Journal Club

Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer

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ORIGINAL ARTICLE

Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer

J. Cortés, S.-B. Kim, W.-P. Chung, S.-A. Im, Y.H. Park, R. Hegg, M.H. Kim, L.-M. Tseng, V. Petry, C.-F. Chung, H. Iwata, E. Hamilton, G. Curigliano, B. Xu, C.-S. Huang, J.H. Kim, J.W.Y. Chiu, J.L. Pedrini, C. Lee, Y. Liu, J. Cathcart, E. Bako, S. Verma, and S.A. Hurvitz, for the DESTINY-Breast03 Trial Investigators*

Outline

01

Background

Overview of Breast cancer

1st — Cause of cancer death in women

0.052% — Prevalence in Taiwan

TNM — System to characterize

15-20% — Proportion of breast cancer

Poor — Prognosis before mAb

2012-2018 In the US

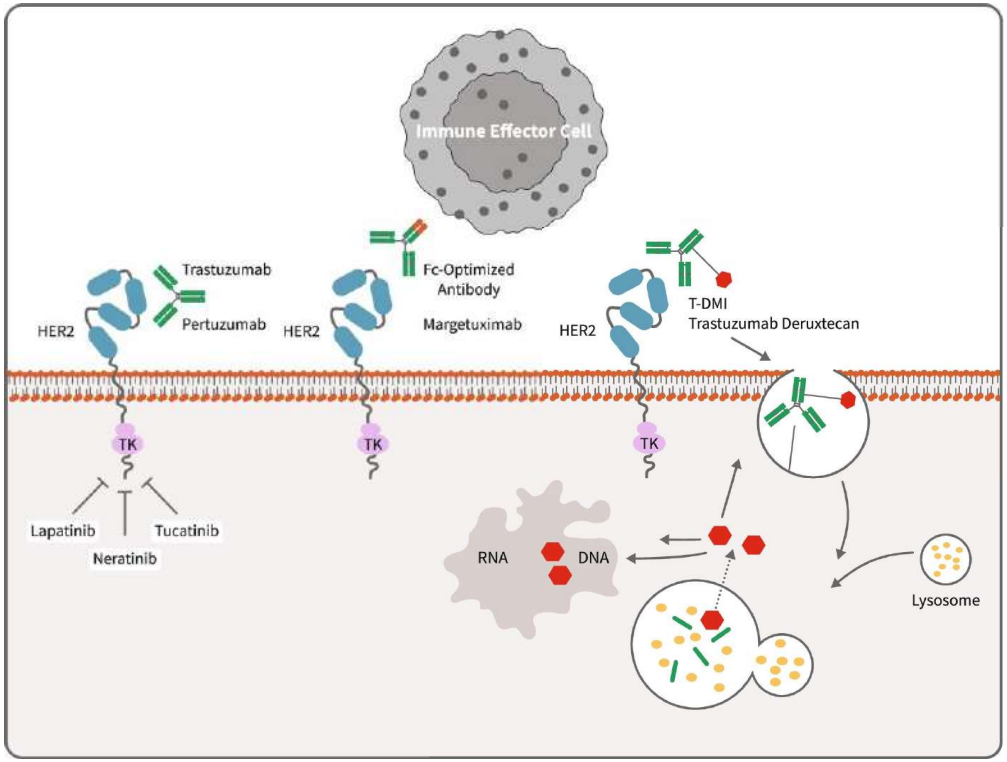
5-year survival

90.7% — HR(+) HER2(+)

84.8% — HR(-) HER2(+)

HER2(+)-Breast cancer

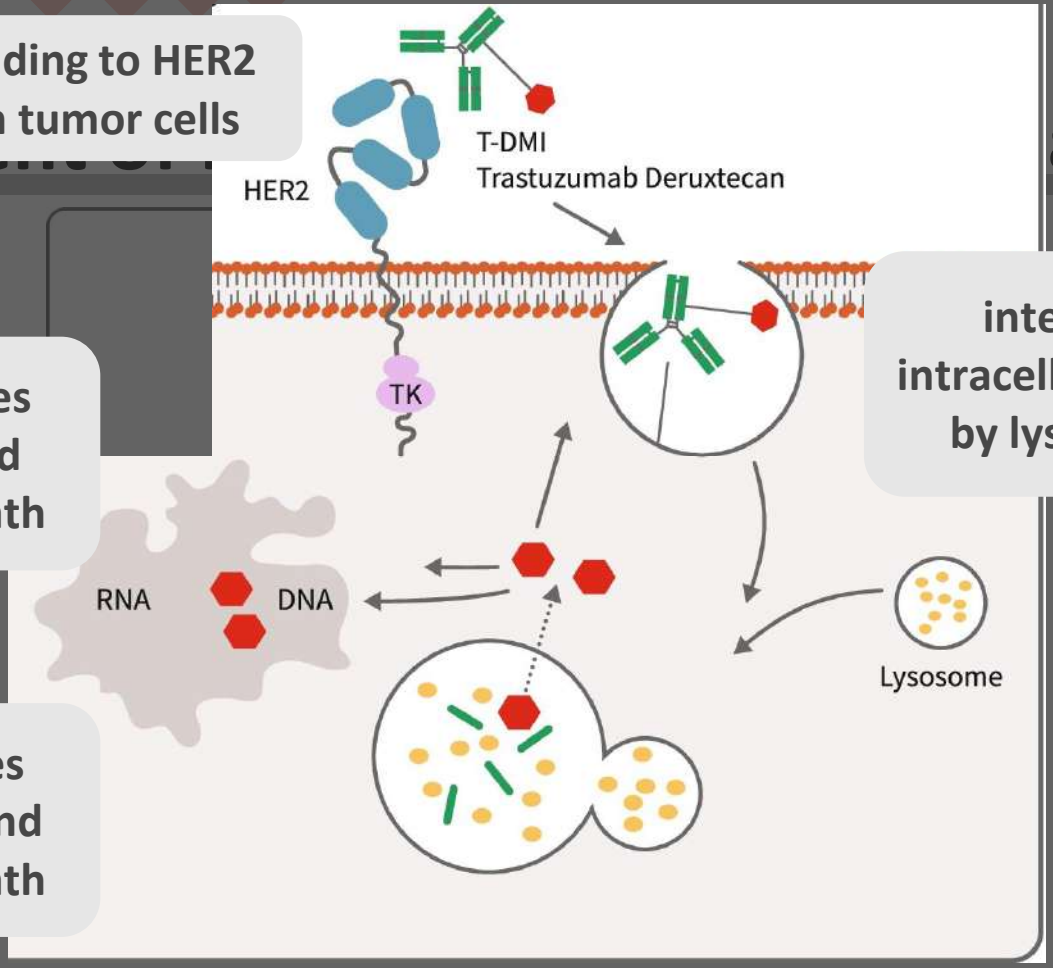
Treatment of HER2 – positive breast cancer



Wynn, C. S. and S.-C. Tang (2022). "Anti-HER2 therapy in metastatic breast cancer: many choices and future directions." Cancer and Metastasis Reviews **41**(1): 193-209.

Treatment of [illegible] ancer

binding to HER2 on tumor cells



internalization and intracellular linker cleavage by lysosomal enzymes

deruxtecan causes DNA damage and apoptotic cell death

emtansine causes cell cycle arrest and apoptotic cell death

Wynn, C. S. and S.-C. Tang (2022). "Anti-HER2 therapy in metastatic breast cancer: many choices and future directions." Cancer and Metastasis Reviews **41**(1): 193-209.

Destiny-Breast 01

Open-label, multicenter, phase 2 study

Inclusion criteria :

- ≥18 years old with unresectable or metastatic HER2(+) breast cancer
- Prior use T-DM1
- No history or current ILD/ pneumonitis
- Stable and treated brain metastases were allowed

Baseline characteristics :

- Race : White(54.9%)、Asian(38%)
- HR status : 52.7%(+)、45.1%(-)
- HER2 expression : IHC 3+(83.7%)
- Previous cancer regimen : 6

Safety :

- Interstitial lung disease 13.6%
- Prolonged QT interval 4.9%
- Decreased LVEF 1.6%
- Infusion-related reaction 2.2%

Results :

1st outcome :

- Overall response rate (ORR) = 60.9% (53.4 to 68.0)

2nd outcome :

- Disease controlled rate (DCR) = 97.3% (93.8 to 99.1)
- Median Progression-free survival (PFS) = 16.4 mon (12.7 to NR)
- 12-month Overall Survival (OS) = 86.2% (79.8 to 90.7)

Other :

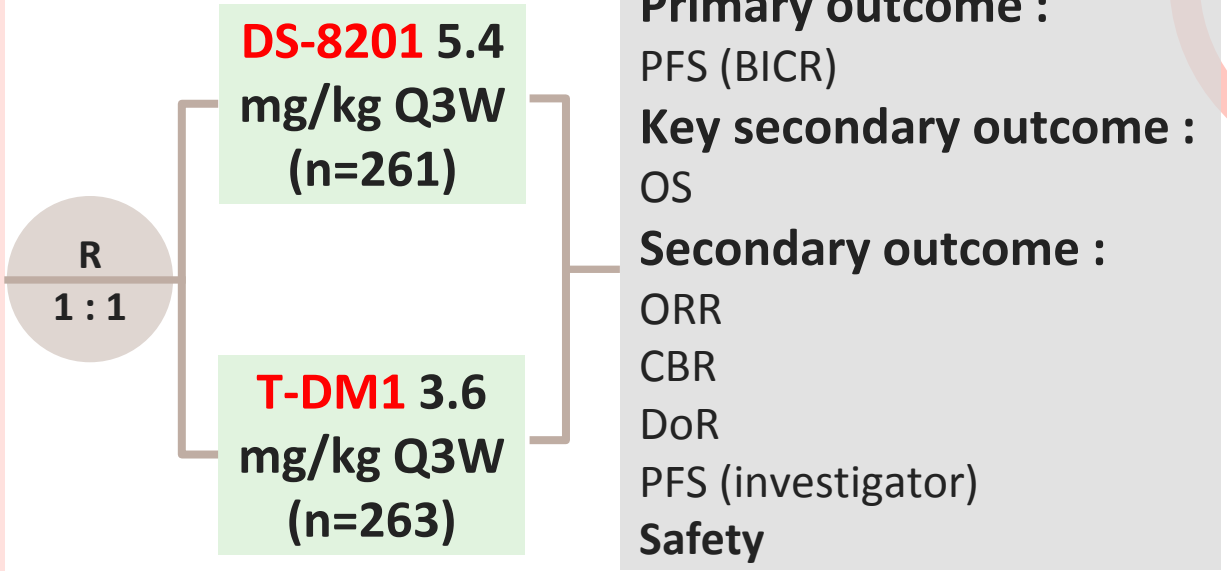
no significant difference of objective response between all subgroup

02

Methods

Inclusion criteria :

- **≥18 y/o with unresectable or metastatic HER2(+) breast cancer**
- **Previously treated with trastuzumab and taxane in the advanced/metastatic setting or progressed in 6 month after treatment**
- Brain metastases patients should be clinically stable and previously treated



Stratification factors :

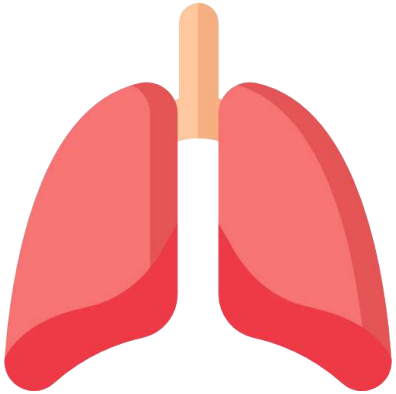
- HR status (+/-)
- Prior use pertuzumab
- History of visceral disease

PFS, Progression-free survival; BICR, Blinded independent central review; OS, overall survival; ORR, objective response rate; CBR, clinical benefit rate; DoR, Duration of response.

