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Recent advances in the management of HER2 positive metastatic breast cancer

Outline of the Presentation

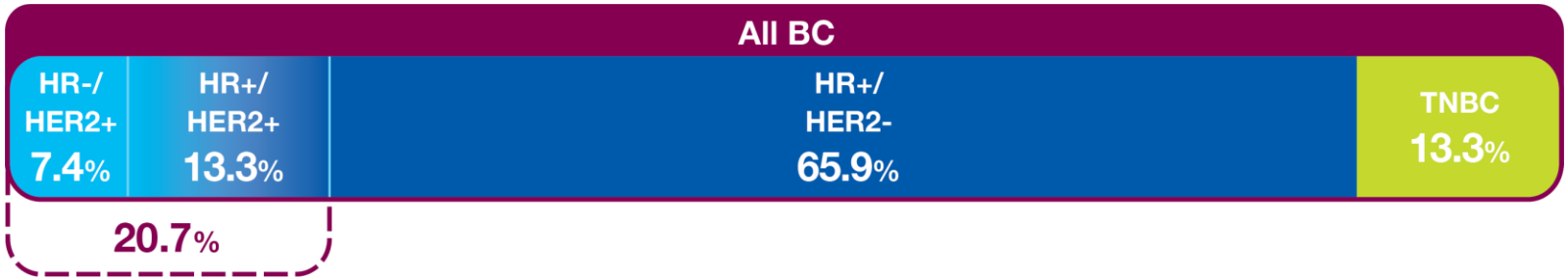
1. Introduction: HER2 Positive mBC
2. Current Treatment algorithm for HER2 Positive mBC
3. Unmet Need for 2L+ HER2 Positive mBC
4. Recent advances in the HER2 positive mBC
   Trastuzumab deruxtecan, Neratinib, Tucatinib, Margetuximab
5. Guideline Recommendations
6. Future considerations: HER 2 Low mBC
7. Take home messages

Introduction: HER2 Positive mBC

HER2 Positive BC Is an Aggressive Disease

- BC is the most frequently diagnosed cancer and the leading cause of cancer-related deaths among women worldwide[1]
- **Approximately 30% of all BC cases will become metastatic** after diagnosis, and most BC deaths are due to metastatic disease[2-4]
- HER2 positive BC cells are associated with aggressive disease that is more likely to metastasize[5,6]
- **15% to 20% of invasive BC cases are HER2 positive** (defined by high expression of protein (IHC 3+ or IHC 2+) with HER2 gene amplification on ISH)[7,8]

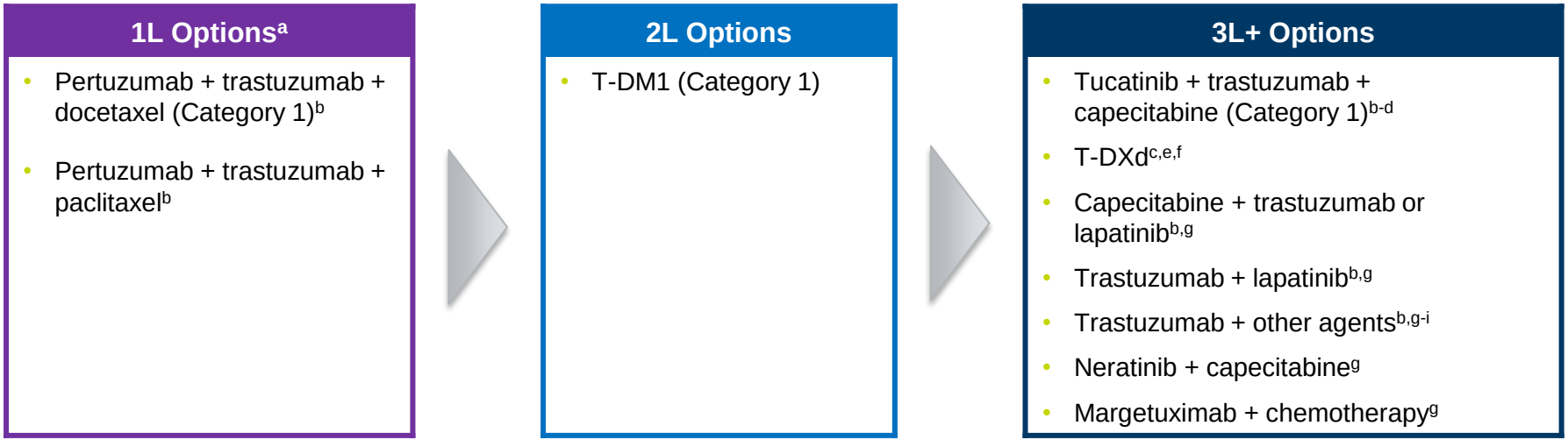
BC Subtypes[9]



1. Bray F, et al. *CA Cancer J Clin.* 2018;68(6):394-424. **2.** Schunkert EM, et al. *Biomed Hub.* 2018;(3):49292. **3.** Breastcancer.org. www.breastcancer.org/symptoms/types/recur_metast. Accessed July 16, 2021. **4.** Cancer.net. www.cancer.net/cancer-types/breast-cancer-metastatic/statistics. Accessed July 16, 2021. **5.** Inwald EC, et al. *Breast Cancer Res Treat.* 2015;153(3):647-658. **6.** American Cancer Society website. Breast cancer HER2 status. https://www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-her2-status.html. Accessed July 16, 2021. **7.** Wolff AC, et al. *J Clin Oncol.* 2013;31(31):3997-4013. **8.** Wolff AC, et al. *J Clin Oncol.* 2018;36(20):2105-2122. **9.** Brouckaert O, et al. *Breast Cancer Res.* 2017;19(1):119.

Current Treatment algorithm for HER2 Positive mBC

Current Treatment Options for HER2 Positive mBC



Cross-trial comparisons are complicated by variations in study designs and patient populations.
Note: All recommendations are category 2A unless otherwise indicated.
[a]Maintenance trastuzumab/pertuzumab after response with concurrent endocrine therapy if ER+, HER2+ mBC. [b]An FDA-approved biosimilar is an appropriate substitute for trastuzumab. [c]May be used as a 3L or 4L option; the optimal sequence for 3L+ therapy is not known. [d]Tucatinib + trastuzumab + capecitabine is preferred in patients with both systemic and CNS progression on T-DM1. However, tucatinib + trastuzumab + capecitabine may be given in the 2L setting. [e]T-DXd is preferred in patients with visceral metastases if progression on T-DM1. [f]T-DXd is contraindicated for patients with pneumonitis or ILD. [g]Multiple lines of chemotherapy + trastuzumab or an anti-HER2 TKI offer clinical benefit for recurrent unresectable HER2+ mBC and have been studied in phase 2 or 3 trials. Clinical experience suggests frequent clinical benefit. However, there are no meaningful data for any of these regimens among patients previously treated with pertuzumab-based chemotherapy, T-DM1, T-DXd, or tucatinib + trastuzumab + capecitabine regimens. Thus, the optimal sequence or true benefit of therapy is not known. [h]Trastuzumab + an anthracycline is associated with significant cardiac toxicity. Concurrent trastuzumab and pertuzumab with an anthracycline should be avoided. [i]Trastuzumab may be safely combined with all non-anthracycline containing preferred and other recommended single agents for mBC, including docetaxel, vinorelbine, or paclitaxel ± carboplatin.

Key Data Supporting Preferred Therapies Up to 3L Treatment[1,a]

	1L Therapy	2L Therapy
Study Name	**CLEOPATRA (n = 808)[2,3]**	**EMILIA (n = 991)[4]**
Drug	**THP**	**T-DM1**
Comparator	TH	Lapatinib + capecitabine
Prior therapies **Trastuzumab** **Pertuzumab** **T-DM1**	12% vs 10% – –	84% metastatic; 16% early – –
ORR (CR)	**80% (6% CR)** vs 69% (4% CR)	**44% (1% CR)** vs 31% (0.5% CR)
mPFS	**18.5 mo** vs 12.4 mo (HR, 0.62; [95% CI, 0.51-0.75]; *P* < 0.001)	**9.6 mo** vs 6.4 mo (HR, 0.65; [95% CI, 0.55-0.77]; *P* < 0.001)
mOS	**56.5 mo** vs 40.8 mo (HR, 0.68; [95% CI, 0.56-0.84] *P* < 0.001)	**30.9 mo** vs 25.1 mo (HR, 0.68; [95% CI, 0.55-0.85]; *P* < 0.001)
Common TRAEs (≥20%)	Diarrhea, alopecia, neutropenia, nausea, fatigue, rash, decreased appetite, mucosal inflammation, asthenia, peripheral edema	Diarrhea, fatigue, nausea, elevated AST, thrombocytopenia
Grade ≥3 AEs	2% higher in THP vs TH	16% higher in comparator group

Tables represent an overview of data from the respective studies. Cross-trial comparisons are complicated by variations in study designs and patient populations

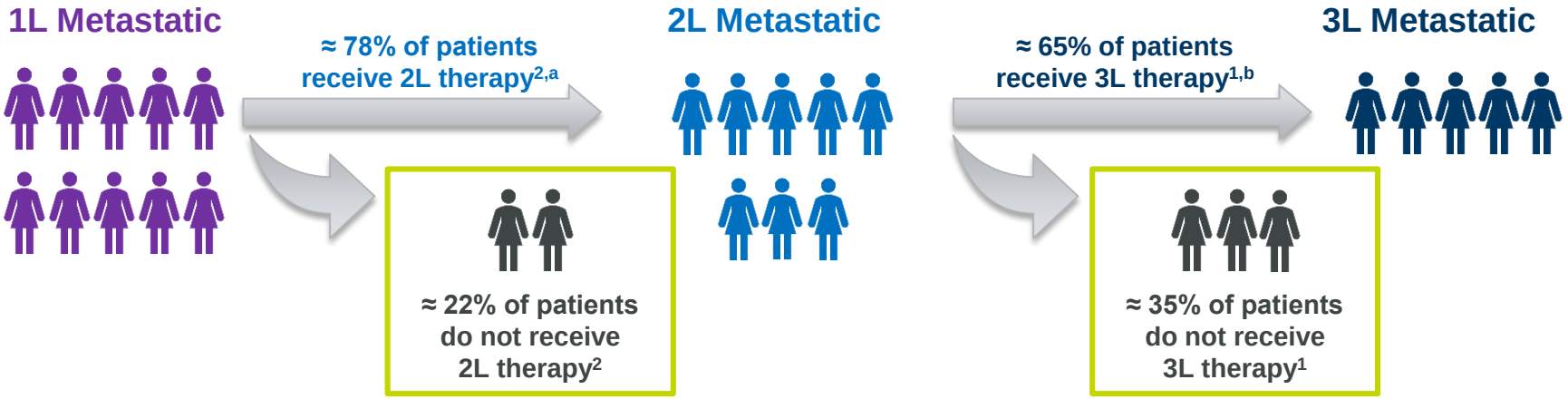
[a]T-DXd is preferred in patients with visceral metastases after progression on T-DM1. [b]Data cutoff: March 26, 2021 with a median follow-up of 26.5 months (range, 0.7-39.1 months).

 2. Baselga J, et al. *N Engl J Med*. 2012;366(2):109-119. **3.** Swain SM, et al. *N Engl J Med.* 2015;372(8):724-734. **4.** Verma S, et al. *N Engl J Med*. 2012;367(19):1783-1791. **5.** Modi S, et al. *N Engl J Med*. 2020;382(7): 610-621. **6.** Modi S, et al. SABCS 2020. Poster PD3-06. **7**. Saura C, et al. ESMO 2021. Poster 279P.

Unmet Need for HER2 Positive mBC

As HER2 Targeted Options Continue to Expand, Physicians Will Weigh Many Factors When Sequencing Treatment

More than one-third of patients will not receive subsequent therapy after 2L treatment and may miss an opportunity to receive a highly effective HER2 targeted agent if it is not prioritized for early use[1]

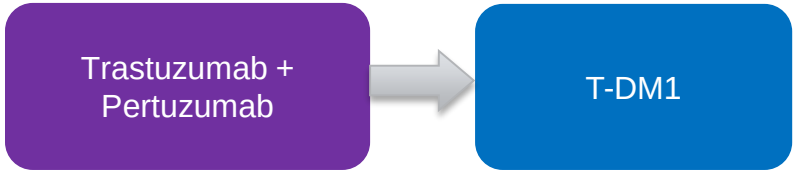


Sequencing decisions depend on previously administered therapies, progression-free intervals, sites of progression, tumor burden, patient preference, and quality of life[3]

[a]Percentage calculated from the total number of patients across both the THP and TH treatment groups in CLEOPATRA. [b]Percentage was calculated by subtracting the percentage of patients who did not go onto 3L therapy from 100.

