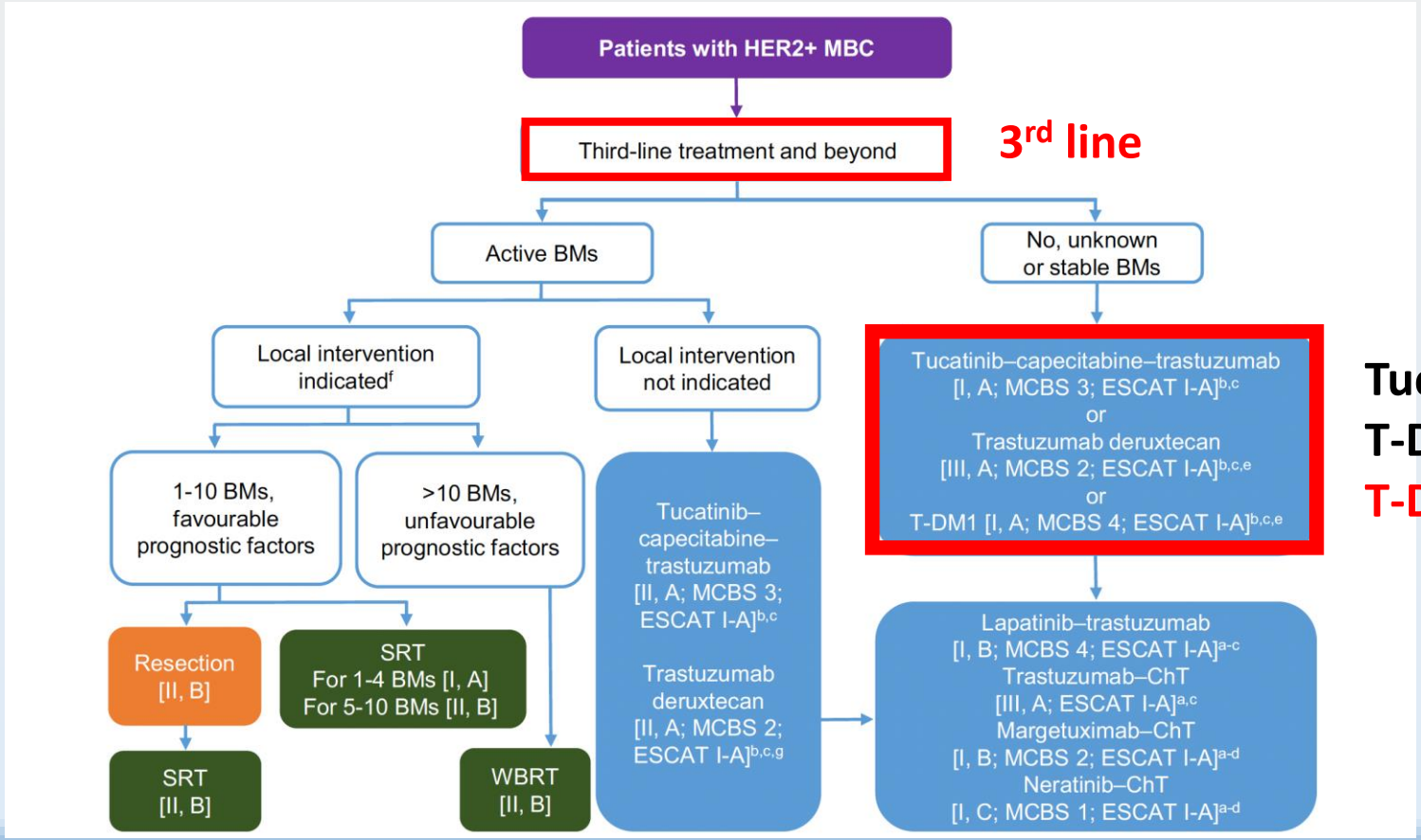
	DB03 (2-3 line)		DB02 (3-4 line)	
	T-DXd arm	**T-DM1 arm**	**T-DXd arm**	**TPC arm**
Prior line of Tx	1 prior line: 41.4% 2 prior line: 23.0%	1 prior line: 38.8% 2 prior line:24.3%	2 prior line: 47% 3 prior line: 30%	2 prior line: 46% 3 prior line: 31%
ORR	**78.9%**	**36.9%**	**70%**	**29%**
CR	12.6%	4.2%	14%	5%
PR	66.3%	32.7%	56%	24%
Median PFS	**29.0 m**	**7.2 m**	**17.8 m**	**6.9 m**
HR	**0.30**		**0.35**	
Median OS	**52.6m**	**42.7m**	**39.2 m**	**26.5 m**
HR	**0.73**		**0.65**	