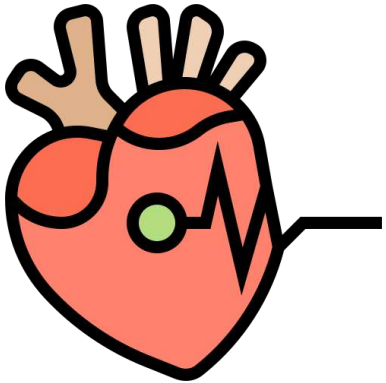
Statistical Analysis

- **ITT** Analysis
- **α = 0.05**
- **PFS & OS :** Kaplan-Meier estimates
- **ORR & CBR :** Cochran-Mantel-Haenszel tests
- **hazard ratio (HR) :** Cox proportional hazards regression model

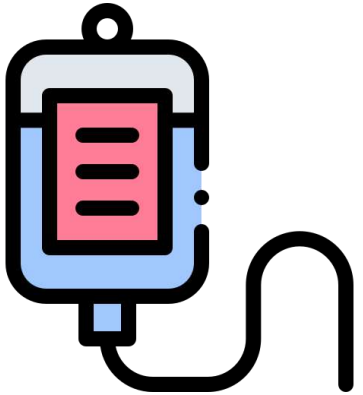
Adverse Events of Special Interest



Interstitial Lung Disease/ Pneumonitis

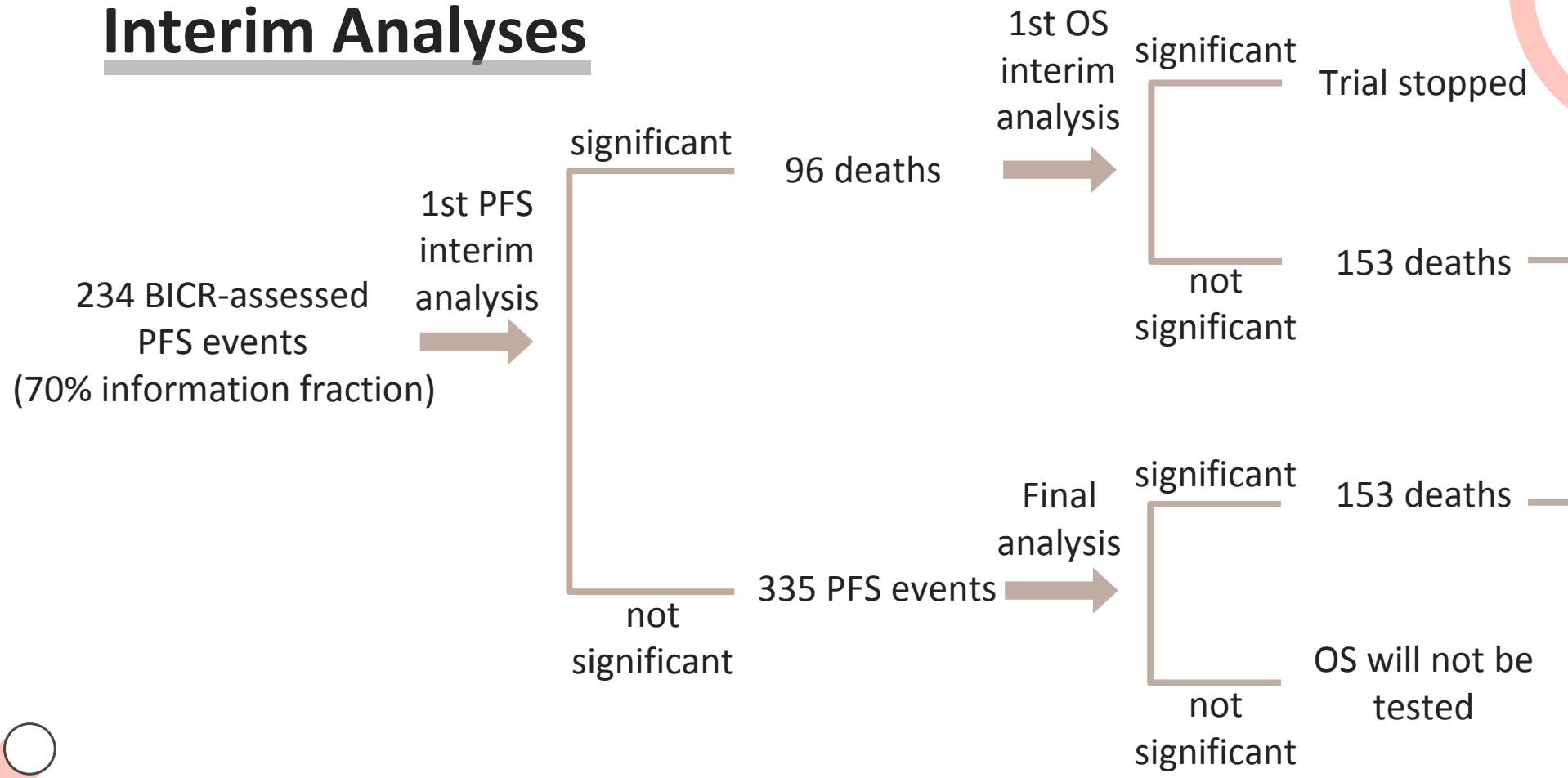


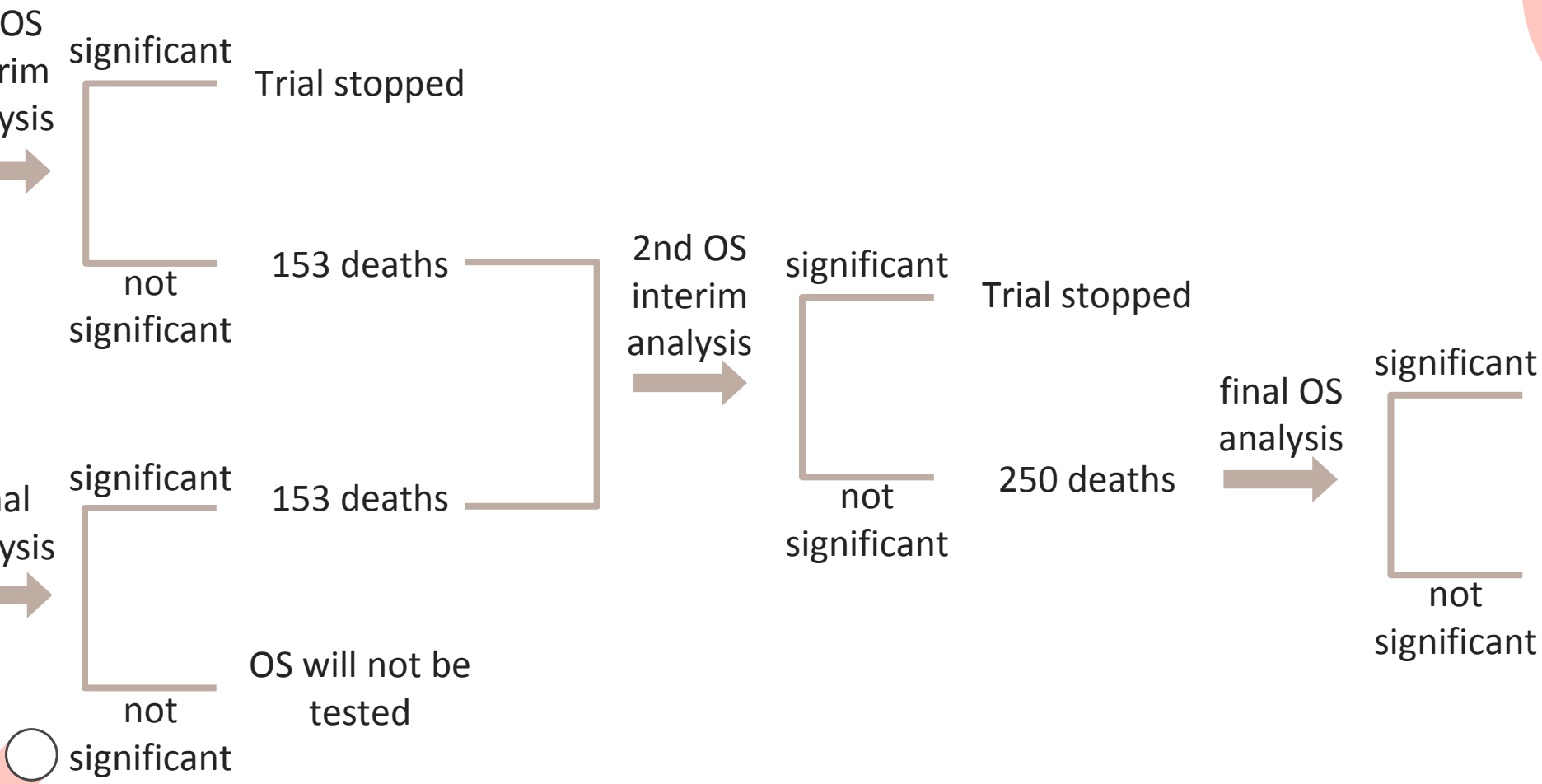
Cardiotoxicity



Infusion Related Reactions

Interim Analyses

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2nd OS
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OS will not be
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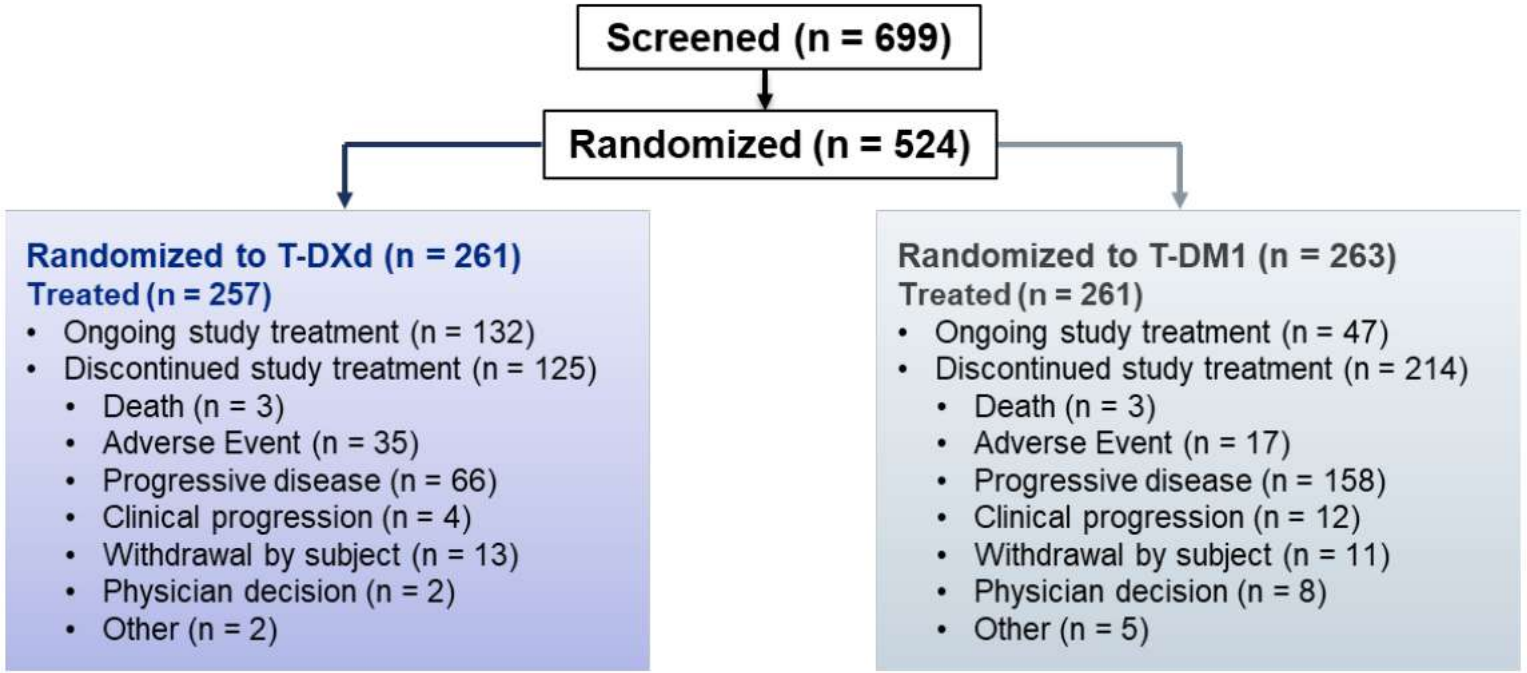
03