1. Collins J, et al. SABCS 2020. Abstract PS7-82. **2.** Swain SM, et al. *N Engl J Med.* 2015;372(8):724-734. **3.** Martínez-Sáez O, Prat A. *JCO Oncol Pract.* Epub ahead of print. June 2, 2021.

Evidence Suggests that PFS Outcomes for 2L T-DM1 Are Worse in Patients Who Received Prior Pertuzumab[1-5]



Two large real-world Italian studies evaluated 2L T-DM1 from pertuzumab-exposed vs -naïve populations and reported:

- Significantly worse mPFS outcomes
- Conflicting mOS results, with 1 study reporting a worse OS (12 vs 26 mo) and the other with a similar OS (NR vs 34 mo)[1,2]

mPFS for 2L T-DM1 Therapy

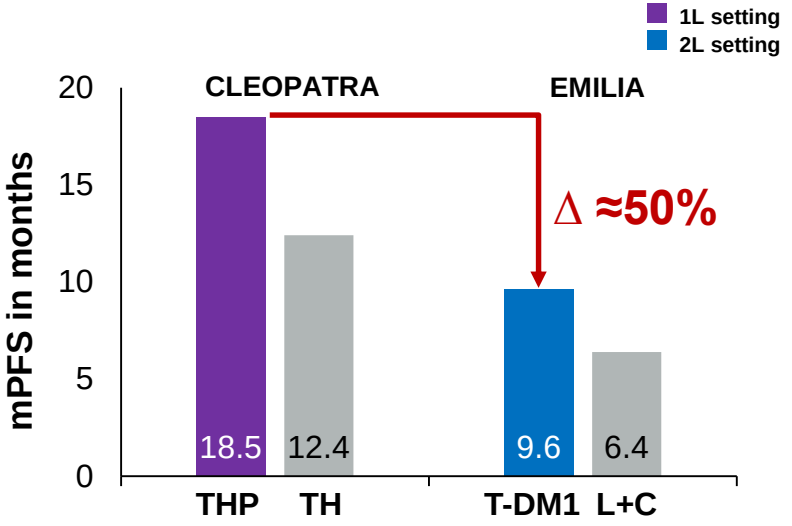
	Pertuzumab exposed (1L THP)	Pertuzumab naïve	*P* value
Italian RWE 1[1] (n = 250)	3.0 mo	8.0 mo	0.0001
Italian RWE 2[2] (SePHER; n = 371)	6.0 mo	10.0 mo	0.03
Other RWE[3,4,a]	6.3 - 7.7 mo	NE	–
RCT: EMILIA[5] (n = 991)	–	9.6 mo	–

[a]Regions of "other RWE" studies include Italy (n=82)[3] and Germany (n=39)[4]

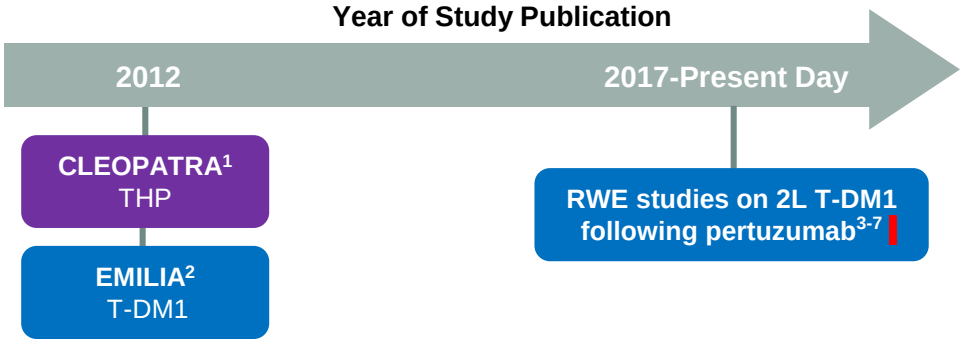
1. Vici P, et al. *Oncotarget*. 2017;9(34):56921-56931. **2.** Bon G, et al. *J Exp Clin Cancer Res.* 2020;39(1):279. **3.** Conte B, et al. *Clin Breast Cancer*. 2020;20(2):e181-e187. **4.** Michel LL, el al. *Cancer (Basel).* 2020;12(10):3021. **5.** Verma S, et al. *N Engl J Med.* 2012;367(19):1783-1791.

More Effective Treatment Options that Further Delay Progression and Extend Survival are Needed in the 2L

mPFS Drops Numerically by Half Moving from 1L THP to 2L T-DM1[1,2]



CLEOPATRA and EMILIA Were Conducted Simultaneously



- 2L T-DM1 was not evaluated in patients with prior pertuzumab treatment[2]
- Outcomes for the 1L THP→ 2L T-DM1 sequence have not been reported from a randomized clinical trial[4,6]
- Available data are limited to RWE and have shown reduced efficacy with T-DM1 following pertuzumab in 1L[3-7]

Chart represents an overview of data from the respective studies. Cross-trial comparisons are complicated by variations in study designs and patient populations

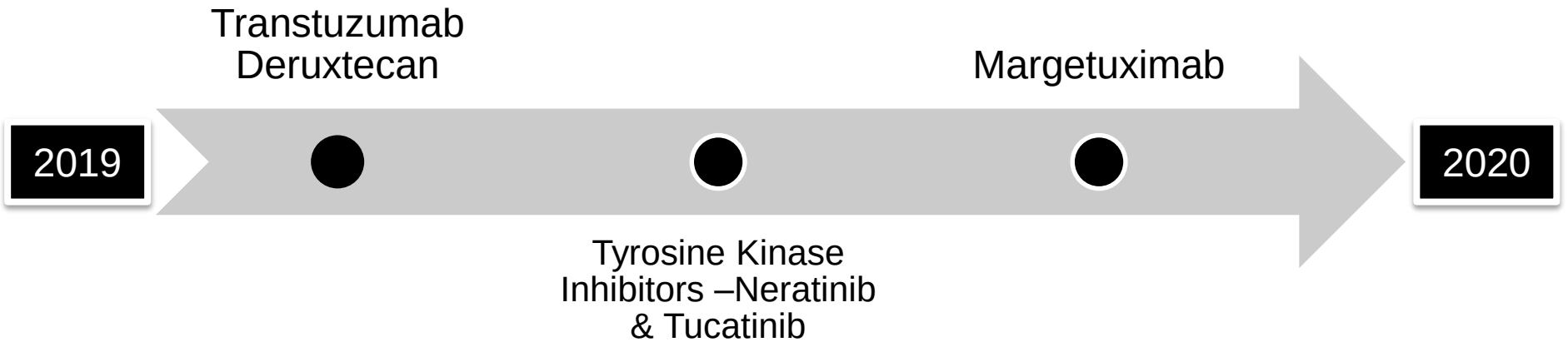
1. Baselga J, et al. *N Engl J Med*. 2012;366(2):109-119. **2.** Verma S, et al. *N Engl J Med*. 2012;367(19):1783-1791. **3.** Vici P, et al. *Oncotarget*. 2017;9(34):56921-56931. **4.** Bon G, et al. *J Exp Clin Cancer Res.* 2020;39(1):279. **5.** Conte B, et al. *Clin Breast Cancer*. 2020;20(2):e181-e187. **6.** Michel LL, el al. *Cancer (Basel).* 2020;12(10):3021. **7**. Daniels B, et al. *Breast*. 2021;58:106-112.

Recent advances in the HER2 positive mBC

Transtuzumab Deruxtecan
Tyrosine Kinase Inhibitors –Neratinib & Tucatinib
Margetuximab

There has been an unprecedented flourishing of the anti HER2 pipeline

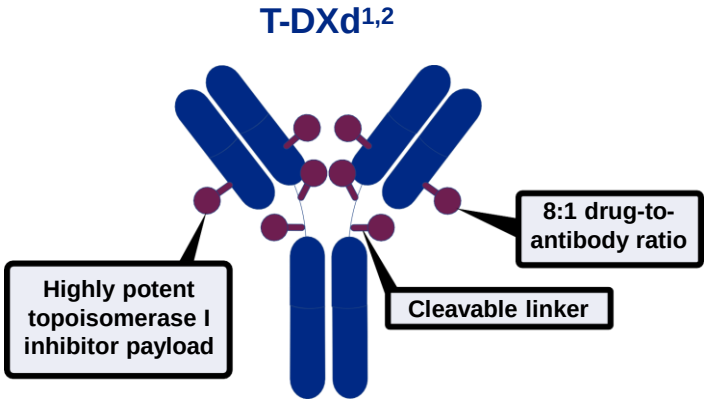
8 anti-HER2 drugs currently authorized by the US-FDA for mBC, a half was approved in the time frame of one single year.



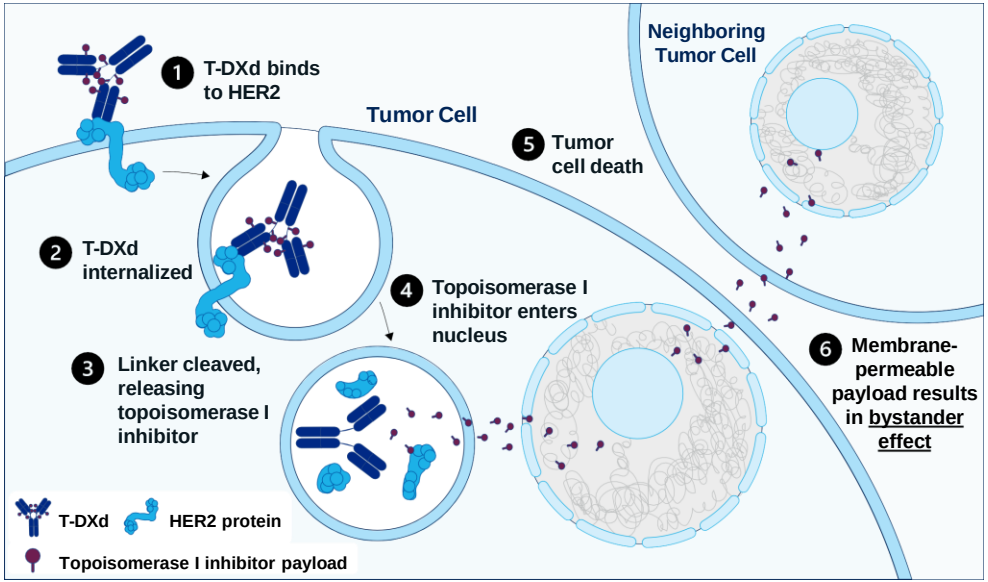
Tarantino P et al. JCO Oncology Practice. 2021; 17(10):605- 606

Trastuzumab Deruxtecan (T-DxD)

Mechanism of action of Trastuzumab deruxtecan



Internalization of T-DXd leads to release of the DXd payload and subsequent cell death in the target tumor cell and neighboring tumor cells through the bystander effect[1,2]



Adapted with permission from Modi S, et al. *J Clin Oncol* 2020;38:1887-96. CC BY ND 4.0.

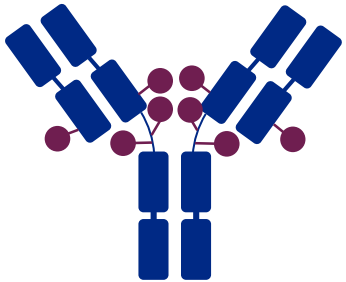
T-Dxd demonstrated response to therapy in 60.9% pretreated patient population with HER2 positive metastatic breast cancer.

HER2, human epidermal growth factor receptor 2; MOA, mechanism of action; mBC, metastatic breast cancer; mPFS, median progression-free survival; ORR, objective response rate; T-DXd, trastuzumab deruxtecan.

1. Nakada T, et al. *Chem Pharm Bull*. 2019;67:173-185. 2. Ogitani Y, et al. *Clin Cancer Res*. 2016;22:5097-5108. 3. Modi S et al. N Engl J Med 2020;382:610-21.