Javier Cortés, et al. Nature Medicine 2024 Fabrice André et al. Lancet Oncology 2023

Contents

ADC, antibody–drug conjugate;; mBC, metastatic breast cancer;

Pan-Asian adapted ESMO guideline for HER2+ MBC



Tucatinib
T-DXd
T-DM1

NCCN guideline for HER2+ MBC

If tucatinib is not available, consider T-DM1

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2024
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

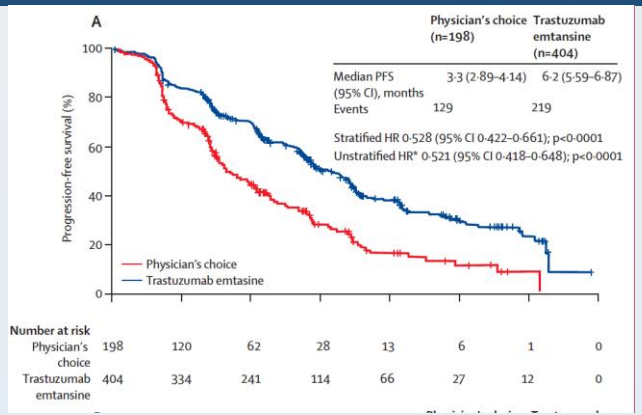
SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[k]

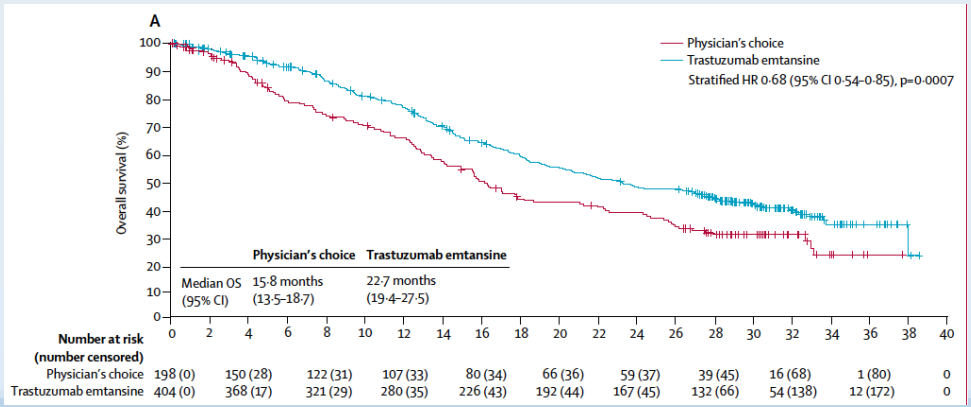
HR-Positive or -Negative and HER2-Positive[j,k]	
Setting	**Regimen**
First Line[l]	Pertuzumab + trastuzumab + docetaxel (Category 1, preferred)
	Pertuzumab + trastuzumab + paclitaxel (preferred)
Second Line[n]	Fam-trastuzumab deruxtecan-nxki[m] (Category 1, preferred)
Third Line	Tucatinib + trastuzumab + capecitabine[n] (Category 1, preferred)
	Ado-trastuzumab emtansine (T-DM1)[o]
Fourth Line and Beyond (optimal sequence is not known)[p]	Trastuzumab + docetaxel or vinorelbine
	Trastuzumab + paclitaxel ± carboplatin
	Capecitabine + trastuzumab or lapatinib
	Trastuzumab + lapatinib (without cytotoxic therapy)
	Trastuzumab + other chemotherapy agents[q,r]
	Neratinib + capecitabine
	Margetuximab-cmkb + chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine)
	Targeted Therapy Options BINV-Q (6)

TH3RESA
T-DM1 has shown PFS and OS benefit vs. TPC in 2L+ patients

All patients had received prior treatment with trastuzumab, lapatinib and a taxane