Results

Trial profile



Baseline Clinical Characteristics

Characteristic	Trastuzumab Deruxtecan (N=261)	Trastuzumab Emtansine (N=263)
Median age (range) — yr	54.3 (27.9–83.1)	54.2 (20.2–83.0)
Geographic region — no. (%)		
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 — no. (%)†		
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)

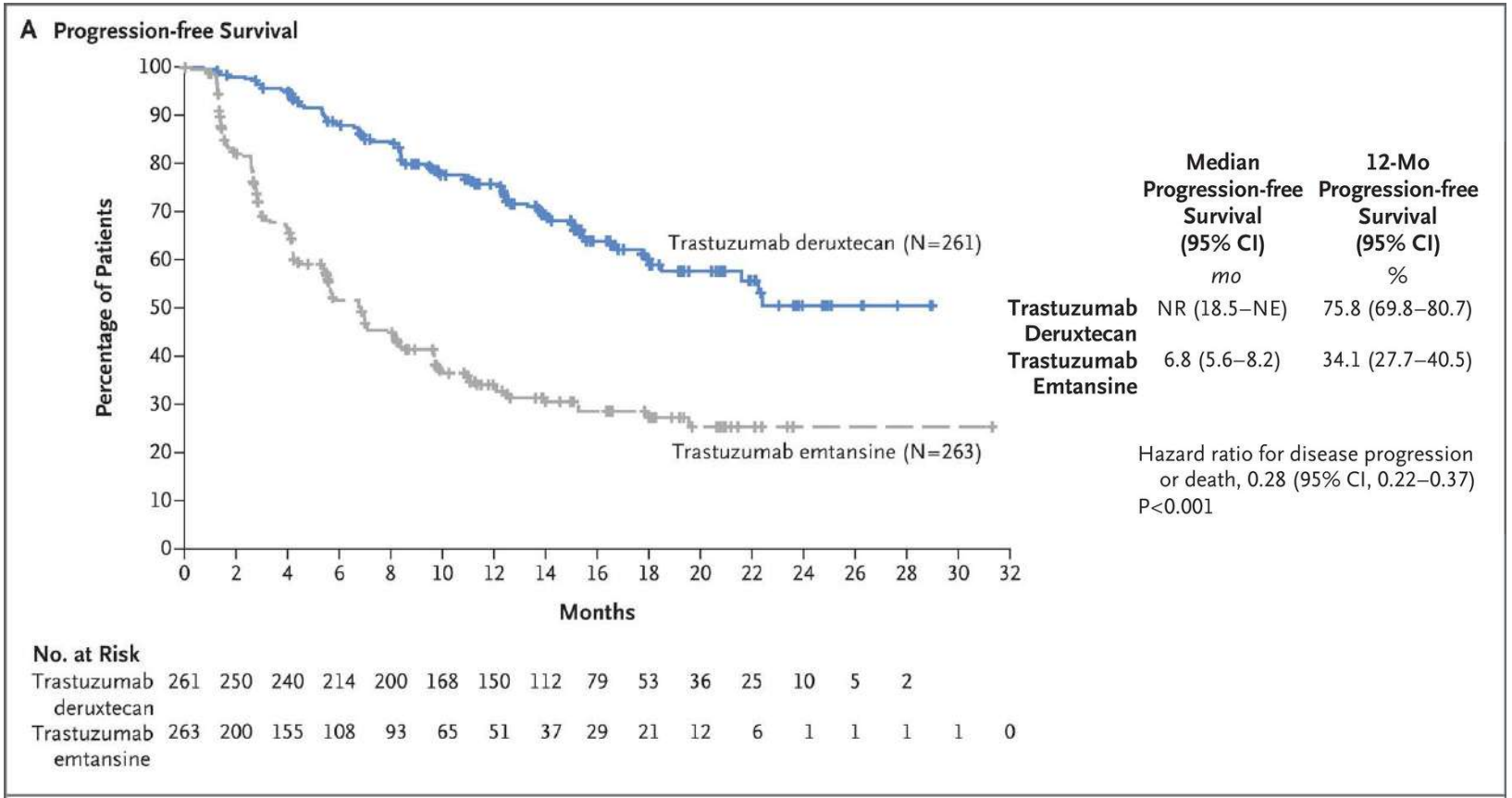
Baseline Clinical Characteristics

Characteristic	Trastuzumab Deruxtecan (N=261)	Trastuzumab Emtansine (N=263)
HER2 status — no. (%)‡		
3+	234 (89.7)	232 (88.2)
2+ with HER2 ISH-positive	25 (9.6)	30 (11.4)
1+	1 (0.4)	0
ECOG performance-status score — no. (%)§		
0	154 (59.0)	175 (66.5)
1	106 (40.6)	87 (33.1)
Hormone-receptor status — no. (%)		
Positive	131 (50.2)	134 (51.0)
Negative	130 (49.8)	129 (49.0)
Stable brain metastases — no. (%)¶	62 (23.8)	52 (19.8)
Visceral disease — no. (%)	184 (70.5)	185 (70.3)

Baseline Clinical Characteristics

Characteristic	Trastuzumab Deruxtecan (N=261)	Trastuzumab Emtansine (N=263)
Previous treatment for metastatic breast cancer — no. (%)	240 (92.0)	234 (89.0)
Lines of previous therapy in the context of metastatic disease‖		
Median number of lines (range)	1 (0–16)	2 (0–14)
Number of lines — no. (%)		
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 — no. (%)**		
Trastuzumab	260 (99.6)	262 (99.6)
Pertuzumab	162 (62.1)	158 (60.1)

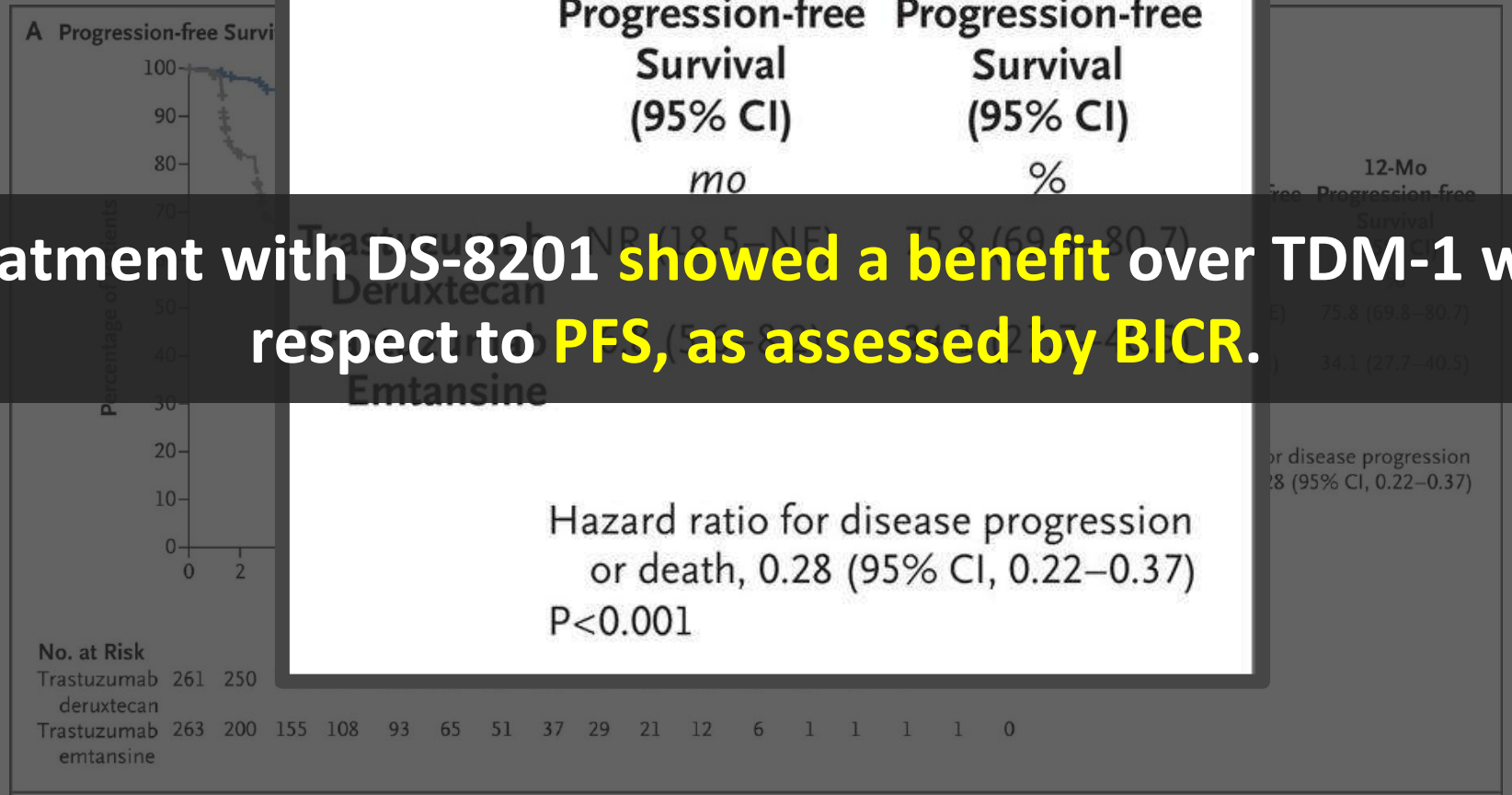
Kaplan–Meier estimates of PFS



	Median Progression-free Survival (95% CI)	12-Mo Progression-free Survival (95% CI)
	mo	%
Trastuzumab Deruxtecan	NR (18.5–NE)	75.8 (69.8–80.7)
Trastuzumab Emtansine	6.8 (5.6–8.2)	34.1 (27.7–40.5)

Hazard ratio for disease progression or death, 0.28 (95% CI, 0.22–0.37)
P<0.001

Kaplan–M



Median Progression-free Survival (95% CI)	12-Mo Progression-free Survival (95% CI)
mo	%
NR (18.5–NE)	75.8 (69.8–80.7)

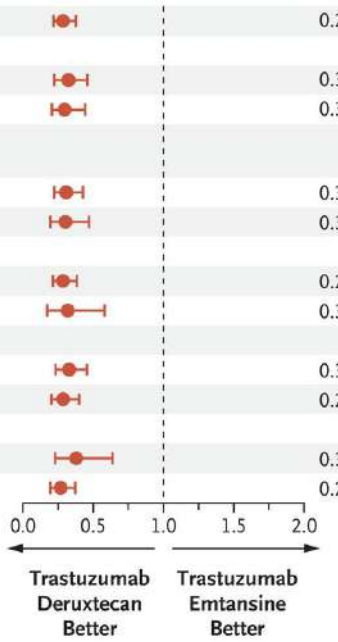
Hazard ratio for disease progression or death, 0.28 (95% CI, 0.22–0.37)
P<0.001

Treatment with DS-8201 showed a benefit over TDM-1 with respect to PFS, as assessed by BICR.