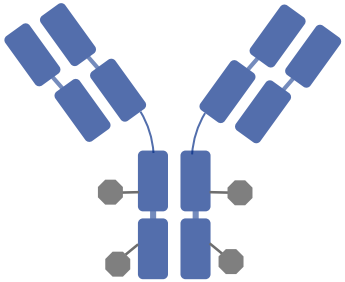
ADC Characteristic Differences Between T-DXd and T-DM1

Trastuzumab deruxtecan (T-DXd)[1]



T-DXd[1-4,a]	ADC Attributes	T-DM1[3-5]
Topoisomerase I inhibitor	**Payload MoA**	Anti-microtubule
~8:1	**Drug-to-antibody ratio**	~3.5:1
Yes	**Tumor-selective cleavable linker?**	No
Yes	**Evidence of bystander anti-tumor effect?**	No

Trastuzumab emtansine (T-DM1)[5]



[a]The clinical relevance of these features is under investigation.

1. Nakada T et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173-85. 2. Ogitani Y et al. *Clin Cancer Res.* 2016;22:5097-108. 3. Trail PA et al. *Pharmacol Ther.* 2018;181:126-42. 4. Ogitani Y et al. *Cancer Sci.* 2016;107:1039-46. 5. LoRusso PM et al. *Clin Cancer Res*. 2011;17:6437-47.

DESTINY-Breast03: Study Design

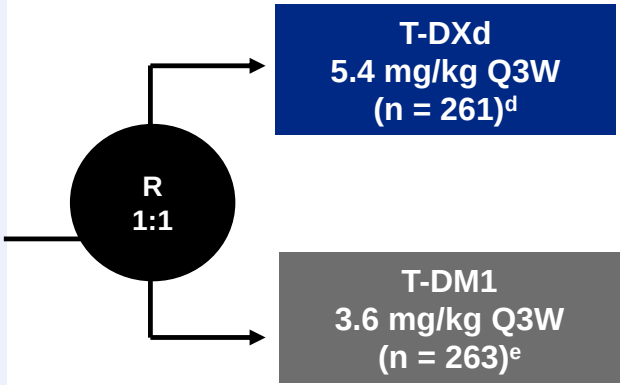
An open-label, multicenter, phase 3 study (NCT03529110)[1-4]

Patients (N = 524)

- Unresectable or metastatic HER2 positive[a] breast cancer that has been previously treated with trastuzumab and taxane[b]
- Could have clinically stable, treated brain metastases[c]
  - ≥2 weeks between end of whole-brain radiotherapy and study enrollment[2,3]

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
- HEOR outcomes (PROs and hospitalization rates)

- **Median follow-up was 15.9 months[3]**
- **At the time of data cutoff (May 21, 2021), 125 (48.6%) T-DXd patients and 214 (82.0%) T-DM1 patients had discontinued treatment[3]**
- **BMs were measured at baseline by CT or MRI and BM progression was monitored throughout the study[3]**

[a]HER2 IHC3+ or IHC2+/ISH+ based on central confirmation. [b]Progression during or <6 months after completing neoadjuvant or adjuvant therapy involving trastuzumab or a taxane. [c]Before protocol amendment, patients with stable, untreated BM were eligible. [d]4 patients were randomly assigned but not treated. [e]2 patients were randomly assigned but not treated.

1. Cortés J et al. *N Engl J Med.* 2022;386:1143-1154. 2. Cortés J et al. *N Engl J Med.* 2022;386:1143-1154 [supplement]. 3. Hurvitz SA et al. Presented at: San Antonio Breast Cancer Symposium 2021; December 7-10, 2021; San Antonio, TX, USA. Presentation GS3-01. 4. Curigliano G et al. Presented at: European Society for Medical Oncology Breast Cancer 2022; May 3-5, 2022; Berlin, Germany. Presentation 163O.

Baseline Characteristics and Prior Therapies were well balanced between the arms[1,2]

Patients were predominately from Asian countries (approx. 60%)

Characteristic	T-DXd (n = 261)	T-DM1 (n = 263)
Age, median (range), years	54.3 (27.9-83.1)	54.2 (20.2-83.0)
Female, n (%)[2]	260 (99.6)	262 (99.6)
Region, n (%)		
Asia	149 (57.1)	160 (60.8)
North America	17 (6.5)	17 (6.5)
Europe	54 (20.7)	50 (19.0)
Rest of world	41 (15.7)	36 (13.7)
Race[a], n (%)[1]		
White	71 (27.2)	72 (27.4)
Black	10 (3.8)	9 (3.4)
Asian	152 (58.2)	162 (61.6)
Multiple	2 (0.8)	0
Other	26 (10.0)	20 (7.6)
Hispanic or Latinx ethnic group[a], n (%)[1]		
Yes	29 (11.1)	29 (11.0)
No	203 (77.8)	209 (79.5)
Unknown	5 (1.9)	6 (2.3)
Data not collected	24 (9.2)	19 (7.2)

[a]Race and ethnic group were reported by the patient. Available options for race included American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, or Other.

1. Cortés J et al. *N Engl J Med*. 2022;386:1143-1154. 2. Hurvitz SA et al. Presented at: San Antonio Breast Cancer Symposium 2021; December 7-10, 2021; San Antonio, TX, USA. Presentation GS3-01.

Baseline Characteristics and Prior Therapies (cont)[1,2]

More than 20% of patients had any recorded history of brain metastases, and approximately 15% of patients had clinically stable brain metastases that were observed at the baseline scan

Characteristic	T-DXd (n = 261)	T-DM1 (n = 263)
HER2 status (IHC[a]), n (%)		
3+	234 (89.7)	232 (88.2)
2+ (ISH positive)	25 (9.6)	30 (11.4)
1+ | Not evaluable	1 (0.4) | 1 (0.4)	0 | 1 (0.4)
ECOG PS[b], n (%)		
0 | 1	154 (59.0) | 106 (40.6)	175 (66.5) | 87 (33.1)
Hormone receptor status, n (%)		
Positive | Negative	131 (50.2) | 130 (49.8)	134 (51.0) | 129 (49.0)
History of brain metastases, n (%)		
Yes | No	62 (23.8) | 199 (76.2)	52 (19.8) | 211 (80.2)
Brain metastases at baseline[c], n (%)[2]		
Yes | No	43 (16.5) | 218 (83.5)	39 (14.8) | 224 (85.2)
Visceral disease, n (%)		
Yes | No	184 (70.5) | 77 (29.5)	185 (70.3) | 78 (29.7)

[a]HER2 status was evaluated by immunohistochemical analysis at a central laboratory. HER2 ISH positive refers to positive results on in situ hybridization. HER2 status was not able to be evaluated for 1 patient in each treatment group. [b]ECOG status was missing for 1 patient in each treatment group. [c]Patients with BM at baseline is the patient population analysis presented in the Hurvitz et al presentation at SABCS 2021.

1. Cortés J et al. *N Engl J Med*. 2022;386:1143-1154. 2. Hurvitz SA et al. Presented at: San Antonio Breast Cancer Symposium 2021; December 7-10, 2021; San Antonio, TX, USA. Presentation GS3-01.

Baseline Characteristics and Prior Therapies (cont)[1,2]

Approximately 60% of patients in each arm received prior pertuzumab

Characteristic	T-DXd (n = 261)	T-DM1 (n = 263)
Previous treatment for mBC, n (%)		
No	21 (8.0)	29 (11.0)
Yes	240 (92.0)	234 (89.0)
Lines of previous therapy in the context of metastatic disease (includes patients with rapid progression as one line of treatment)[a], n (%)		
Median (range)	1 (0-16)	2 (0-14)
0	2 (0.8)	3 (1.1)
1	130 (49.8)	123 (46.8)
2	56 (21.5)	65 (24.7)
3	35 (13.4)	35 (13.3)
4	15 (5.7)	19 (7.2)
≥5	23 (8.8)	18 (6.8)
Previous cancer therapy[b], n (%)		
Trastuzumab	260 (99.6)	262 (99.6)
Pertuzumab	162 (62.1)	158 (60.1)
Taxane	260 (99.6)	262 (99.6)
Other anti-HER2 antibody	42 (16.1)	38 (14.4)
Anti-HER2 TKI	42 (16.1)	36 (13.7)
Other anti-HER2 antibody or ADC	2 (0.8)	3 (1.1)
Hormone therapy	109 (41.8)	112 (42.6)
Other systemic therapy	260 (99.6)	262 (99.6)

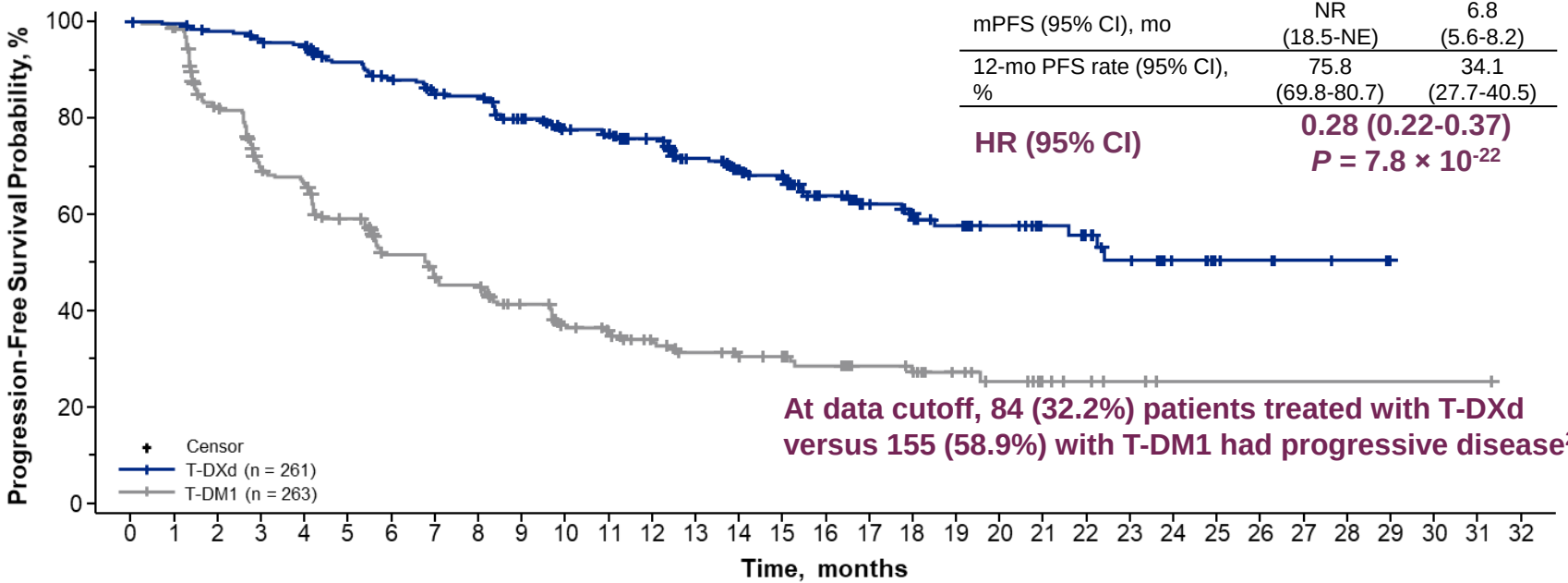
[a]Patients who had had rapid progression (i.e., progression that had occurred within 6 months after receipt of neoadjuvant or adjuvant therapy or within 12 months after receipt of a neoadjuvant or adjuvant pertuzumab-containing regimen) were considered to have had one line of previous therapy. Lines of previous therapy did not include endocrine therapy. [b]All patients received at least 1 previous cancer therapy. One patient who had previously received T-DM1 treatment was enrolled in error in the T-DXd arm.

1. Cortés J et al. *N Engl J Med*. 2022;386:1143-1154. 2. Hurvitz SA et al. Presented at: San Antonio Breast Cancer Symposium 2021; December 7-10, 2021; San Antonio, TX, USA. Presentation GS3-01.