	T-DM1	TPC
ORR (%)	31	9
PFS (m)	6.2	3.3
	HR:0.528(0.422, 0.661) p<0.0001	
OS (m)	22.7	15.8
	HR:0.68(0.54, 0.85) p<0.0007	

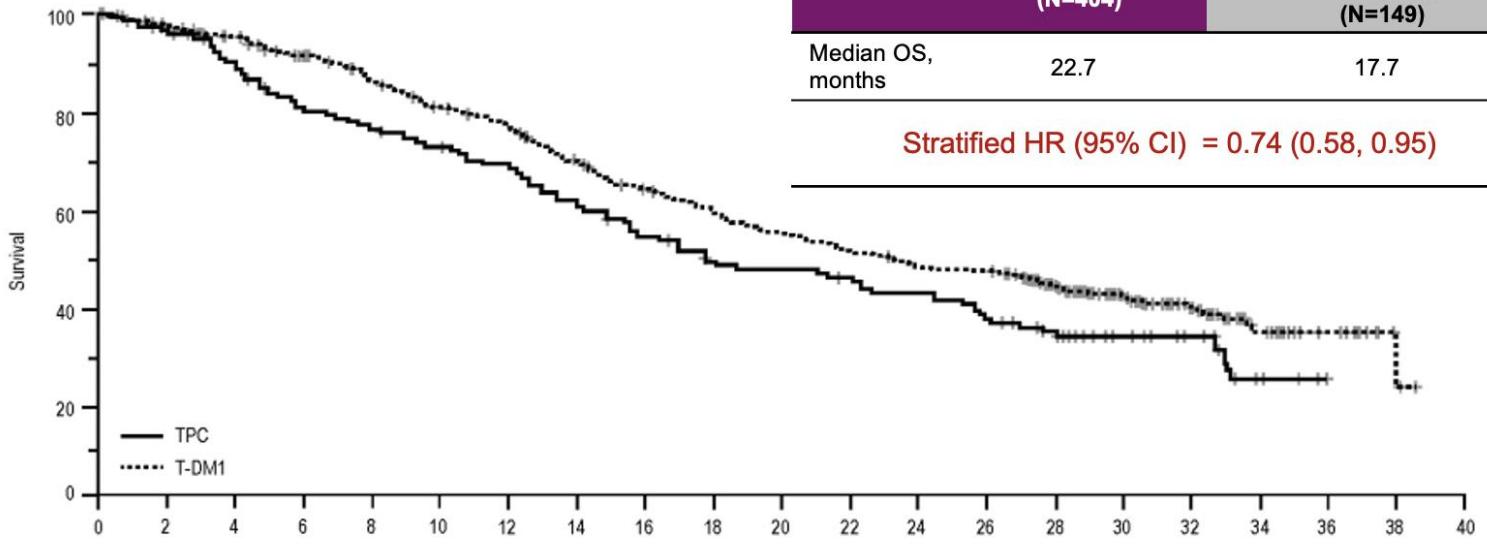




T-DM1 provide longer OS than other trastuzumab-based Tx

	Kadcyla (N=404)	TPC with a trastuzumab-containing regimen (N=149)
Median OS, months	22.7	17.7

Stratified HR (95% CI) = 0.74 (0.58, 0.95)



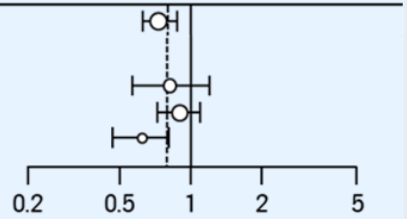
Number at risk (censored)											
TPC	149 (0)	125 (10)	104 (12)	92 (14)	71 (15)	60 (17)	53 (18)	34 (26)	15 (45)	0	0
T-DM1	404 (0)	368 (17)	321 (29)	280 (35)	226 (43)	192 (44)	167 (45)	132 (66)	54 (138)	12 (172)	0

Clinical data cut-off: 13 February 2015. 1. Krop IE, *et al.* Lancet Oncol 2014;**15:**689–699. 2. Krop IE, *et al. Lancet Oncol* 2017;**18:**743–754.

T-DM1 provide longer OS in later line MBC

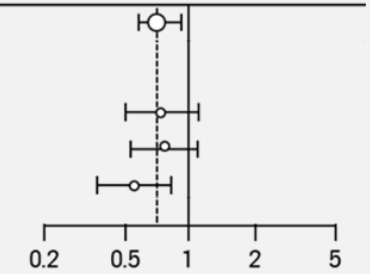
EMILIA: Final OS Subgroup Analysis[1]

Baseline characteristic	Total (n)	Lap+Cap (n = 496) Median (mo)	T-DM1 (n = 495) Median (mo)	Unstratified HR (95% CI)
All patients	991	25.9	29.9	0.77 (0.66, 0.90)
Line of therapy				
1st line	159	23.7	26.3	0.79 (0.54, 1.17)
2nd line	565	28.6	30.8	0.86 (0.70, 1.07)
3rd line	267	20.1	31.6	0.59 (0.44, 0.80)



TH3RESA: OS Subgroup Analysis[1,2]