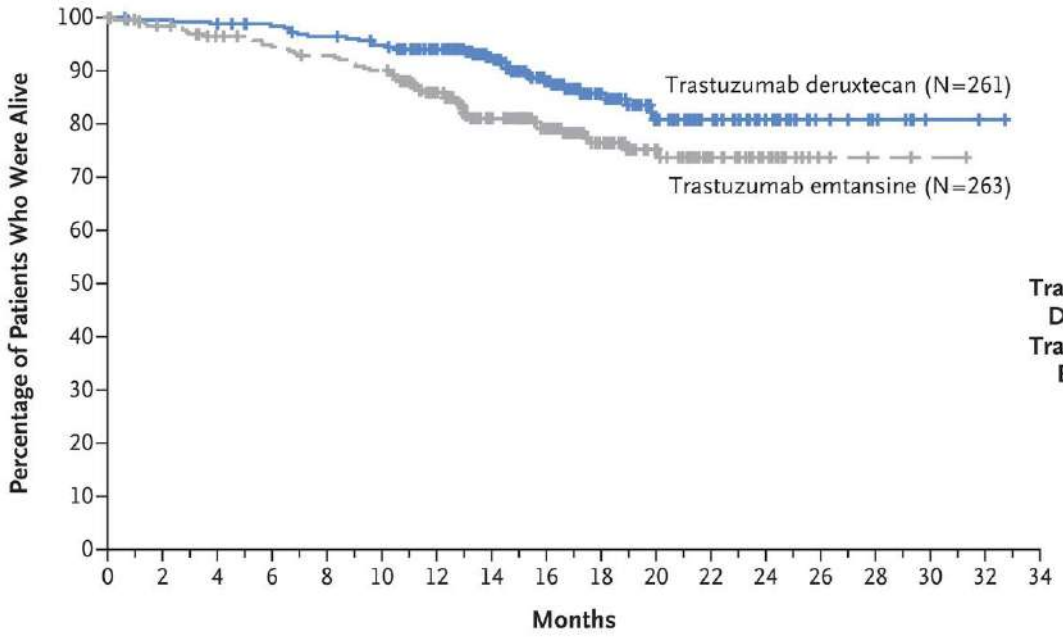
PFS in Prespecified Subgroups

B Progression-free Survival in Prespecified Subgroups

Subgroup	No. of Patients	No. of Events/No. of Patients		Median Progression-free Survival (95% CI)		Hazard Ratio for Disease Progression or Death (95% CI)
				mo		
		Trastuzumab deruxtecan	Trastuzumab emtansine	Trastuzumab deruxtecan	Trastuzumab emtansine	
All patients		87/261	158/263	NE (18.5–NE)	6.8 (5.6–8.2)	0.28 (0.22–0.37)
Hormone-receptor status						
Positive	272	46/133	84/139	22.4 (17.7–NE)	6.9 (4.2–9.8)	0.32 (0.22–0.46)
Negative	248	41/126	73/122	NE (18.0–NE)	6.8 (5.4–8.3)	0.30 (0.20–0.44)
Previous pertuzumab treatment						
Yes	320	57/162	98/158	NE (18.5–NE)	6.8 (5.4–8.3)	0.30 (0.22–0.43)
No	204	30/99	60/105	NE (16.5–NE)	7.0 (4.2–9.7)	0.30 (0.19–0.47)
Visceral disease						
Yes	384	72/195	123/189	22.2 (16.5–NE)	5.7 (4.2–7.0)	0.28 (0.21–0.38)
No	140	15/66	35/74	NE (NE–NE)	11.3 (6.8–NE)	0.32 (0.17–0.58)
Lines of previous therapy						
0 or 1	258	46/132	75/126	22.4 (17.9–NE)	8.0 (5.7–9.7)	0.33 (0.23–0.48)
≥2	266	41/129	83/137	NE (16.8–NE)	5.6 (4.2–7.1)	0.28 (0.19–0.41)
Stable brain metastases						
Yes	114	31/62	31/52	15.0 (12.6–22.2)	5.7 (2.9–7.1)	0.38 (0.23–0.64)
No	410	56/199	127/211	NE (22.4–NE)	7.0 (5.5–9.7)	0.27 (0.19–0.37)



Kaplan–Meier estimates of OS



	Median Overall Survival (95% CI)	12-Mo Overall Survival (95% CI)
	mo	%
Trastuzumab Deruxtecan	NE (NE–NE)	94.1 (90.3–96.4)
Trastuzumab Emtansine	NE (NE–NE)	85.9 (80.9–89.7)

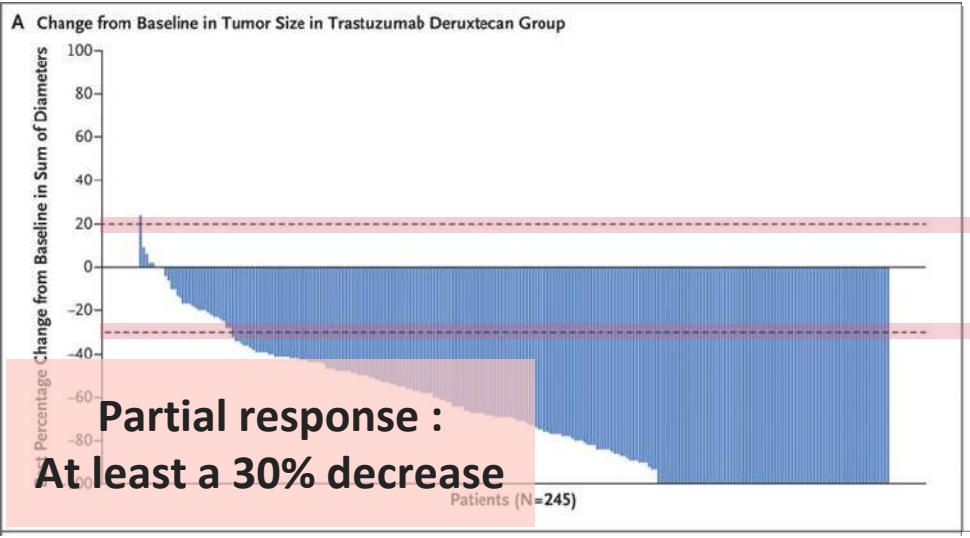
Hazard ratio for death, 0.55 (95% CI, 0.36–0.86)
P=0.007

No. at Risk																			
Trastuzumab deruxtecan	261	256	254	249	243	237	218	180	133	86	56	42	24	11	7	6	2	2	1	0
Trastuzumab emtansine	263	253	243	236	231	224	188	151	120	75	52	32	18	5	3	3	1	1	0	

Response rate

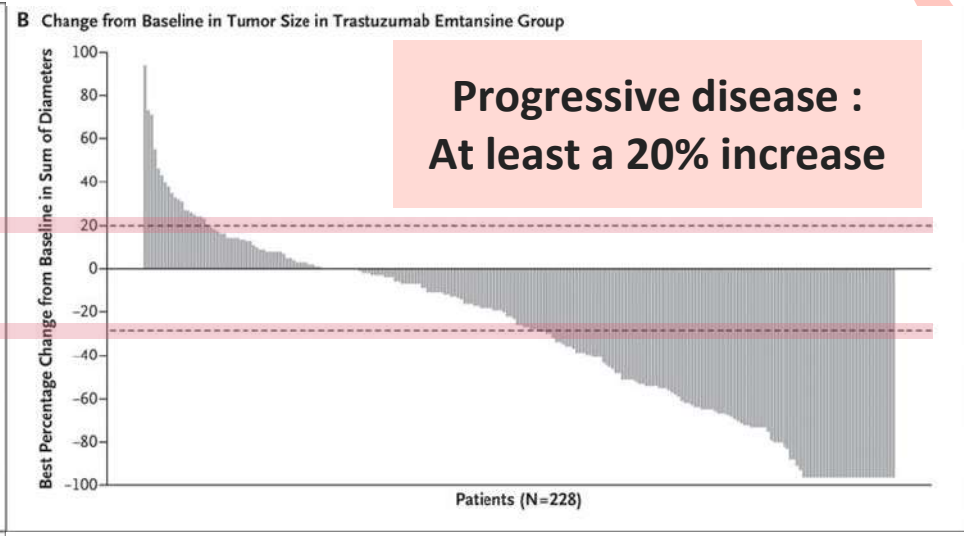
Response Assessment by Independent Central Review	Trastuzumab Deruxtecan (n = 261)	Trastuzumab Emtansine (n = 263)
Confirmed objective response, n (%) [95% CI]	208 (79.7) [74.3–84.4]	90 (34.2) [28.5–40.3]
	P<0.0001	
Complete response, n (%)	42 (16.1)	23 (8.7)
Partial response, n (%)	166 (63.6)	67 (25.5)
Stable disease, n (%)	44 (16.9)	112 (42.6)
Progressive disease, n (%)	3 (1.1)	46 (17.5)
Not evaluable, n (%)	6 (2.3)	15 (5.7)
Disease control rate, n %	252 (96.6)	202 (76.8)
Median time to first complete or partial response, months (range)	1.64 (1.1–17.1)	1.43 (1.2–9.5)

DS-8201 group



Partial response :
At least a 30% decrease

T-DM1 group



Progressive disease :
At least a 20% increase

Overall response rate : DS-8201 (79.7%) to T-DM1 (34.2%)
Complete response rate : DS-8201 (16.1%) to T-DM1 (8.7%)

Post-study anticancer treatment

Patients,[a] n (%)	Trastuzumab Deruxtecan (n = 261)	Trastuzumab Emtansine (n = 263)
Post anticancer systemic treatment		
Trastuzumab	23 (8.8)	66 (25.1)
Trastuzumab deruxtecan	0	30 (11.4)
Trastuzumab emtansine	43 (16.5)	17 (6.5)
Pertuzumab	11 (4.2)	25 (9.5)
Taxane	5 (1.9)	16 (6.1)
Taxane & trastuzumab	3 (1.1)	15 (5.7)
Other anti-HER2	16 (6.1)	73 (27.8)
Anti-HER2 TKI	13 (5.0)	66 (25.1)
Other anti-HER2 antibody or ADC	3 (1.1)	13 (4.9)
Hormone therapy	13 (5.0)	21 (8.0)
Other systemic therapy	40 (15.3)	126 (47.9)

Safety

Table S5. Overall Safety Summary.