Primary Endpoint: PFS by BICR[1-3]

72% reduction in the progression or death

	T-DXd	T-DM1
mPFS (95% CI), mo	NR (18.5-NE)	6.8 (5.6-8.2)
12-mo PFS rate (95% CI), %	75.8 (69.8-80.7)	34.1 (27.7-40.5)
HR (95% CI)	**0.28 (0.22-0.37)**	
	***P* = 7.8 × 10^{-22}**	



At data cutoff, 84 (32.2%) patients treated with T-DXd versus 155 (58.9%) with T-DM1 had progressive disease[2,3]

Patients Still at Risk:

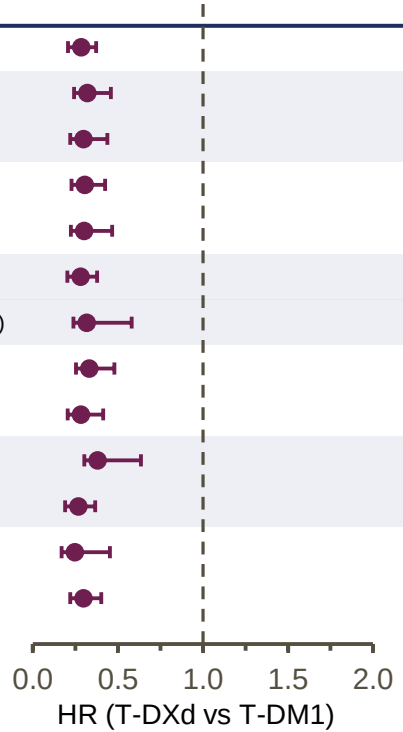
T-DXd (261)	261	256	250	244	240	224	214	202	200	183	168	164	150	132	112	105	79	64	53	45	36	29	25	19	10	6	5	3	2	0
T-DM1 (263)	263	252	200	161	155	132	108	96	93	78	65	60	51	43	37	34	29	23	21	16	12	8	6	4	1	1	1	1	1	0

Median PFS follow-up for T-DXd was 15.5 months (95% CI, 15.1-16.6) and for T-DM1 was 13.9 months (95% CI, 11.8-15.1).[1]

1. Cortés J et al. *N Engl J Med*. 2022. in press. 2. Cortés J et al. *N Engl J Med.* 2022 [supplement]. In press. 3. Hurvitz SA et al. Presented at: San Antonio Breast Cancer Symposium 2021; December 7-10, 2021. Presentation GS3-01.

PFS in Key Subgroups[1-3]

		Number of Events		Median PFS (mo, 95% CI)		HR (95% CI)
		T-DXd	T-DM1	T-DXd	T-DM1	
All patients		87/261	158/263	NE (18.5-NE)	6.8 (5.6-8.2)	0.2840 (0.2165-0.3727)
Hormone receptor status	Positive (n = 272)	46/133	84/139	22.4 (17.7-NE)	6.9 (4.2-9.8)	0.3191 (0.2217-0.4594)
	Negative (n = 248)	41/126	73/122	NE (18.0-NE)	6.8 (5.4-8.3)	0.2965 (0.2008-0.4378)
Prior pertuzumab treatment	Yes (n = 320)	57/162	98/158	NE (18.5-NE)	6.8 (5.4-8.3)	0.3050 (0.2185-0.4257)
	No (n = 204)	30/99	60/105	NE (16.5-NE)	7.0 (4.2-9.7)	0.2999 (0.1924-0.4675)
Visceral disease	Yes (n = 384)	72/195	123/189	22.2 (16.5-NE)	5.7 (4.2-7.0)	0.2806 (0.2083-0.3779)
	No (n = 140)	15/66	35/74	NE (NE-NE)	11.3 (6.8-NE)	0.3157 (0.1718-0.5804)
Prior lines of therapy[a]	0-1 (n = 258)	46/132	75/126	22.4 (17.9-NE)	8.0 (5.7-9.7)	0.3302 (0.2275-0.4794)
	≥2 (n = 266)	41/129	83/137	NE (16.8-NE)	5.6 (4.2-7.1)	0.2828 (0.1933-0.4136)
History of brain metastases[1]	Yes (n = 114)	31/62	31/52	15.0 (12.6-22.2)	5.7 (2.9-7.1)	0.3796 (0.2267-0.6357)
	No (n = 410)	56/199	127/211	NE (22.4-NE)	7.0 (5.5-9.7)	0.2665 (0.1939-0.3665)
Brain metastases at baseline[2]	Yes (n = 82)	22/43	27/39	15.0 (12.5-22.2)	3.0 (2.8-5.8)	0.2465 (0.1341-0.4529)
	No (n = 442)	65/218	131/224	NE (22.4-NE)	7.1 (5.6-9.7)	0.2971 (0.2199-0.4014)



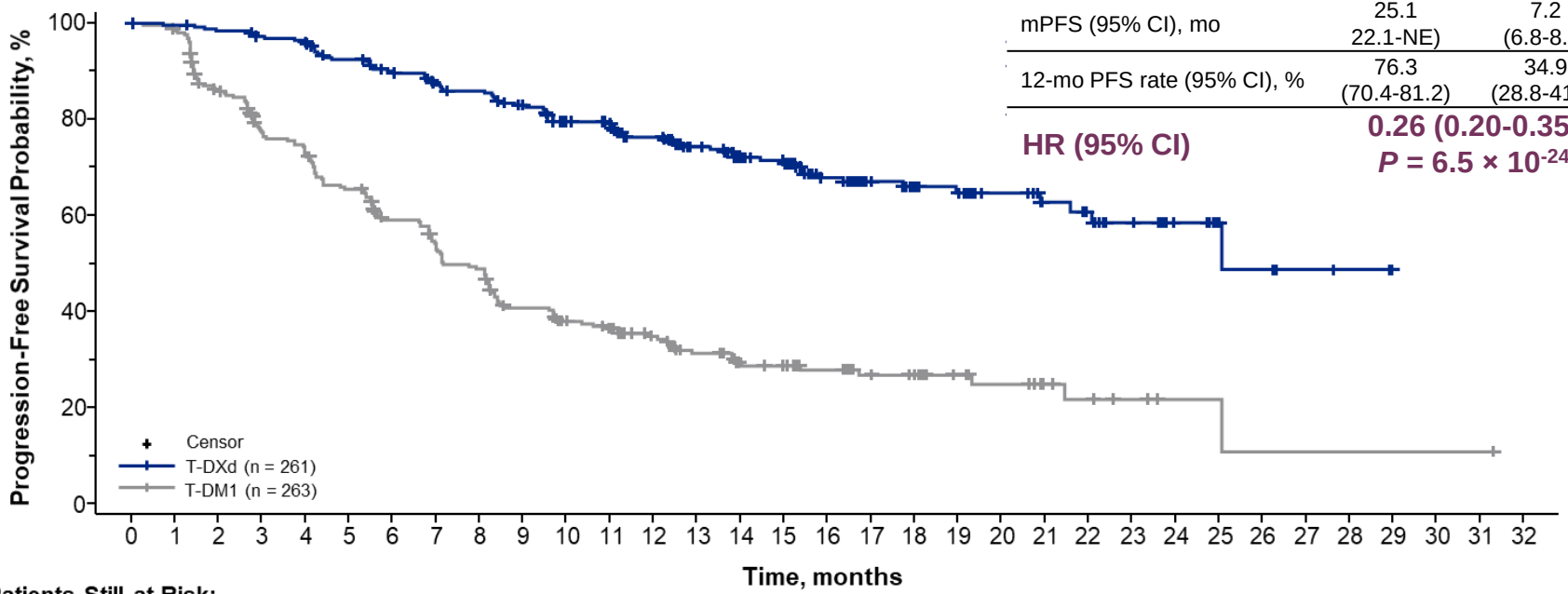
[a]Patients who had rapid progression (i.e., progression that had occurred within 6 months after receipt of neoadjuvant or adjuvant therapy or within 12 months after receipt of a neoadjuvant or adjuvant pertuzumab-containing regimen) were considered to have had one line of previous therapy. Lines of previous therapy did not include endocrine therapy.

1. Cortés J et al. *N Engl J Med*. 2022;386:1143-1154. 2. Hurvitz SA et al. Presented at: San Antonio Breast Cancer Symposium 2021; December 7-10, 2021; San Antonio, TX, USA. Presentation GS3-01. 3. Cortés J et al. Presented at: ESMO Virtual Congress 2021; September 16-21, 2021. Presentation 2525.

Secondary Endpoint: PFS by Investigator Assessment

74% reduction in the progression or death

	T-DXd	T-DM1
mPFS (95% CI), mo	25.1 (22.1-NE)	7.2 (6.8-8.3)
12-mo PFS rate (95% CI), %	76.3 (70.4-81.2)	34.9 (28.8-41.2)
HR (95% CI)	0.26 (0.20-0.35)	
	$P = 6.5 \times 10^{-24}$	



Patients Still at Risk:

T-DXd (261)	261	256	252	247	244	230	221	209	205	195	179	176	158	140	120	113	85	64	53	48	37	31	27	20	11	7	5	3	2	0
T-DM1 (263)	263	253	216	185	175	156	136	119	110	88	78	72	61	51	43	39	34	25	23	16	13	9	7	5	2	2	1	1	1	1	1	0

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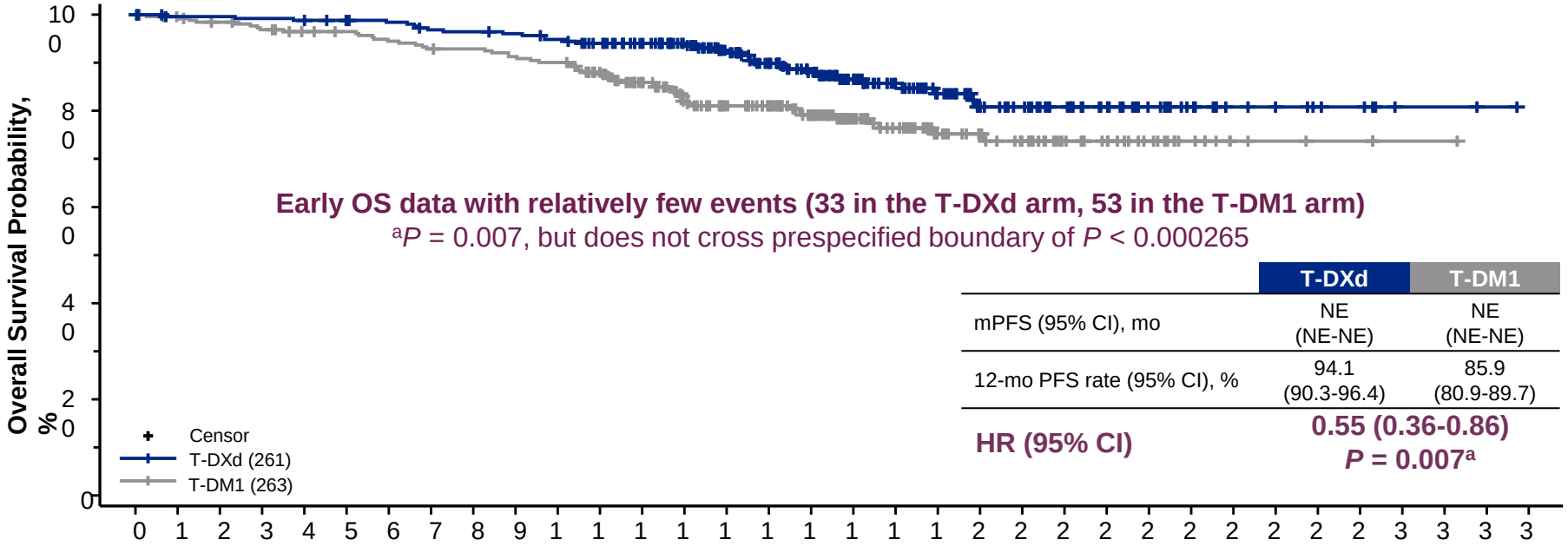
PFS by investigator was a secondary endpoint and the *P* value was nominal. Although the *P* value is accurate and reflective of the data, it cannot be used to claim statistical significance.

Cortés J et al. *N Engl J Med.* 2022;386:1143-1154 [supplement].

Key Secondary Endpoint: encouraging OS trend



Early OS data with relatively few events (33 in the T-DXd arm, 53 in the T-DM1 arm)

[a]*P* = 0.007, but does not cross prespecified boundary of *P* < 0.000265

	T-DXd	T-DM1
mPFS (95% CI), mo	NE (NE-NE)	NE (NE-NE)
12-mo PFS rate (95% CI), %	94.1 (90.3-96.4)	85.9 (80.9-89.7)
HR (95% CI)	**0.55 (0.36-0.86)**	
	***P* = 0.007[a]**	

Patients Still at Risk:

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33
T-DXd (261)	261	256	256	255	254	251	249	244	243	241	237	230	218	202	180	158	153	108	86	71	56	50	42	33	24	18	11	10	7	6	2	2	1	0
T-DM1 (263)	263	258	253	248	243	241	236	232	231	227	224	210	188	165	151	140	120	91	75	58	52	44	32	27	18	11	5	4	3	3	1	1	0	

Cortés J et al. *N Engl J Med*. 2022;386:1143-1154.