Baseline characteristic	Total (n)	TPC (n = 198) Median (mo)	T-DM1 (n = 404) Median (mo)	Unstratified HR (95% CI)
All patients	602	15.8	22.7	0.69 (0.55, 0.86)
Number of prior regimens in advanced setting (excluding hormonal therapy)				
≤3	200	17.0	24.0	0.73 (0.49, 1.09)
4–5	217	16.1	20.3	0.75 (0.52, 1.09)
>5	185	13.3	21.7	0.54 (0.36, 0.81)



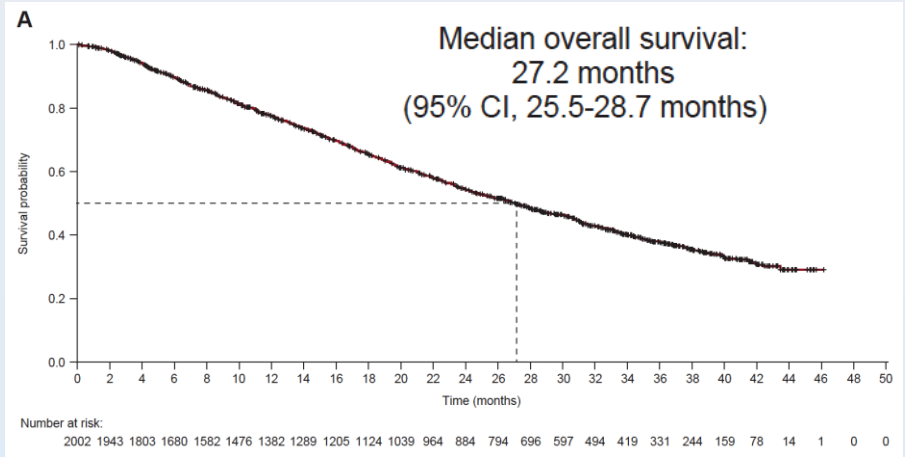
CI, confidence interval; HR, hazard ratio; OS, overall survival; TPC, treatment of physician's choice.

1. Roche, Data on file; 2. Wildiers H, *et al*. SABCS 2015 (Abstract S5-05; oral presentation).

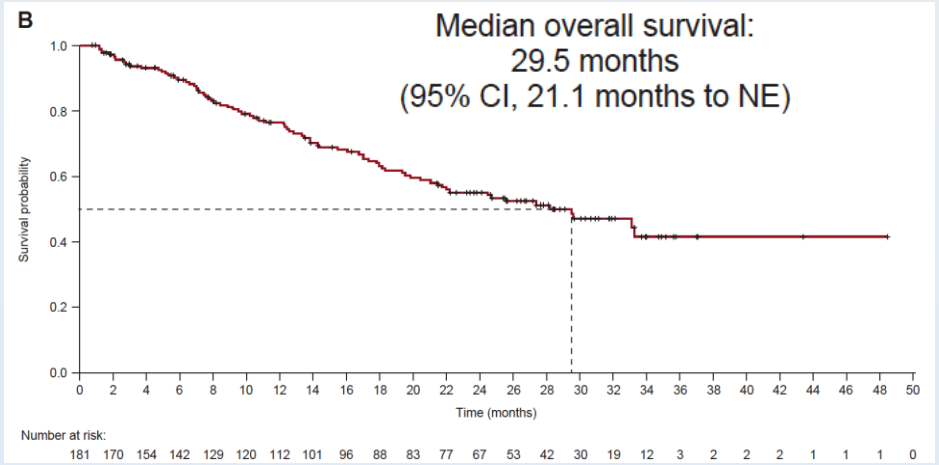
KAMILLA: Efficacy results for the largest cohort of T-DM1-treated participants to date were consistent with prior randomised studies

- 2002 patients(cohort 1, Global) and 181 patients(cohort 2, Asian) with HER2-positive breast cancer were treated with T-DM1 in a single-arm, open-label, international, Phase IIIb study. The majority of patients received ≥2 prior metastatic treatment lines

Cohort 1, Global N=2002



Cohort 2, Asian N=181



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ADC, antibody–drug conjugate;; mBC, metastatic breast cancer;

Summary

- Kadcyla (T-DM1) is one of the effective 2L treatments for HER2-positive MBC patients including those with brain metastases
- For patients who have progressive disease after T-DXd, Kadcyla is also a valid 3L option
- Kadcyla is well tolerated with a favorable toxicity profile
- Adverse effects may be considered when determining the treatment sequence for HER2+ metastatic breast cancer (MBC) in the real-world setting

Thank you!

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