Type of Adverse Events, n (%)	Trastuzumab Deruxtecan (n = 257)	Trastuzumab Emtansine (n = 261)
TEAEs	256 (99.6)	249 (95.4)
Grade ≥3	134 (52.1)	126 (48.3)
Drug-related TEAEs	252 (98.1)	226 (86.6)
Grade ≥3	116 (45.1)	104 (39.8)
Serious TEAEs	49 (19.1)	47 (18.0)
Drug-related	28 (10.9)	16 (6.1)
TEAEs associated with dose discontinuations	35 (13.6)	19 (7.3)
Drug-related	33 (12.8)	13 (5.0)
TEAEs associated with dose interruptions	113 (44.0)	61 (23.4)
Drug-related	91 (35.4)	34 (13.0)
TEAEs associated with dose reductions	55 (21.4)	33 (12.6)
Drug-related	55 (21.4)	33 (12.6)
TEAEs associated with deaths	5 (1.9)	5 (1.9)
Drug-related	0	0

TEAE, treatment-emergent adverse event.

Safety

Event	Trastuzumab Deruxtecan (N = 257)		Trastuzumab Emtansine (N = 261)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Most common drug-related adverse events				
Blood and lymphatic system disorders				
Neutropenia*	110 (42.8)	49 (19.1)	29 (11.1)	8 (3.1)
Anemia†	78 (30.4)	15 (5.8)	37 (14.2)	11 (4.2)
Leukopenia‡	77 (30.0)	17 (6.6)	20 (7.7)	1 (0.4)
Thrombocytopenia§	64 (24.9)	18 (7.0)	135 (51.7)	65 (24.9)
Gastrointestinal disorders				
Nausea	187 (72.8)	17 (6.6)	72 (27.6)	1 (0.4)
Vomiting	113 (44.0)	4 (1.6)	15 (5.7)	1 (0.4)
Diarrhea	61 (23.7)	1 (0.4)	10 (3.8)	1 (0.4)
Constipation	58 (22.6)	0	25 (9.6)	0

Safety

Event	Trastuzumab Deruxtecan (N=257)		Trastuzumab Emtansine (N=261)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
General disorders				
Fatigue¶	115 (44.7)	13 (5.1)	77 (29.5)	2 (0.8)
Investigations				
Aspartate aminotransferase increased	60 (23.3)	2 (0.8)	97 (37.2)	13 (5.0)
Alanine aminotransferase increased	50 (19.5)	4 (1.6)	71 (27.2)	12 (4.6)
Metabolism and nutrition disorders				
Decreased appetite	67 (26.1)	3 (1.2)	33 (12.6)	0
Skin and subcutaneous tissue disorders				
Alopecia‖	93 (36.2)	1 (0.4)	6 (2.3)	0
Adjudicated drug-related interstitial lung disease or pneumonitis**	27 (10.5)	2 (0.8)	5 (1.9)	0

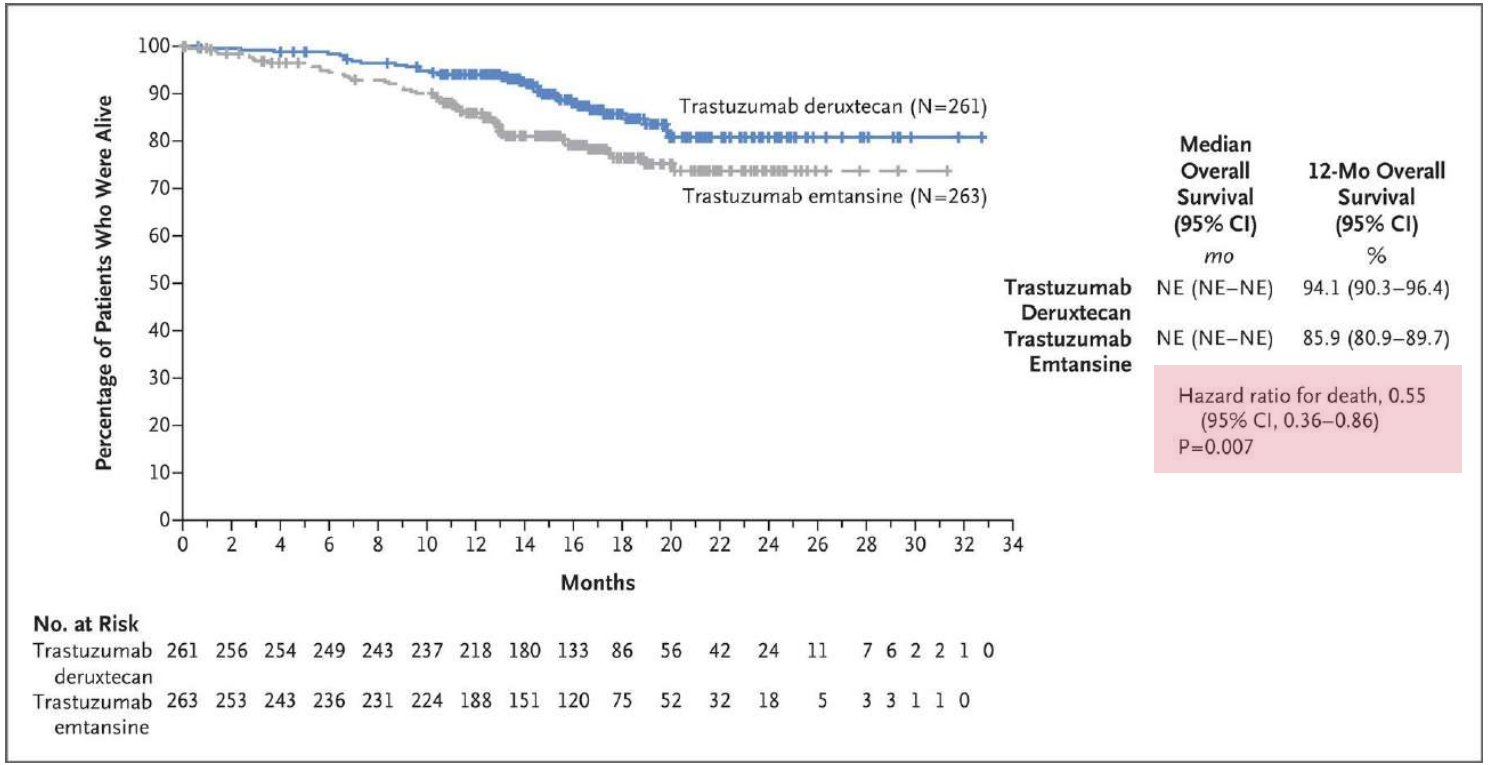
Outcomes of ILD/pneumonitis events

Outcome of the Worst Interstitial Lung Disease/Pneumonitis Event, n (%)[a]	Trastuzumab Deruxtecan (n = 257)	Trastuzumab Emtansine (n = 261)
Fatal	0	1 (20.0)[b]
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

04

Discussion

Trend of overall survival



	Median Overall Survival (95% CI)	12-Mo Overall Survival (95% CI)
	mo	%
Trastuzumab Deruxtecan	NE (NE–NE)	94.1 (90.3–96.4)
Trastuzumab Emtansine	NE (NE–NE)	85.9 (80.9–89.7)

Hazard ratio for death, 0.55 (95% CI, 0.36–0.86)
P=0.007

Impact of previous use of pertuzumab

B Progression-free Survival in Prespecified Subgroups

Subgroup	No. of Patients	No. of Events/No. of Patients		Median Progression-free Survival (95% CI) mo		Hazard Ratio for Disease Progression or Death (95% CI)
		Trastuzumab deruxtecan	Trastuzumab emtansine	Trastuzumab deruxtecan	Trastuzumab emtansine	
All patients		87/261	158/263	NE (18.5–NE)	6.8 (5.6–8.2)	0.28 (0.22–0.37)
Hormone-receptor status						
Positive	272	46/133	84/139	22.4 (17.7–NE)	6.9 (4.2–9.8)	0.32 (0.22–0.46)
Negative	248	41/126	73/122	NE (18.0–NE)	6.8 (5.4–8.3)	0.30 (0.20–0.44)
Previous pertuzumab treatment						
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Visceral disease						
Yes	384	72/195	123/189	22.2 (16.5–NE)	5.7 (4.2–7.0)	0.28 (0.21–0.38)
No	140	15/66	35/74	NE (NE–NE)	11.3 (6.8–NE)	0.32 (0.17–0.58)
Lines of previous therapy						
0 or 1	258	46/132	75/126	22.4 (17.9–NE)	8.0 (5.7–9.7)	0.33 (0.23–0.48)
≥2	266	41/129	83/137	NE (16.8–NE)	5.6 (4.2–7.1)	0.28 (0.19–0.41)
Stable brain metastases						
Yes	114	31/62	31/52	15.0 (12.6–22.2)	5.7 (2.9–7.1)	0.38 (0.23–0.64)
No	410	56/199	127/211	NE (22.4–NE)	7.0 (5.5–9.7)	0.27 (0.19–0.37)

Comparisons with previous trials

	EMILIA trial(2012)	KATE2 trial(2020)	DESTINY-Breast03(2022)
Median PFS	9.6 mon	6.8 mon	6.8 mon
HR	0.65 [0.55,0.77]	0.82 [0.55,1.23]	0.28 [0.22,0.37]
P value	P < 0.001	P = 0.33	P < 0.001

Difference in PFS of T-DM1?

- **CLEOPATRA trial (2015) : dual anti-HER2 therapy in mBC**
- **APHINITY study (2017) : dual anti-HER2 therapy as adjuvant**

Safety

	DESTINY-Breast01(2020)	DESTINY-Breast03(2022)
ILD/pneumonitis	25/184 (13.6%)	27/257 (10.5%)
CV event	12/184 (6.5%)	7/257 (2.7%)

Lower adverse event rate

- earlier line of therapy
- increased recognition of adverse events

Adverse events management

	Prevention	Dose modification		
Infusion-related reaction	Diphenhydramine Initial infusion time from 90 min	Grade 1 or 2 : 50% infusion rate Grade 3 or 4 : DC		
ILD/pneumonitis	sign and symptoms high resolution CT Consult pulmonologist	Grade 1 : interrupt + steroids Grade 2 : DC + steroids		
LVEF reduction	Echo or MUGA scan Q3M	40-45% & ≤10%↓	continue	Reassess 3 weeks later Reuse if recover DC when aggreviate
		40-45% & 10-20%↓	interrupt	
		≤40% or ≥20%↓		
		CHF	DC	

Adverse events management

	Day 1 (before anticancer therapy)	Day 2.3
Moderate emetic risk (30-90%)	5-HT3 RA + Dexamethasone	5-HT3 RA / Dexamethasone
	Olanzapine + Palonosetron + Dexamethasone	Olanzapine
	NK1 RA + 5-HT3 RA + Dexamethasone	Aprepitant + Dexamethasone

Limitations

not distinguish the use of pertuzumab

Some patients received later lines of therapy

The NEW ENGLAND JOURNAL of MEDICINE

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Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer

S. Modi, W. Jacot, T. Yamashita, J. Sohn, M. Vidal, E. Tokunaga, J. Tsurutani, N.T. Ueno, A. Prat, Y.S. Chae, K.S. Lee, N. Niikura, Y.H. Park, B. Xu, X. Wang, M. Gil-Gil, W. Li, J.-Y. Pierga, S.-A. Im, H.C.F. Moore, H.S. Rugo, R. Yerushalmi, F. Zagouri, A. Gombos, S.-B. Kim, Q. Liu, T. Luo, C. Saura, P. Schmid, T. Sun, D. Gambhire, L. Yung, Y. Wang, J. Singh, P. Vitazka, G. Meinhardt, N. Harbeck, and D.A. Cameron, for the DESTINY-Breast04 Trial Investigators*

ABSTRACT

BACKGROUND

Among breast cancers without human epidermal growth factor receptor 2 (HER2) amplification, overexpression, or both, a large proportion express low levels of HER2 that may be targetable. Currently available HER2-directed therapies have been ineffective in patients with these "HER2-low" cancers.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Modi can be contacted at modis@mskcc.org or at the Memorial Sloan Kettering Cancer Center, 1275 York

Current problem?