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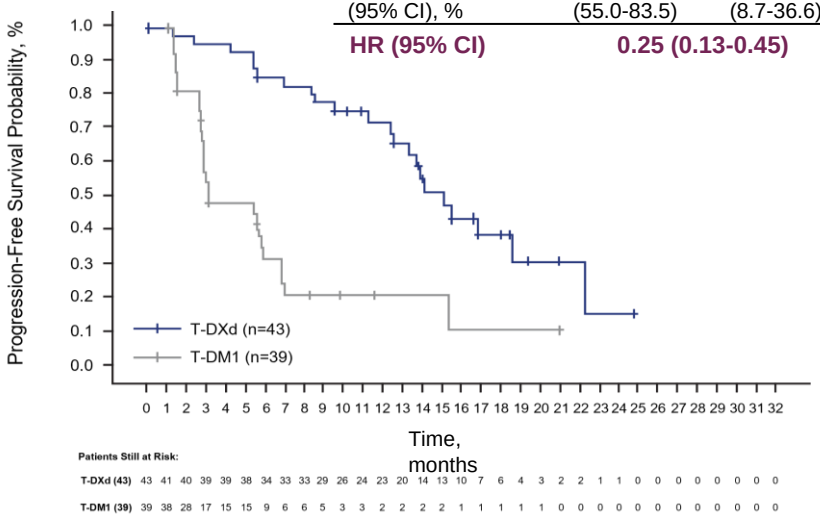
PFS KM Curves for Patients With and Without BM

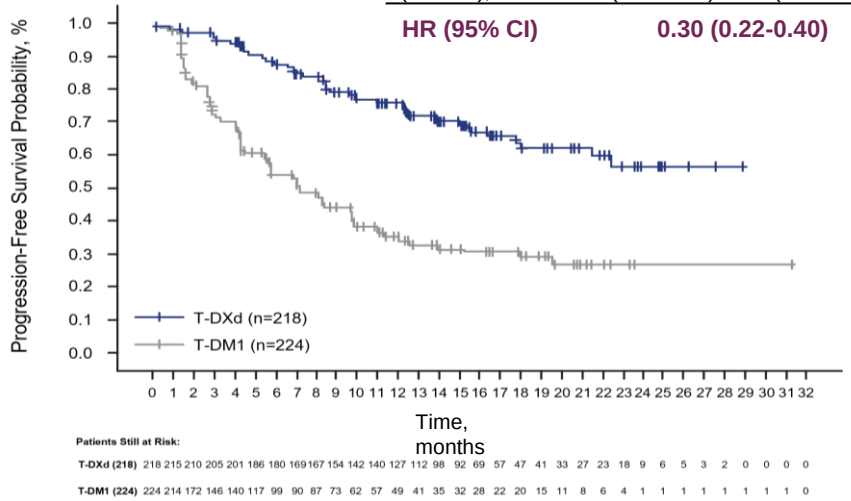
Brain Metastases at Baseline

	T-DXd	T-DM1
mPFS (95% CI), mo	15.0 (12.5-22.2)	3.0 (2.8-5.8)
12-mo PFS rate (95% CI), %	72.0 (55.0-83.5)	20.9 (8.7-36.6)
HR (95% CI)	**0.25 (0.13-0.45)**	



No Brain Metastases at Baseline

	T-DXd	T-DM1
mPFS (95% CI), mo	NE (22.2-NE)	7.1 (5.6-9.7)
12-mo PFS rate (95% CI), %	76.5 (70.0-81.8)	36.4 (29.4-43.4)
HR (95% CI)	**0.30 (0.22-0.40)**	



At data cutoff, in patients with BMs at baseline, PD was observed:

- In 21/43 treated with T-DXd versus 27/39 with T-DM1
  - In the brain in 9/21 treated with T-DXd versus 11/27 with T-DM1

At data cutoff, in patients without BMs at baseline, PD was observed:

- In 63/218 treated with T-DXd versus 128/224 with T-DM1
  - In the brain in 4/63 treated with T-DXd versus 1/128 with T-DM1

Hurvitz SA et al. Presented at: San Antonio Breast Cancer Symposium 2021; December 7-10, 2021; San Antonio, TX, USA. Presentation GS3-01.

Also see: PFS in Key Subgroups

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Overall and Exposure-Adjusted Safety Summary[1-3]

Type of adverse events[1,3]	T-DXd (n = 257)	T-DM1 (n = 261)
Any TEAEs		
n (%)	256 (99.6)	249 (95.4)
Exposure-adjusted incidence per patient-year[a]	0.87	1.43
TEAE of grade ≥3		
n (%)	134 (52.1)	126 (48.3)
Exposure-adjusted incidence per patient-year[a]	0.46	0.72
Serious TEAE		
n (%)	49 (19.1)	47 (18.0)
Exposure-adjusted incidence per patient-year[a]	0.17	0.27
TEAE associated with discontinuation		
n (%)	35 (13.6)	19 (7.3)
Exposure-adjusted incidence per patient-year[a]	0.12	0.11
TEAE associated with dose reduction		
n (%)	55 (21.4)	33 (12.6)
Exposure-adjusted incidence per patient-year[a]	0.19	0.19
TEAE associated with an outcome of death		
n (%)	5 (1.9)	5 (1.9)
Exposure-adjusted incidence per patient-year[a]	0.02	0.03

- **Median treatment duration was 14.3 months (range, 0.7-29.8) for T-DXd and 6.9 months (range, 0.7-25.1) for T-DM1[1,2]**
- **Although rates of any TEAEs and TEAEs of grade ≥3 were generally similar between arms, exposure-adjusted rates were lower with T-DXd versus T-DM1[1,2]**
- **Although rates of TEAEs associated with discontinuation were greater with T-DXd versus T-DM1, exposure-adjusted rates were generally similar[1,2]**

Relationship to study drug was determined by the treating investigator.
[a]Total patient-years of exposure were 297.86 years for T-DXd and 174.48 years for T-DM1. Patient-years of exposure are the treatment duration with year as unit.
1. Hurvitz SA et al. Presented at: San Antonio Breast Cancer Symposium 2021; December 7-10, 2021; San Antonio, TX, USA. Presentation GS3-01. 2. Cortés J et al. *N Engl J Med*. 2022;386:1143-1154. 3. Cortés J et al. *N Engl J Med*. 2022;386:1143-1154 [supplement].

Overall and Exposure-Adjusted Safety Summary[1-3]

- Note that exposure-adjusted incidence per patient year is **presented to account for the differences in duration of treatment among treatment arms**, with T-DXd patients having longer treatment exposure.
- Exposure-adjusted incidence is a standardized measure of risk per patient year and assuming a constant risk over time, accounts for the timing of the first event during the follow-up
- Although rates of TEAEs associated with discontinuation were greater with T-DXd versus T-DM1, **exposure-adjusted rates were generally similar**
- Although there were 5 patients with TEAEs associated with an outcome of death in each treatment arm (1.9% in each arm), **there were no drug-related deaths during the study**

Relationship to study drug was determined by the treating investigator.
aTotal patient-years of exposure were 297.86 years for T-DXd and 174.48 years for T-DM1. Patient-years of exposure are the treatment duration with year as unit.
1. Hurvitz SA et al. Presented at: San Antonio Breast Cancer Symposium 2021; December 7-10, 2021; San Antonio, TX, USA. Presentation GS3-01. 2. Cortés J et al. *N Engl J Med*. 2022;386:1143-1154. 3. Cortés J et al. *N Engl J Med*. 2022;386:1143-1154 [supplement].

Adverse Events of Special Interest

*There were **no grade 4 or 5 adjudicated drug-related ILD/pneumonitis events** observed, and **most events were grade 1 or 2***

Adjudicated as drug-related ILD/pneumonitis[a], n (%)						
n (%)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Any Grade**
T-DXd (n = 257)	7 (2.7)	18 (7.0)	2 (0.8)	0	0	27 (10.5)
T-DM1 (n = 261)	4 (1.5)	1 (0.4)	0	0	0	5 (1.9)

- There were no grade 4 or 5 adjudicated drug-related ILD/pneumonitis events observed with T-DXd
- In the T-DXd arm, 21 patients (8.2%) discontinued treatment due to ILD/pneumonitis
- In the T-DM1 arm, 3 patients (1.1%) discontinued treatment due to ILD/pneumonitis

LVEF decrease, n (%)						
n (%)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Any Grade**
T-DXd (n = 257)	1 (0.4)[b]	6 (2.3)[c]	0	0	0	7 (2.7)
T-DM1 (n = 261)	0	1 (0.4)[c]	0	0	0	1 (0.4)

- **In the T-DXd arm, all reported adverse events of LVEF decrease were asymptomatic and no cases of cardiac failure occurred**

[a]Patients with prior history of ILD/pneumonitis requiring steroids were excluded. [b]Left ventricular dysfunction. [c]Decreased ejection fraction.

Cortés J et al. *N Engl J Med*. 2022;386:1143-1154.

Outcomes of ILD/Pneumonitis Events

Outcome of the worst ILD/pneumonitis events, n (%)	T-DXd (n = 257)	T-DM1 (n = 261)
Fatal	0	1 (20.0)[a]
Not Recovered/Not Resolved	8 (29.6)	0
Recovering/Resolving	2 (7.4)	0
Recovered/Resolved with Sequelae	2 (7.4)	0
Recovered/Resolved	15 (55.6)	4 (80.0)
Missing/Unknown	0	0

The outcome of the worst interstitial lung disease event denominator is based on the number of events adjudicated as drug-related interstitial lung disease/pneumonitis

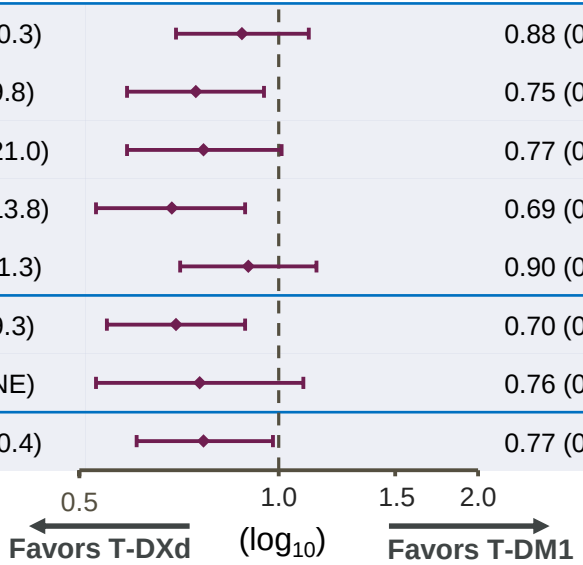
[a]The majority of interstitial lung disease/pneumonitis events in both treatment arms resolved, with 1 fatal case reported in the trastuzumab emtansine arm. This subject had an event of pulmonary embolism that the investigator considered to be grade 5. This event was initially reported as respiratory failure; however, the patient was subsequently updated to pulmonary embolism. The interstitial lung disease adjudication committee adjudicated this event as drug-related grade 1 interstitial lung disease/pneumonitis. The death was not evaluable for adjudication. The investigator recorded disease progression as the primary cause of death.

Cortés J et al. *N Engl J Med*. 2022;386:1143-1154 [supplement].

ESMO 2022 update: Time to Definitive Deterioration in PRO measures was numerically prolonged with Tdxd

Overall health status and QoL was maintained with T-DXd, based on mean change from baseline

		Median (95% CI) TDD, months		HR (95% CI)	Nominal *P* value
		T-DXd (n = 261)	T-DM1 (n = 263)		
EORTC QLQ-C30	Global health status/QoL[a]	9.7 (7.3-12.5)	8.3 (7.0-10.3)	0.88 (0.70-1.11)	0.2829
	Pain symptoms[b]	10.8 (8.3-14.0)	8.3 (6.6-9.8)	0.75 (0.59-0.95)	0.0146
	Physical functioning[b]	16.7 (14.5-NE)	10.3 (8.3-21.0)	0.77 (0.59-1.01)	0.0529
	Emotional functioning[b]	16.4 (14.1-19.9)	10.5 (9.0-13.8)	0.69 (0.53-0.89)	0.0049
	Social functioning[b]	11.1 (7.3-13.4)	9.0 (7.1-11.3)	0.90 (0.71-1.14)	0.3577
EORTC QLQ-BR45	Arm symptoms[b]	11.1 (8.5-14.8)	7.0 (5.6-9.3)	0.70 (0.55-0.89)	0.0033
	Breast symptoms[b]	26.4 (26.4-NE)	NE (NE-NE)	0.76 (0.53-1.09)	0.1329
EQ-5D-5L	VAS[b]	13.2 (10.1-15.3)	8.5 (7.3-10.4)	0.77 (0.61-0.98)	0.0354



EORTC, European Organization for Research and Treatment of Cancer; EQ-5D-5L, EuroQol 5-dimension, 5-level questionnaire; GHS, global health status; HR, hazard ratio; PRO, patient-reported outcome; QLQ-BR45, Quality of Life Breast cancer questionnaire; QLQ-C30, Quality of Life Core 30 questionnaire; QoL, quality of life; TDD, time to definitive deterioration; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; VAS, visual analog scale.

P values are not adjusted for multiple testing. TDD is defined as a >10-point change from baseline. [a]Primary PRO variable of interest. [b]Secondary PRO variable of interest.

Conclusions of DB-03 trial

In the first randomized phase 3 trial in breast cancer, T-DXd demonstrated[1]:

- **Clinically meaningful and statistically significant improvement in PFS compared with T-DM1 in patients with HER2 positive mBC**
  - PFS by BICR HR of 0.28 ($P = 7.8\times10^{-22}$)[2]
  - Consistent benefit seen across key subgroups and efficacy endpoints, with a confirmed ORR for T-DXd of 79.7% vs 34.2% for TDM1 (CR, 16.1% vs 8.7%)
- **Encouraging OS trend at the time of first interim analysis**
  - The 12-month OS rate for T-DXd was 94.1% vs 85.9% for T-DM1
- **A safety profile that is comparable between the two arms**
  - Similar rates of all grade and grade ≥3 drug-related TEAEs were observed between arms
  - There were no grade 4 or 5 ILD/pneumonitis events in either arm

These data support T-DXd becoming the standard of care for 2L HER2 positive mBC

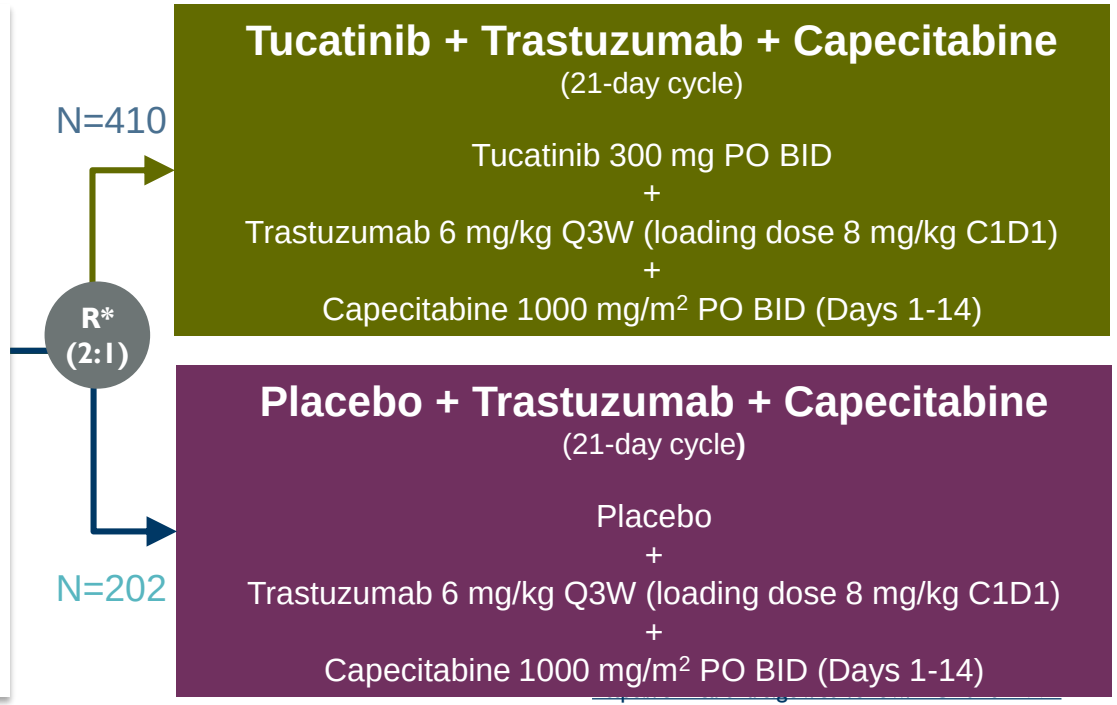
1. Cortés J et al. *N Engl J Med*. 2022;386:1143-1154. 2. Hurvitz SA et al. Presented at: San Antonio Breast Cancer Symposium 2021; December 7-10, 2021; San Antonio, TX, USA. Presentation GS3-01.

Tucatinib

HER2CLIMB Trial: Randomized, double-blind, multicenter, international, placebo-controlled, phase 2 study

Key Eligibility Criteria

- HER2+ metastatic breast cancer
- Prior treatment with trastuzumab, pertuzumab, and T-DM1
- ECOG performance status 0 or 1
- Brain MRI at baseline
  - Previously treated stable brain metastases
  - Untreated brain metastases not needing immediate local therapy
  - Previously treated progressing brain metastases not needing immediate local therapy
  - No evidence of brain metastases



*Stratification factors: presence of brain metastases (yes/no), ECOG status (0 or 1), and region (US or Canada or rest of world)

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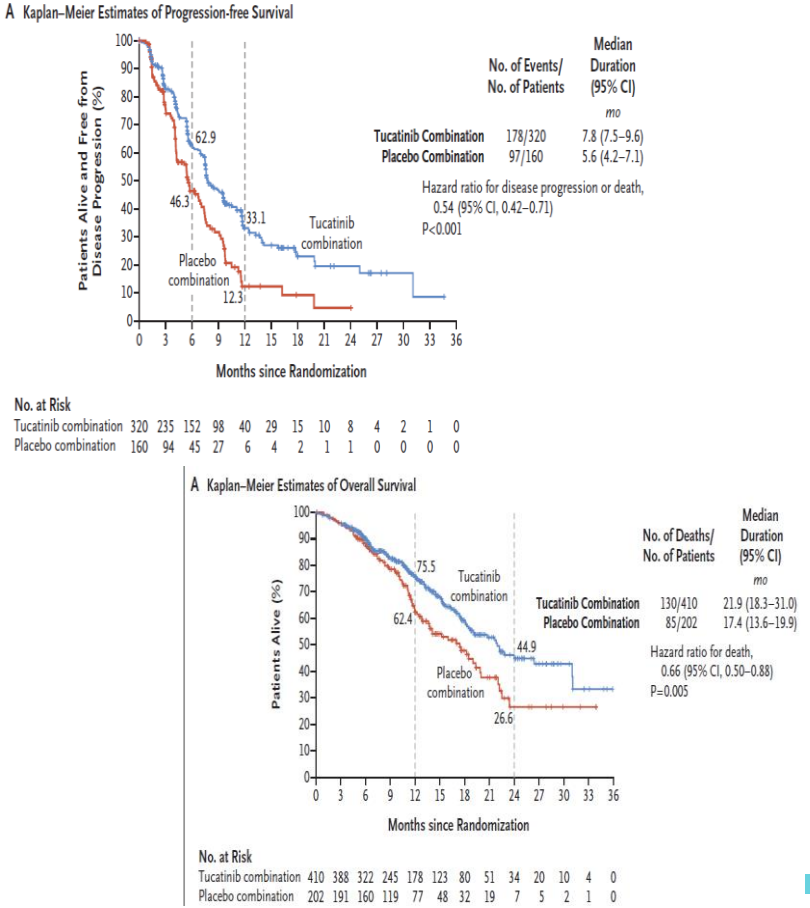
Murthy S et al. N Engl J Med 2020;382:597-609.

HER2CLIMB Trial: Adding Tucatinib to Trastuzumab and Capecitabine resulted in better progression-free survival and overall survival outcomes

Study Name	HER2CLIMB (n = 480/612)
Drug	**Tucatinib + trastuzumab + capecitabine[b]**
Comparator	Trastuzumab + capecitabine
Prior therapies **Trastuzumab** **Pertuzumab** **T-DM1** **Lapatinib**	 100% 100% 100% -
ORR (CR)	**41% (1% CR)** vs 23% (1% CR)
mPFS	**7.8 mo** vs 4.9 mo (HR, 0.54, [95% CI, 0.42-0.71]; *P* < 0.001)
mOS	**21.9 mo** vs. 17.4 mo (HR, 0.73, [95% CI, 0.50-0.88]; *P* = 0.005)
Common AEs (≥20%)	Diarrhea, PPE syndrome, nausea, fatigue, vomiting, decreased appetite, stomatitis, headache, elevated AST/ALT, anemia, elevated bilirubin
Grade ≥3 AEs	61% vs 51%



Murthy S et al. N Engl J Med 2020;382:597-609.

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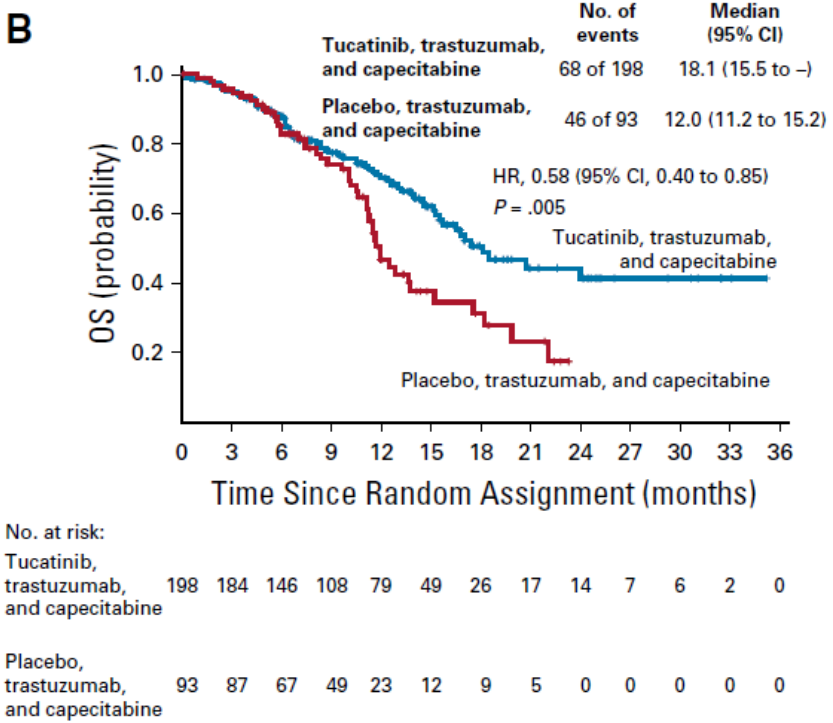
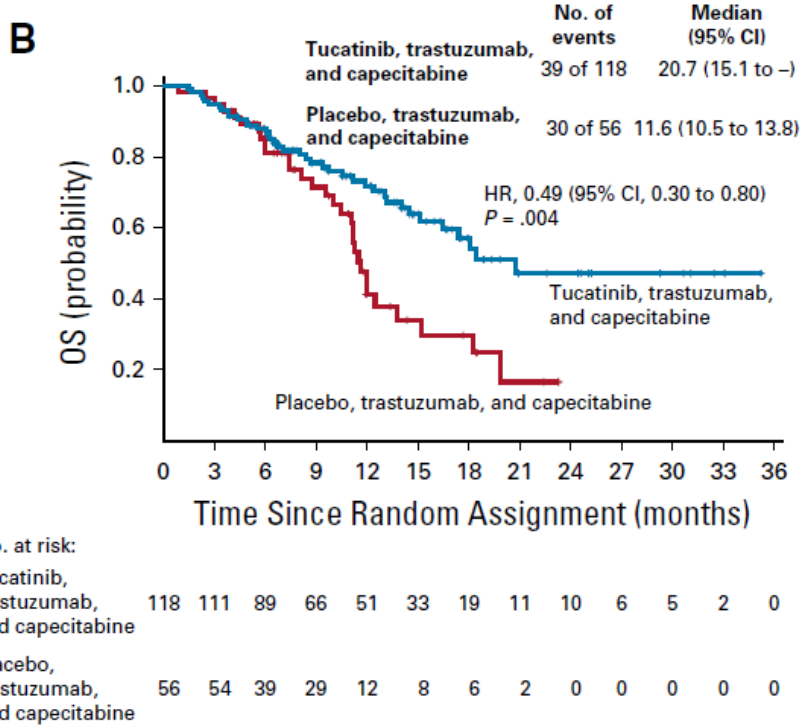
Exploratory **OS** in patients with **Brain Mets**