Treat HER2-low [IHC=1+ or 2+]
As HER2-zero [IHC=0]

What's new?

Therapy of HER2-low

Outcome

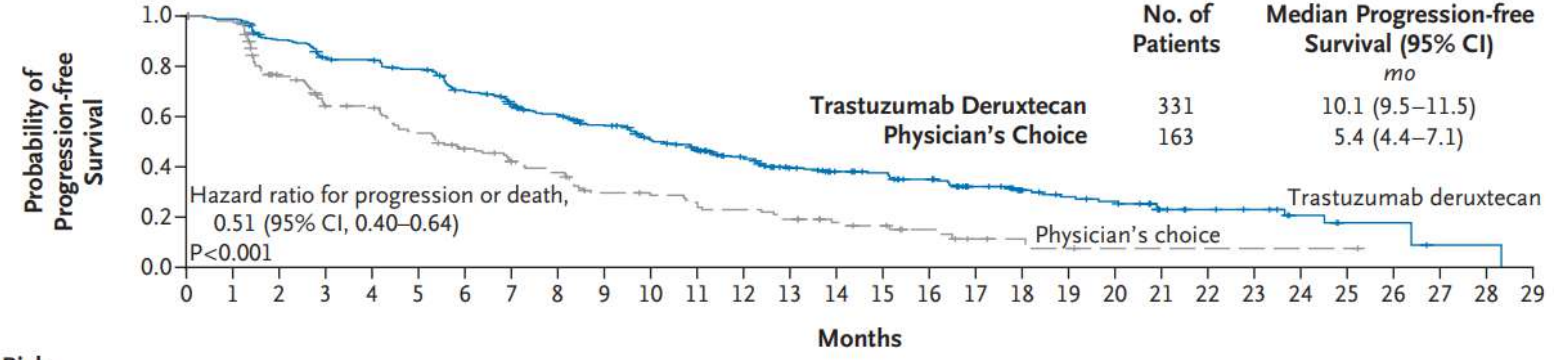
1st : PFS among patients with HR(+) disease
2nd : PFS among all patients and OS in the HR(+)

IHC : immunohistochemistry

Table 2. Overall Efficacy in All Cohorts.*

Variable	Hormone Receptor–Positive Cohort		All Patients		Hormone Receptor–Negative Cohort	
	Trastuzumab Deruxtecan	Physician's Choice of Chemotherapy	Trastuzumab Deruxtecan	Physician's Choice of Chemotherapy	Trastuzumab Deruxtecan	Physician's Choice of Chemotherapy
Progression-free and overall survival						
No. of patients evaluated	331	163	373	184	40	18
Median progression-free survival (95% CI) — mo	10.1 (9.5–11.5)	5.4 (4.4–7.1)	9.9 (9.0–11.3)	5.1 (4.2–6.8)	8.5 (4.3–11.7)	2.9 (1.4–5.1)
Hazard ratio for disease progression or death (95% CI)	0.51 (0.40–0.64)		0.50 (0.40–0.63)		0.46 (0.24–0.89)	
P value	<0.001		<0.001		—	
Median overall survival (95% CI) — mo	23.9 (20.8–24.8)	17.5 (15.2–22.4)	23.4 (20.0–24.8)	16.8 (14.5–20.0)	18.2 (13.6–NE)	8.3 (5.6–20.6)
Hazard ratio for death (95% CI)	0.64 (0.48–0.86)		0.64 (0.49–0.84)		0.48 (0.24–0.95)	
P value	0.003		0.001		—	

A Progression-free Survival in Hormone Receptor–Positive Cohort

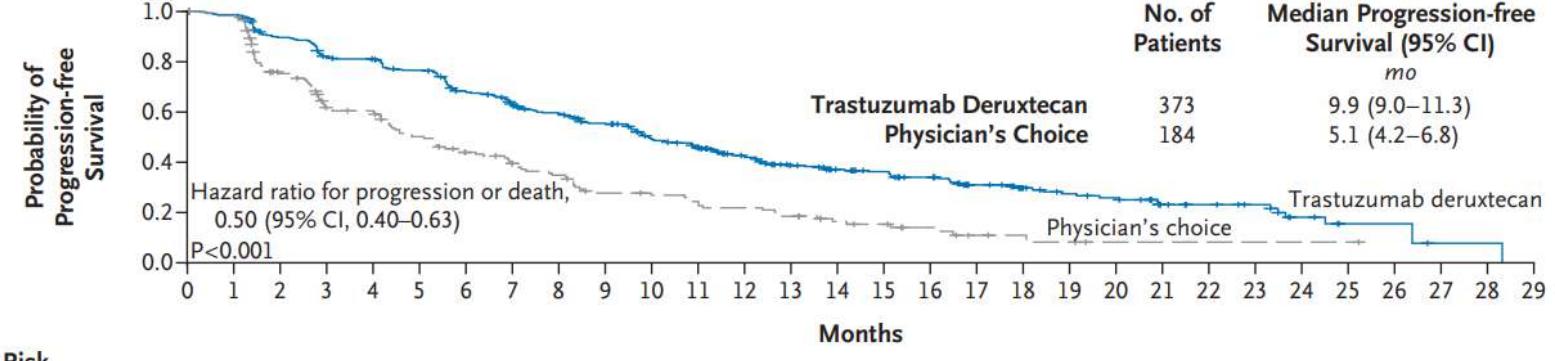


	No. of Patients	Median Progression-free Survival (95% CI) mo
Trastuzumab Deruxtecan	331	10.1 (9.5–11.5)
Physician's Choice	163	5.4 (4.4–7.1)

No. at Risk

Trastuzumab deruxtecan	331	324	290	265	262	248	218	198	182	165	142	128	107	89	78	73	64	48	37	31	28	17	14	12	7	4	4	1	1	0
Physician's choice	163	146	105	85	84	69	57	48	43	32	30	27	24	20	14	12	8	4	3	2	1	1	1	1	1	1	0			

B Progression-free Survival among All Patients

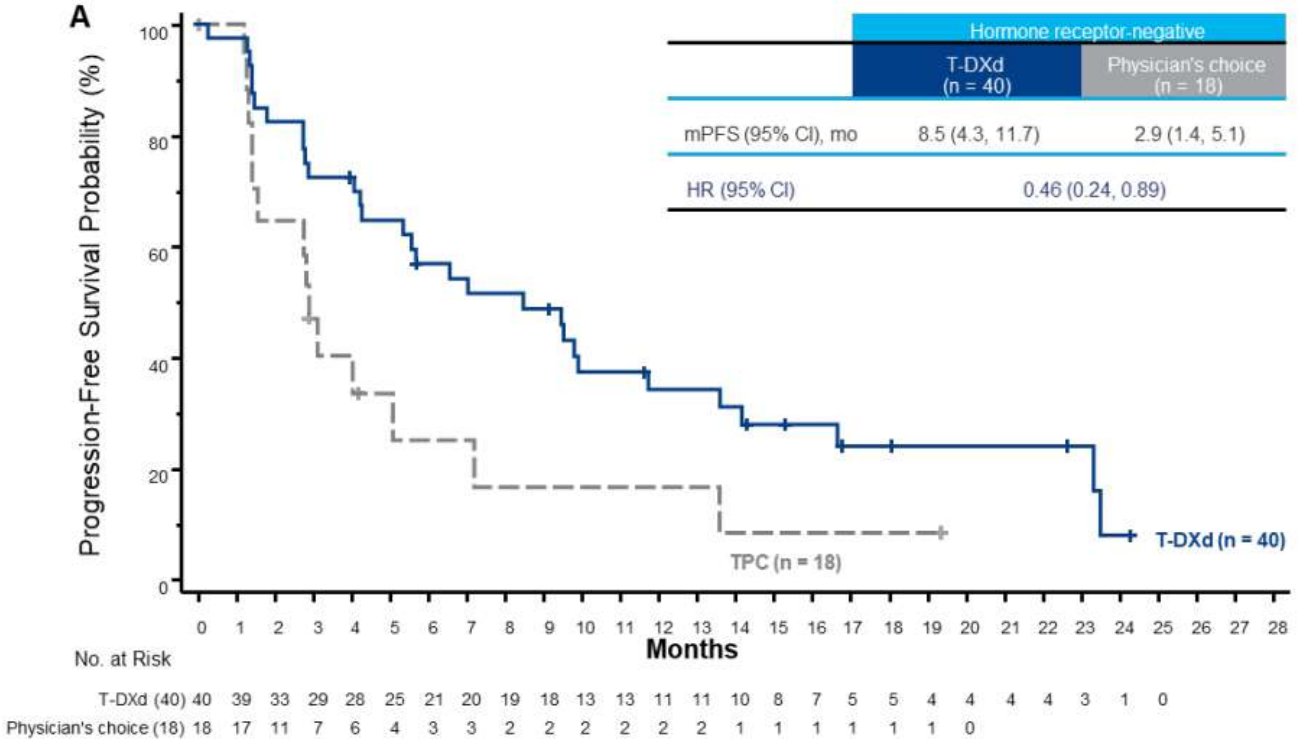


	No. of Patients	Median Progression-free Survival (95% CI) mo
Trastuzumab Deruxtecan	373	9.9 (9.0–11.3)
Physician's Choice	184	5.1 (4.2–6.8)

No. at Risk

Trastuzumab deruxtecan	373	365	325	295	290	272	238	217	201	183	156	142	118	100	88	81	71	53	42	35	32	21	18	15	8	4	4	1	1	0
Physician's choice	184	166	119	93	90	73	60	51	45	34	32	29	26	22	15	13	9	5	4	3	1	1	1	1	1	1	0			

Figure S3. Kaplan–Meier Analysis of Progression-Free Survival and Overall Survival in the Hormone Receptor–Negative Cohort. Panel A shows the Kaplan–Meier analysis of progression-free survival, as assessed by blinded independent central review, in the hormone receptor–negative cohort as derived by the electronic data capture. Panel B shows Kaplan–Meier analysis of overall survival in the hormone receptor–negative cohort as derived by the electronic data capture.



DESTINY-Breast03

	Any Grade	Grade ≥3
		number of pat
Most common drug-related adverse events		
Blood and lymphatic system disorders		
Neutropenia*	110 (42.8)	49 (19.1)
Anemia†	78 (30.4)	15 (5.8)
Leukopenia‡	77 (30.0)	17 (6.6)
Thrombocytopenia§	64 (24.9)	18 (7.0)
Gastrointestinal disorders		
Nausea	187 (72.8)	17 (6.6)
Vomiting	113 (44.0)	4 (1.6)
Diarrhea	61 (23.7)	1 (0.4)
Constipation	58 (22.6)	0
Fatigue¶	115 (44.7)	13 (5.1)
Decreased appetite	67 (26.1)	3 (1.2)
Aspartate aminotransferase increased	60 (23.3)	2 (0.8)
Alanine aminotransferase increased	50 (19.5)	4 (1.6)
Alopecia‖	93 (36.2)	1 (0.4)

DESTINY-Breast04

	All Grades	Grade ≥3
		number of pa
Blood and lymphatic system disorders		
Neutropenia†	123 (33.2)	51 (13.7)
Anemia‡	123 (33.2)	30 (8.1)
Thrombocytopenia§	88 (23.7)	19 (5.1)
Leukopenia¶	86 (23.2)	24 (6.5)
Gastrointestinal disorders		
Nausea	271 (73.0)	17 (4.6)
Vomiting	126 (34.0)	5 (1.3)
Diarrhea	83 (22.4)	4 (1.1)
Constipation	79 (21.3)	0
General disorders: fatigue**	177 (47.7)	28 (7.5)
Metabolism and nutrition disorders: decreased appetite	106 (28.6)	9 (2.4)
Investigations: increased aminotransferase levels‖	87 (23.5)	12 (3.2)
Skin and subcutaneous tissue disorders: alopecia	140 (37.7)	0

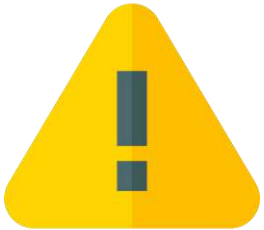
05

Conclusion & clinical benefit

Conclusion

- Stronger efficacy than T-DM1
- Available in earlier line of therapy
- Benefit across all subgroups

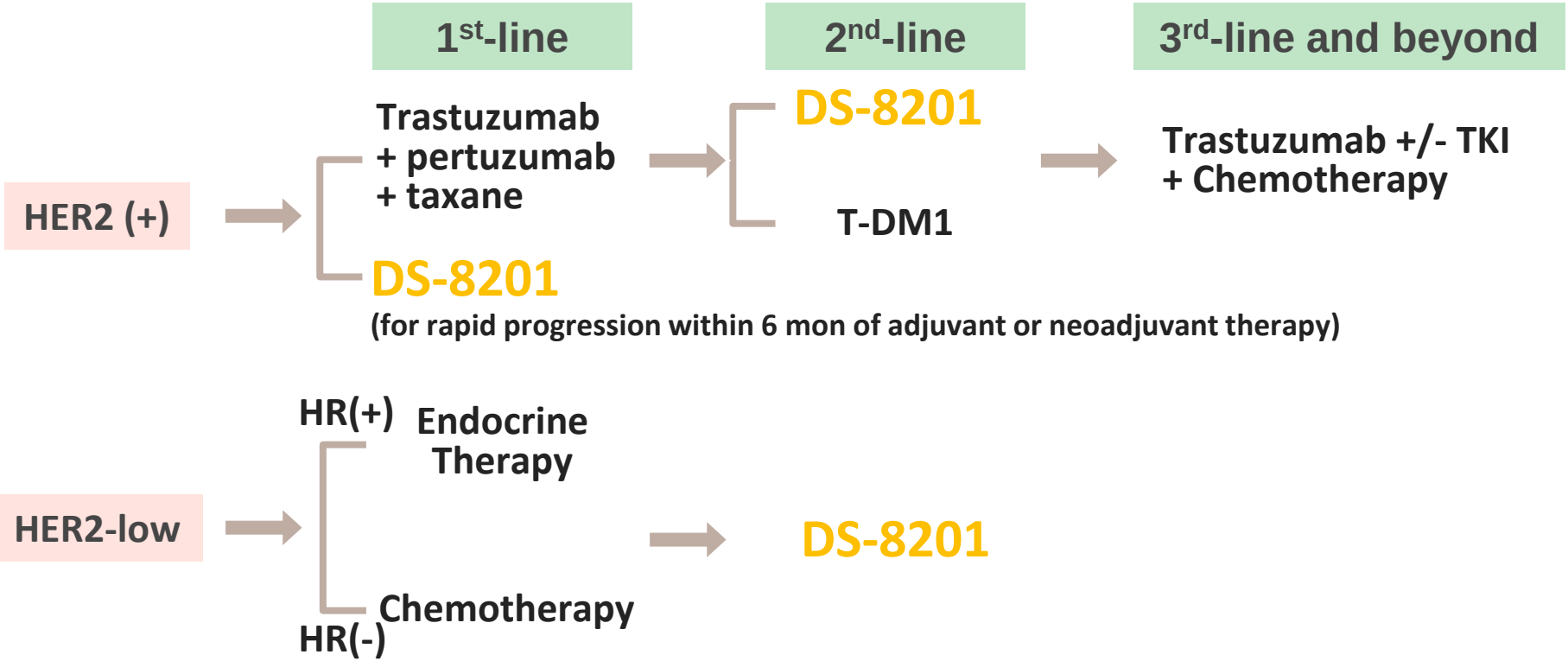
- More adverse events



- Closely monitor sign or symptoms of potential events
- Contraindicated : ILD/pneumonitis

Clinical benefit

Recurrent unresectable or Stage IV (M1) disease



	Trastuzumab deruxtecan (ENHERTU®)	Trastuzumab emtansine (KADCYLA®)
Dosage	➢ Breast cancer : **5.4 mg/kg Q3W** until progression or unacceptable toxicity ➢ Gastric cancer : **6.4 mg/kg Q3W** until progression or unacceptable toxicity.	➢ **3.6 mg/kg given Q3W** until disease progression or unacceptable toxicity ➢ **A total of 14 cycles** for patients with early-stage breast cancer
Warning and precaution	**ILD/pneumonitis**, embryo-fetal harm, neutropenia, Left Ventricular Dysfunction	**ILD/pneumonitis**, embryo-fetal harm, Left Ventricular Dysfunction, Infusion-Related Reactions, Hemorrhage, Thrombocytopenia, Neurotoxicity
Drug-antibody ratio	**8 : 1**	**3.5 : 1**

06

Appraisal

CRITICAL APPRAISAL SKILLS PROGRAMME

CASP

1. Did the study address a clearly focused research question?

METHODS

We conducted a phase 3, multicenter, open-label, randomized trial to compare the efficacy and safety of trastuzumab deruxtecan (a HER2 antibody–drug conjugate) with those of trastuzumab emtansine in patients with HER2-positive metastatic breast cancer previously treated with trastuzumab and a taxane. The primary end point was progression-free survival (as determined by blinded independent central review); secondary end points included overall survival, objective response, and safety.

Yes Can't tell No

2. Was the assignment of participants to interventions randomised?

5.1.2. Method of Treatment Allocation

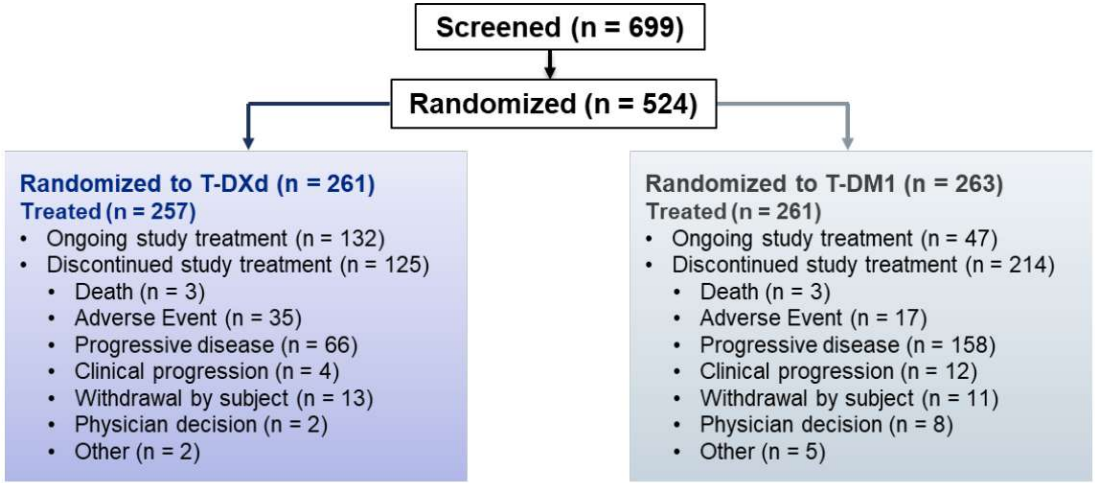
Prior to randomization of a subject, all eligibility criteria must be met and a signed informed consent obtained.

Subjects will be randomized into 1 of the 2 treatment groups (DS-8201a versus T-DM1) in a 1:1 ratio. The randomization will be stratified by hormone receptor status (positive, negative), prior treatment with pertuzumab (yes, no), and history of visceral disease (yes, no). Randomization will be managed through an Interactive Web/Voice Response System (IXRS) for subjects meeting all eligibility criteria. The directions on how to use the system will be provided in the IXRS Quick Reference Manual.

The system will assign a unique SID number and treatment arm for that subject (ie, DS-8201a versus T-DM1).

Yes Can't tell No

3. Were all participants who entered the study accounted for at its conclusion?



-**ITT** Analysis Set

-almost all discontinued treatment participants were **given reasons**

-**Interim analysis** be performed when approximately 70% events have been observed.

Yes Can't tell No

4. Blinding ?

Were the participants ‘blind’ to intervention they were given?

Yes Can’t tell No

Were the investigators ‘blind’ to the intervention they were giving to participants?

Yes Can’t tell No

Were the people assessing/analysing outcome/s ‘blinded’?

Yes Can’t tell No

5.1.3. Blinding

It is not feasible to blind treatment allocations for individual subjects because of different administration protocols and different AE profiles between DS-8201a and T-DM1. The primary endpoint of BICR-assessed PFS is a robust endpoint and bias due to lack of blinding should be minimal. The study team will not perform or have access to efficacy analysis/summary during the study.

An independent biostatistician, not otherwise part of the Sponsor study team, will generate the randomization schedule.

5. Were the study groups similar at the start of the randomised controlled trial?

Table 1. Demographic and Baseline Clinical Characteristics.*

Characteristic	Trastuzumab Deruxtecan (N=261)	Trastuzumab Emtansine (N=263)
Median age (range) — yr	54.3 (27.9–83.1)	54.2 (20.2–83.0)
Geographic region — no. (%)		
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 — no. (%)†		
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 — no. (%)†		
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)
HER2 status — no. (%)‡		
3+	234 (89.7)	232 (88.2)
2+ with HER2 ISH-positive	25 (9.6)	30 (11.4)
1+	1 (0.4)	0
ECOG performance-status score — no. (%)§		
0	154 (59.0)	175 (66.5)
1	106 (40.6)	87 (33.1)
Hormone-receptor status — no. (%)		
Positive	131 (50.2)	134 (51.0)
Negative	130 (49.8)	129 (49.0)
Stable brain metastases — no. (%)¶	62 (23.8)	52 (19.8)
Visceral disease — no. (%)	184 (70.5)	185 (70.3)
Previous treatment for metastatic breast cancer — no. (%)	240 (92.0)	234 (89.0)
Lines of previous therapy in the context of metastatic disease‖		
Median number of lines (range)	1 (0–16)	2 (0–14)
Number of lines — no. (%)		
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 — no. (%)**		
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 tyrosine kinase inhibitor	42 (16.1)	36 (13.7)
Other anti-HER2 antibody or antibody–drug conjugate	2 (0.8)	3 (1.1)
Hormone therapy	109 (41.8)	112 (42.6)
Other systemic therapy	260 (99.6)	262 (99.6)

Yes Can't tell No

6. Apart from the experimental intervention, did each study group receive the same level of care (that is, were they treated equally)?