Exploratory **OS** in patients with **Active Brain Mets**



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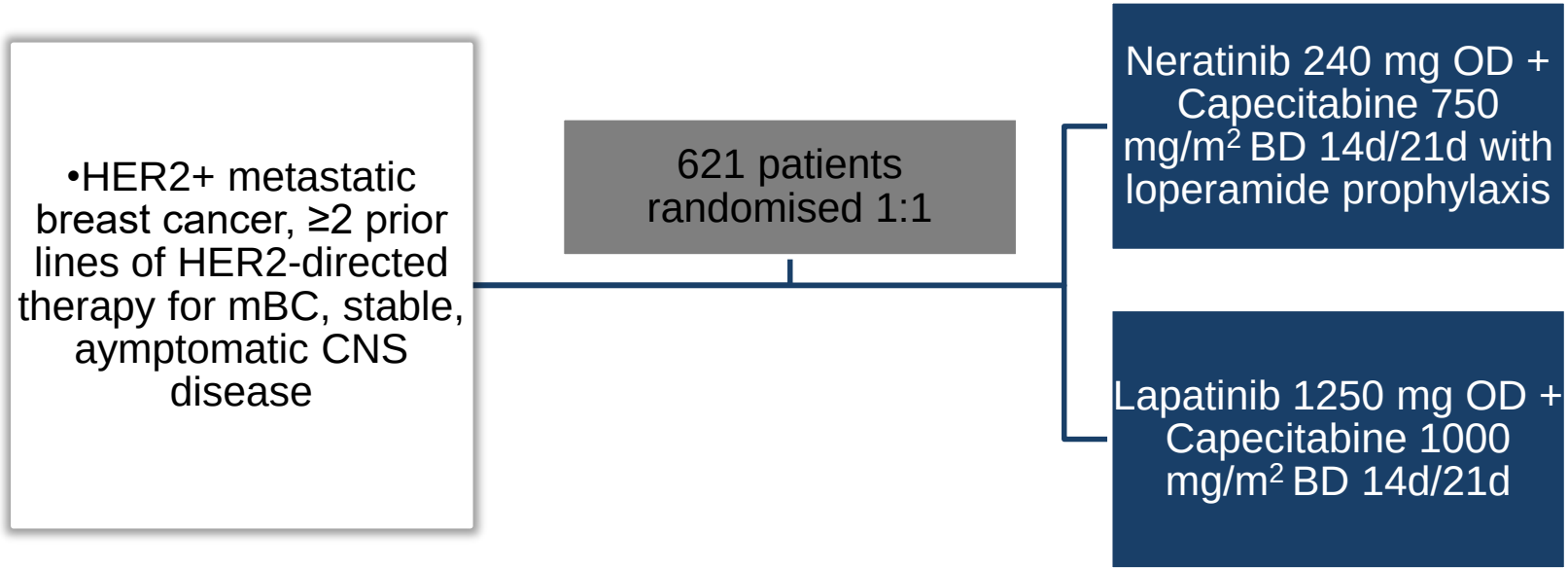
Lin et al. J Clin Oncol.2020; 38:2610-2619.

Neratinib

NALA Trial: Neratinib + Capecitabine versus Lapatinib + Capecitabine in HER2 +ve MBC previously treated with >2 HER regimens



Coprimary Endpoints : PFS & OS

Secondary Ednpoints: CNS disease intervention, investigator-assessed PFS, objective response rate (ORR), duration of response (DoR), clinical benefit rate, safety, and health-related quality of life (HRQoL).

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Saura et al. J Clin Oncol .2020;38:3138-3149

NALA trial: Statistically significant benefit in PFS favouring N+C, translating to a 2.2-month mean PFS improvement without a significant benefit in OS.

Study Name	NALA (n = 621)
Drug	Neratinib + capecitabine
Comparator	Lapatinib + capecitabine
Prior therapies Trastuzumab Pertuzumab T-DM1 Lapatinib	 100% 41% 52% -
ORR (CR)	**33% (2% CR)** vs 27% (1% CR)
mPFS	**8.8 mo** vs 6.6 mo (HR, 0.76, [95% CI, 0.63-0.93]; *P* = 0.0003)
mOS	**24.0 mo** vs 22.2 mo (HR, 0.88, [95% CI, 0.72-1.07]; *P* = 0.2086)
Common AEs (≥20%)	Diarrhea, nausea, PPE syndrome, vomiting, decreased appetite, fatigue, constipation, stomatitis, weight decreased
Grade ≥3 AEs	Diarrhea: 24% vs 13%

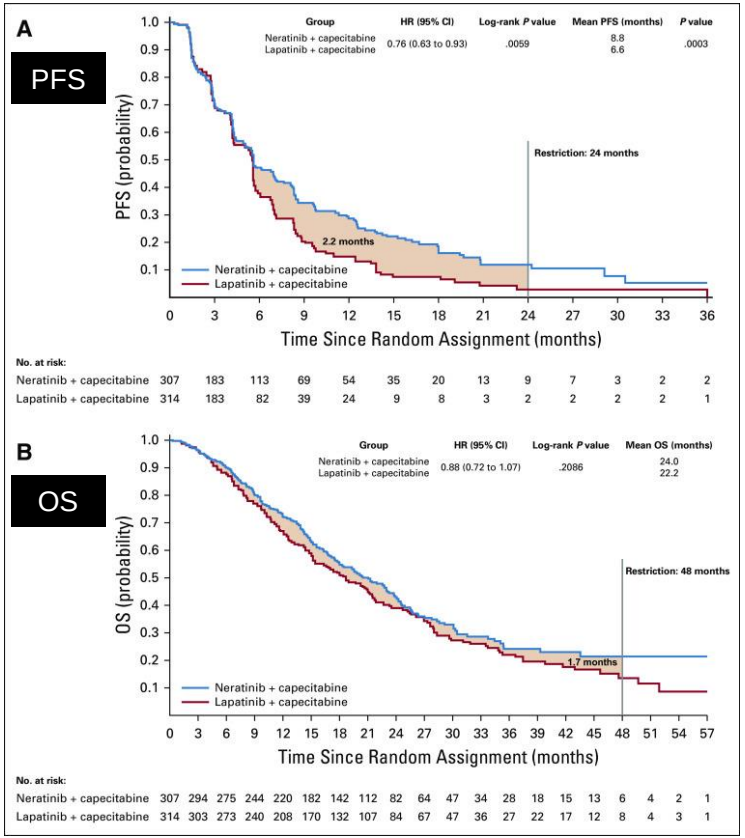


Table represents an overview of data from the respective studies.

5. Saura C, et al. *J Clin Oncol*. 2020;38(27):3138-3149.

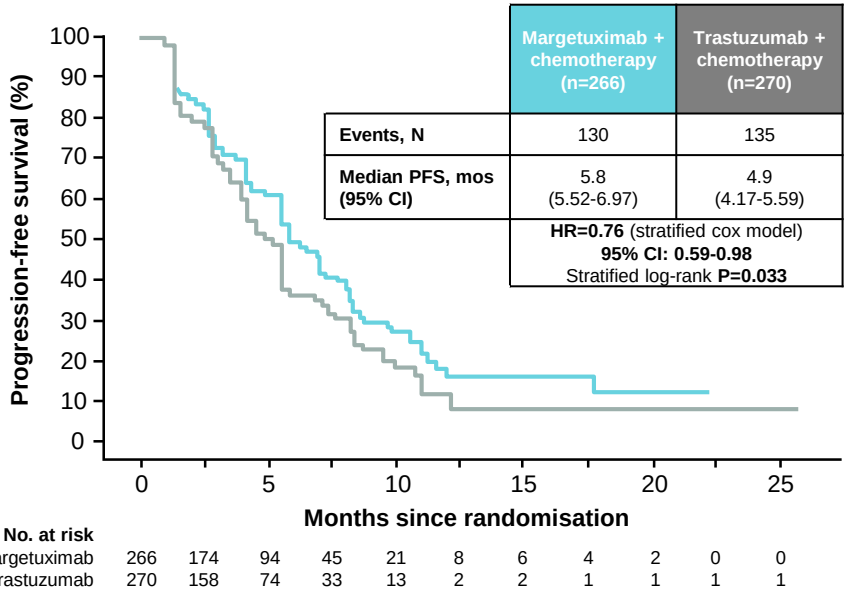
Margetuximab

SOPHIA Trial: Investigated Margetuximab + Chemotherapy versus Trastuzumab + Chemotherapy

- **536 patients** with HER2+ advanced breast cancer, who had received **≥2 prior anti-HER2 therapies (including pertuzumab)** and 1–3 prior treatment lines in the metastatic setting were randomised to the trial in a 1:1 ratio following investigator's choice of chemotherapy*
- **Primary endpoints: PFS and OS** (BICR, assessed sequentially using the stratified log-rank test)
- Secondary and exploratory endpoints: ORR, PFS (investigator-assessed), CBR, safety and tolerability

Safety: Most common **Grade ≥3 AE** (≥10%) in the margetuximab arm was **neutropenia**

Primary PFS analysis by CBA[1] (ITT population, N=536)



*Capecitabine, eribulin, gemcitabine or vinorelbine)

2H19=second half of 2019; AE=adverse event; BICR=blinded independent central review; BLA=Biologics License Application; CBA=centrally blinded assessment; CBR=clinical benefit ratio; CI=confidence interval; FDA=FDA, US Food and Drug Administration; HR=hazard ratio; ITT=intention-to-treat; OS=overall survival; PFS=progression-free survival

Daiichi-Sankyo | AstraZeneca

1. Rugo HS et al. Presented at: ASCO Annual Meeting; May 31–June 4, 2019; Chicago, IL. 2. MacroGenics Inc. press release. Published February 6, 2019.

SOPHIA: OS update in 2021

<< Back

Sep 7, 2021

MacroGenics Announces Final Overall Survival Results from SOPHIA Study of MARGENZA™ in Patients with HER2-Positive Metastatic Breast Cancer

- Final overall survival (OS) analysis did not demonstrate a statistically significant advantage for MARGENZA over trastuzumab
- OS was greater with MARGENZA plus chemotherapy in exploratory subgroups of patients carrying a CD16A 158F allele compared to trastuzumab plus chemotherapy arm, while the OS for trastuzumab plus chemotherapy was greater than MARGENZA plus chemotherapy for the small exploratory subgroup of patients homozygous for the CD16A 158V allele
- The safety profile remains similar to what has been reported previously

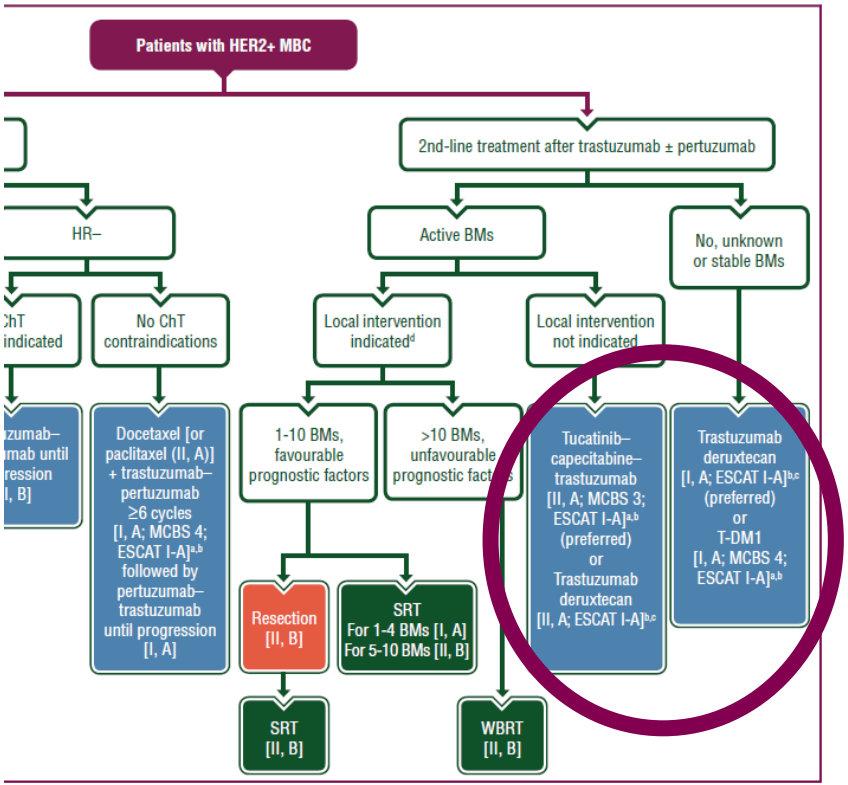
The final OS analysis of the SOPHIA study was performed after 385 OS events occurred in the intent-to-treat (ITT) population.