- Schedule of visits is clearly defined in protocol
- follow-up intervals are equal in two groups

Table 17-2: Schedule of Events – Treatment and Follow-up Period

Visit/Cycle	Cycle 1				Cycle 2		Cycle 3		Cycle 4 and Subsequent Cycles		Q6W	EOT[c]	Follow-up	
Study Day	1		8	15	1		1		1				40-day[b]	LTFU[c]
Window (D)	BI	EOI	±1	±1	BI	EOI	BI	EOI	BI	EOI	±7		+7	±14
Procedures														
HEOR outcomes: EORTC QLQ-C30 & EORTC QLQ-BR45, EQ-5D-5L[d]	X						X		X			X	X	X[e]
Physical Examination	X[f]				X[f]		X[f]		X[f]			X	X	
Weight	X[f]				X[f]		X[f]		X[f]			X	X	
ECOG PS	X[f]				X[f]		X[f]		X[f]			X	X	
AEs	←												→	
Concomitant Medications	←												→	
Hospitalization-related records	←												→	
Vital Signs	X[f]	X	X	X	X[f]	X	X[f]	X	X[f]	X		X	X	
SpO2	X[f]	X	X	X	X[f]	X	X[f]	X	X[f]	X		X	X	
12-lead ECG in triplicate[g]	X				X		X		X			X		
Echo or MUGA (LVEF)									X[h]			X		
Ophthalmologic Assessments					X[fi]				X[fi]			X		
Pregnancy Test (Urine or Serum)[i]	X[f]				X[f]		X[f]		X[f]			X		
Hematology, Chemistry	X[f]		X	X	X[f]		X[f]		X[f]			X	X	
Coagulation[k]												X	X	
Troponin[l]		X				X		X		X				
PK Blood (Serum) Sample	X[m]	X[n,o]			X[m]	X[n]	X[m]	X[n]	X[m]	X[n]				
ADA Blood Sample	X[p]				X[p]				X[p]			X[p]	X[p]	
Serum biomarkers (eg, HER2ECD) Sample							X		X[q]			X		
Visit/Cycle	**Cycle 1**				**Cycle 2**		**Cycle 3**		**Cycle 4 and Subsequent Cycles**		**Q6W**	**EOT[c]**	**Follow-up**	
Study Day	1		8	15	1		1		1				40-day[b]	LTFU[c]
Window (D)	BI	EOI	±1	±1	BI	EOI	BI	EOI	BI	EOI	±7		+7	±14
Exploratory Biomarker Blood Samples	X								X[r]			X		
Pharmacogenomics Blood Sample	X[s]													
Administer Study Treatment[t]		X				X		X		X				
Tumor Assessment (CT/MRI of the chest, abdomen, pelvis, and any other sites of disease)											X	X		
CT/MRI of the Brain[u]											X	X		
Survival Follow-up														X

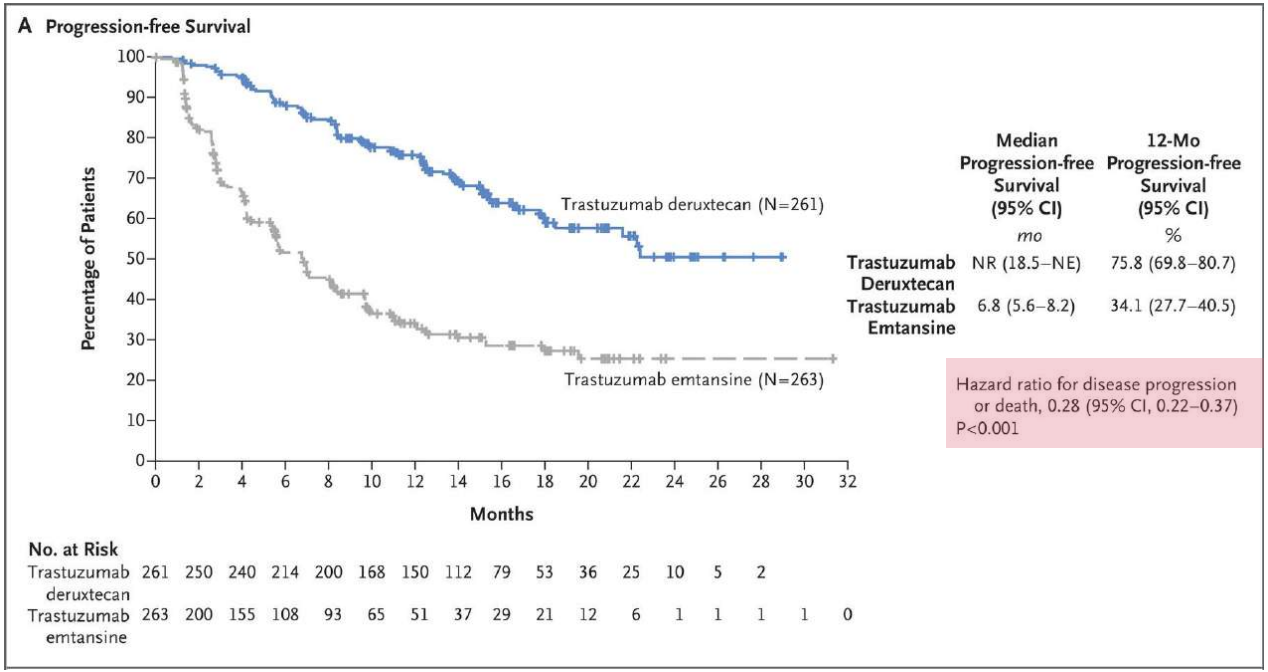
Yes Can't tell No

7. Were the effects of intervention reported comprehensively?

- **90.5% power** and **2-sided significance level of 0.05**
- **p values** were reported
- The PFS and OS will be estimated by **Kaplan-Meier method** for each treatment group.
- **outcomes were clearly specified** and assessed by blinded independent central review(BICR)
- **Hazard ratio (HR) and its 95% CI were estimated**, using stratified Cox proportional hazards regression model stratified by stratification factors.
- Drop-out rate is higher in T-DM1 group than DS-8201 group.

Yes Can't tell No

8. Was the precision of the estimate of the intervention or treatment effect reported?



	Median Progression-free Survival (95% CI)	12-Mo Progression-free Survival (95% CI)
	mo	%
Trastuzumab Deruxtecan	NR (18.5–NE)	75.8 (69.8–80.7)
Trastuzumab Emtansine	6.8 (5.6–8.2)	34.1 (27.7–40.5)

Hazard ratio for disease progression or death, 0.28 (95% CI, 0.22–0.37)
P<0.001

Yes Can't tell No

9. Do the benefits of the experimental intervention outweigh the harms and costs?

- Among patients with HER2-positive metastatic breast cancer previously treated with trastuzumab and a taxane, **hazard ratio** for disease progression or death from any cause was significantly **lower in DS-8201 group**. (HR=0.28, 95% CI, 0.22 to 0.37; P<0.001) The benefit was consistent across all subgroup.

- **More adverse events** happened in DS-8201 group, including blood and lymphatic system disorders, GI disorder, alopecia and drug-related ILD/pneumonitis.

Yes Can't tell No

9. Do the benefits of the experimental intervention outweigh the harms and costs?

- DS-8201 for HER2(+) breast cancer is **not approved Taiwan's National Healthcare insurance**. For example, a 60 kilogram patient without dose adjustment will spend average NTD153450 every 3 weeks.
(每買3瓶即贈1瓶，限符合健保身分及適應症)

- It can also be explained that to **protect 1% more patients** alive with no objective disease progression in 12 month **cost 2024 NTD**.

Yes Can't tell No

9. Do the benefits of the experimental intervention outweigh the harms and costs?

9.87. Trastuzumab emtansine（如 Kadcyla）：(110/2/1)

1. 限單獨使用於 HER2過度表現（IHC3+或 FISH+)之轉移性乳癌患者作為二線治療，且同時符合下列情形：
   (1)之前分別接受過 trastuzumab 與一種 taxane 藥物治療，或其合併療法，或 pertuzumab 與 trastuzumab 與一種 taxane 藥物治療。
   (2)之前已經接受過轉移性癌症治療，或在輔助療法治療期間或完成治療後6個月內癌症復發。
   (3)合併有主要臟器(不包含骨及軟組織)轉移。
2. 經事前審查核准後使用，核准後每12週須檢附療效評估資料再次申請，若疾病有惡化情形即不應再行申請，每位病人至多給付10個月(13個療程為上限)。
3. Trastuzumab emtansine 和 lapatinib 僅能擇一使用，不得互換。

Yes　Can't tell　No

10. Can the results be applied to your local population/in your context?

Table 1. Demographic and Baseline Clinical Characteristics.*

Characteristic	Trastuzumab Deruxtecan (N=261)	Trastuzumab Emtansine (N=263)
Median age (range) — yr	54.3 (27.9–83.1)	54.2 (20.2–83.0)
Geographic region — no. (%)		
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 — no. (%)†		
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 — no. (%)†		
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)
HER2 status — no. (%)‡		
3+	234 (89.7)	232 (88.2)
2+ with HER2 ISH-positive	25 (9.6)	30 (11.4)
1+	1 (0.4)	0
ECOG performance-status score — no. (%)§		
0	154 (59.0)	175 (66.5)
1	106 (40.6)	87 (33.1)

Yes Can't tell No

11. Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?

- Among patients with HER2(+) metastatic breast cancer previously treated with trastuzumab and a taxane, DS-8201 seemed to be numerically more effective than trastuzumab emtansine though it was expensive and not approved by Taiwan's National Healthcare insurance.

- Overall, if patients **can afford the price**, **DS-8201 might be better medication than T-DM1 as an second-line therapy** of HER2(+) metastatic breast cancer.

Yes Can't tell No

Thanks!

Do you have any questions?

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Inclusion criteria :

- **≥18 years old with unresectable or metastatic HER2(+) breast cancer**
- brain metastases patients should be clinically stable and previously treated
- **Previously treated with trastuzumab and taxane in the advanced/ metastatic setting or progressed in 6 month after treatment**

Exclusion criteria :

- **Prior treatment with an HER2-antibody ADC**
- **Uncontrolled CV disease**
- **History, current or can't ruled out noninfectious ILD/pneumonitis**
- **clinically active CNS metastases**

1 : 1 Randomized Interactive Web/Voice Response System (IXRS)

DS-8201 5.4 mg/kg Q3W (n=261)

TDM-1 3.6 mg/kg Q3W (n=263)

Stratification factors :

- HR status (+/-)
- Prior use pertuzumab
- History of visceral disease

Primary outcome :
PFS(Progression-free survival) (BICR)

Key secondary outcome :
OS(overall survival) : the time from the date of randomization to the date of death for any cause.

Secondary outcome :
ORR (objective response rate) : CR rate + PR rate
CBR (clinical benefit rate) : CR rate + PR rate + more than 6 month SD rate
DoR (Duration of response) : the time from the date of the first documentation of objective response (CR or PR) to the date of the first documentation of disease progression
PFS (investigator)

ITT Analysis

α = 0.05

hazard ratio (HR)
Cox proportional hazards regression model

PFS & OS
Kaplan-Meier estimates

ORR & CBR
Cochran-Mantel-Haenszel tests