"While the OS results in the SOPHIA ITT population are disappointing, the greater OS observed in the CD16A subgroup of patients with the lowest binding allelic variant of CD16 to the Fc region of IgG1 — namely, the F/F allele representing about 40% of all individuals (35.8% in this study) — is consistent with enhancements observed in MARGENZA's engineered Fc region," said Scott Koenig, M.D., Ph.D., President and CEO of MacroGenics.

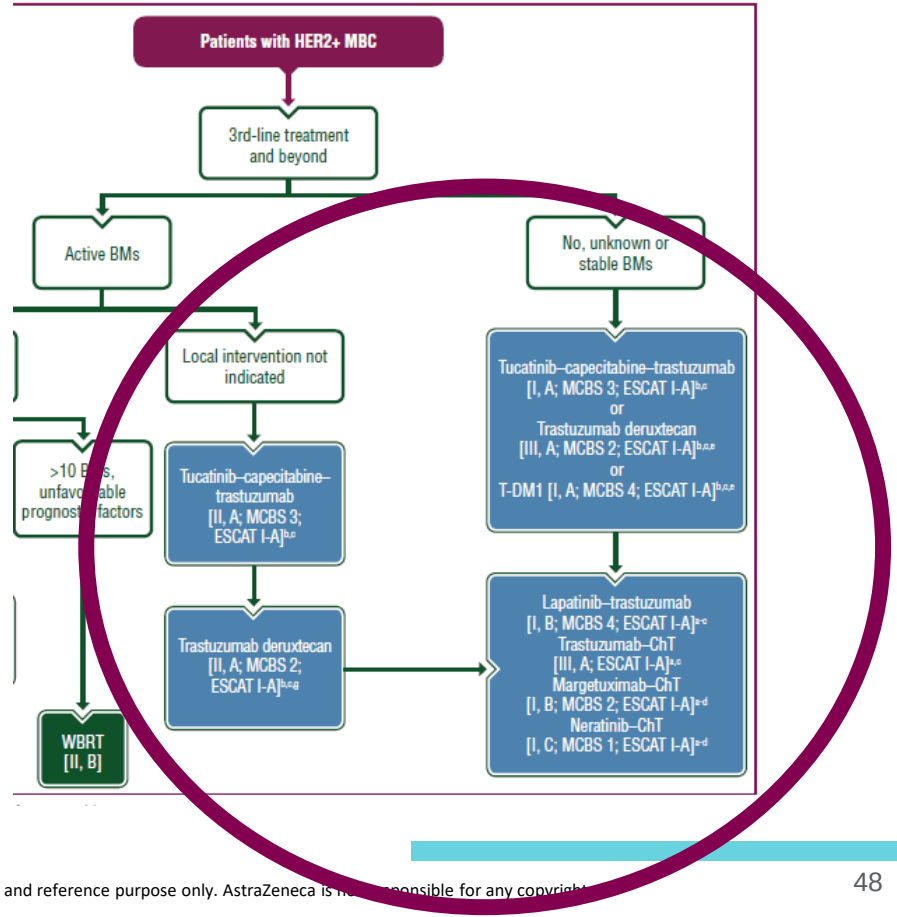
http://ir.macrogenics.com/news-releases/news-release-details/macrogenics-announces-final-overall-survival-results-Sophia.
Accessed 3rd Nov 2022

Guideline recommendations

ESMO 2021 mBC guidelines were adapted to incorporate the novel therapeutic agents in 2nd Line and beyond



2-positive MBC.



AstraZeneca

Gennari A et al. Annals of Oncology. 2021; 32(12):1475-1495

NCCN 2022 mBC guidelines were adapted to incorporate the novel therapeutic agents in 2nd Line and beyond

NCCN Guidelines Recurrent or stage IV disease

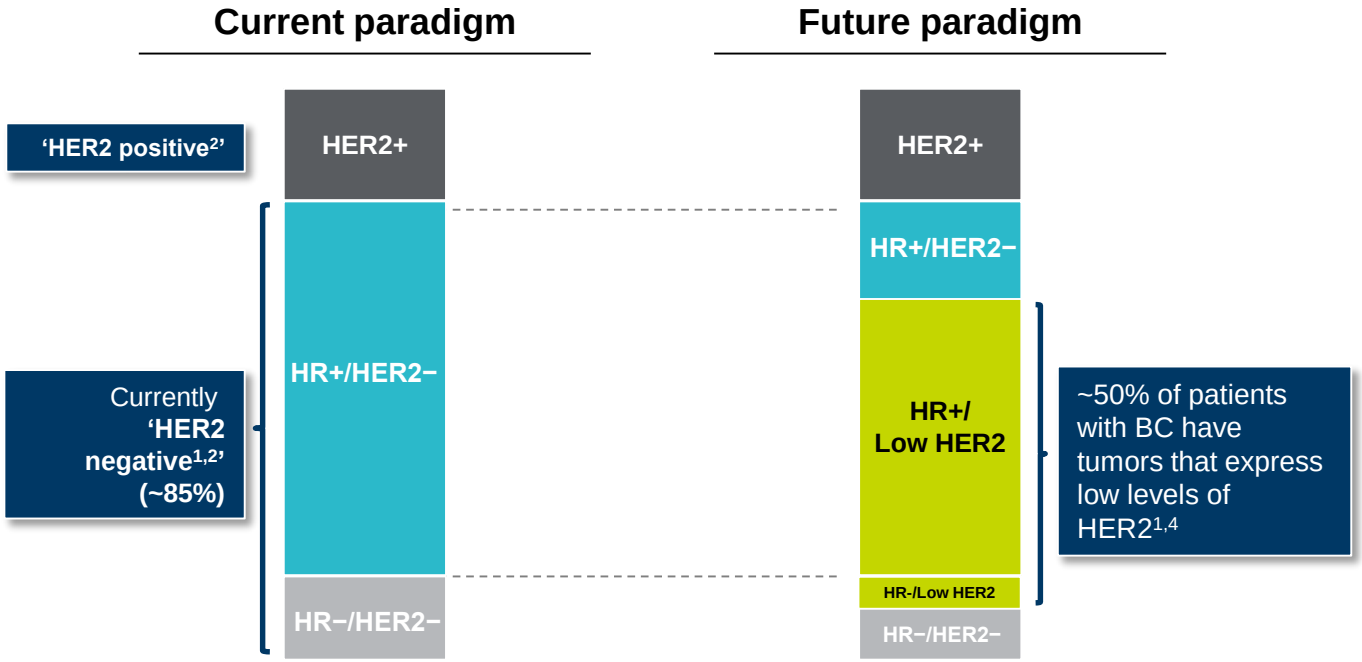
SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[h]

HER2-Positive			
Setting	**Regimen**	**NCCN Category of Preference**	**NCCN Category of Evidence**
First line[i]	Pertuzumab + trastuzumab + docetaxel[k]	Preferred Regimen	1
	Pertuzumab + trastuzumab + paclitaxel[k]	Preferred Regimen	2A
Second line[j]	Fam-trastuzumab deruxtecan-nxki[j,l,m]	Preferred Regimen	1
	Ado-trastuzumab emtansine (T-DM1)[j]	Other Recommended Regimen	2A
Third line and beyond (optimal sequence is not known)	Tucatinib + trastuzumab + capecitabine[k,n]	Other Recommended Regimen[n]	1
	Trastuzumab + docetaxel or vinorelbine[k,o]	Other Recommended Regimen	2A
	Trastuzumab + paclitaxel ± carboplatin[k,o]	Other Recommended Regimen	2A
	Capecitabine + trastuzumab or lapatinib[k,o]	Other Recommended Regimen	2A
	Trastuzumab + lapatinib[k,o] (without cytotoxic therapy)	Other Recommended Regimen	2A
	Trastuzumab + other agents[k,o,p,q]	Other Recommended Regimen	2A
	Neratinib + capecitabine[o]	Other Recommended Regimen	2A
	Margetuximab-cmkb + chemotherapy[o] (capecitabine, eribulin, gemcitabine, or vinorelbine)	Other Recommended Regimen	2A

Future Considerations: HER2 Low mBC

Over half of breast cancers currently categorized as HER2 negative express low levels of HER2, which may be clinically meaningful[1]

Guidelines recommend assessment of HER2 status in all newly diagnosed patients with BC and those patients who develop metastatic disease[3]



1. Tarantino P, et al. *J Clin Oncol.* 2020;38(17):1951-1962; 2. Burstein HJ. *N Engl J Med*. 2005;353(16):1652-1654; 3. Wolff AC, et al. *J Clin Oncol.* 2018;36(20):2105-2122. 4. Marchiò C, et al. *Semin Cancer Biol*. 2021;72:123-135

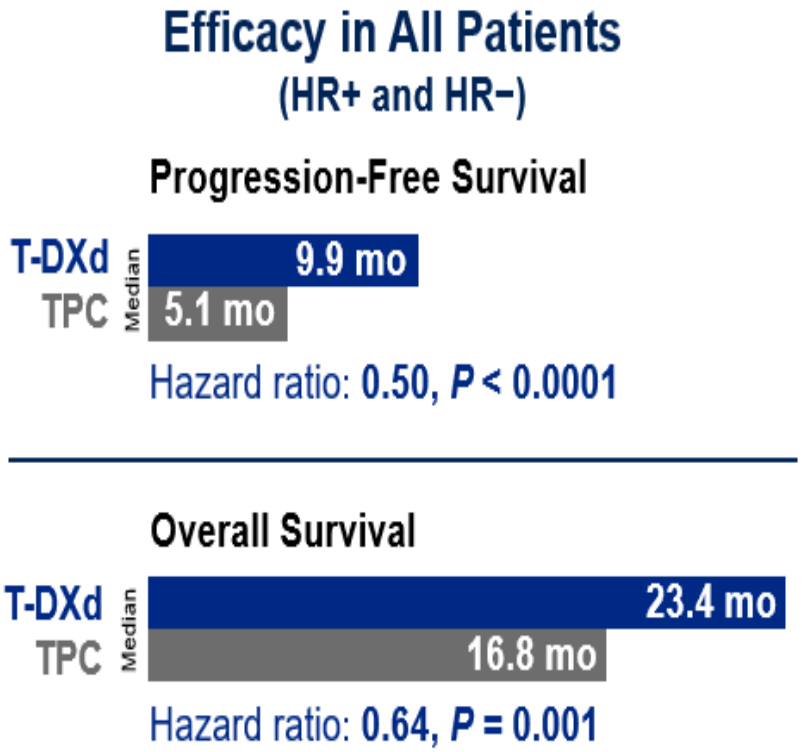
HER2 low: expanding the horizon of HER2 positivity in breast cancer

IHC scores of 1+ or 2+/ISH negative constitutes of HER2 low disease.

HER2 low is a heterogenous population with a high prevalence of HR co-expression and without a distinct biology

HER2-low mBC is treated as HER2− mBC, with limited options for later lines of therapy

T-DXd is the first HER2-targeted therapy to demonstrate improved efficacy in HER2-low mBC



1. Schettini F, et al. *NPJ Breast Cancer*. 2021;7(1):1. 2. Tarantino P, et al. *J Clin Oncol*. 2020;38(17):1951-1962. 3. Aogi K, et al. *Ann Oncol.* 2012;23:1441-1448. 4. Eiger D, et al. *Cancers (Basel).* 2021;13(5):1015. 5. Fehrenbacher L, et al. *J Clin Oncol.* 2019;38(5):444-453

Take home messages

- The evolving treatment paradigm for HER2 positive advanced BC includes **THP followed by T-DM1 after progression as a SOC for initial treatment**, with **multiple 3L options** now available[1-3]

- **mPFS drops numerically by half between 1L THP and 2L T-DM1** treatment settings demonstrating that more effective treatment options that further delay progression and extend survival are needed in the 2L[4,5]

- Major therapeutic improvements have occurred in the recent past challenging the current standard treatment protocols. HER2 directed ADC's & tyrosine kinase inhibitors demonstrate a prominent role in advanced breast cancers. However, the optimal sequence of available HER2-targeted therapies is currently unknown.

- DESTINY-Breast04 demonstrates that **T-DXd** has the potential to improve the treatment outcomes of **HER2-low, HR+/HR− mBC.** T-DXd is the first **HER2-targeted therapy** to demonstrate statistically significant and clinically **meaningful improvement in PFS and OS versus TPC**

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2. Cardoso F, et al. *Ann Oncol*. 2020;31(12):1623-1649. **3.** Shimoi T, et al. *Breast Cancer.* 2020;27(3):322-331. **4**. Verma S, et al. *N Engl J Med*. 2012;367(19):1783-1791. **5**. Baselga J, et al. *N Engl J Med*. 2012;366(2):109-119 .