SABCS 2022 Presentation Materials

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1. **DESTINY-Breast03**
   - Hurvitz, S.A. et al, GS2-02, Oral Presentation
2. **DESTINY-Breast02**
   - Krop, I. et al, GS2-01, Oral Presentation
3. **DESTINY-Breast07**
   - Hamilton E.P. et al, PD18-11, Poster Presentation
4. **BEGONIA (Arm 6)**
   - Schmid, P et al, PD11-08, Poster Presentation

SABCS 2022 Presentation Materials

Dato-DXd

1. **TROPION-PanTumor01 (HR+/ HER2- BC)**
   - Meric-Bernstam, F et al, PD13-08, Poster Presentation
2. **TROPION-PanTumor01 (TNBC)**
   - Bardia, A et al, P6-10-03, Poster Presentation
3. **BEGONIA (Arm 7)**
   - Schmid, P et al, PD11-09, Poster Presentation

Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: Updated results of the randomized, phase 3 study DESTINY-Breast03

Presentation ID: GS2-02

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On behalf of the DESTINY-Breast03 investigators

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Background

Approved treatments for HER2-positive metastatic breast cancer

1L **Trastuzumab + pertuzumab + taxane, CLEOPATRA:** mPFS = 18.7 months[1]

2L+ **T-DM1, EMILIA:** mPFS = 9.6 months[3]

- 1L standard of care was established in the CLEOPATRA trial[1,2]
- EMILIA trial established T-DM1 as 2L+ standard of care[3]

T-DXd in HER2-positive metastatic breast cancer

- Based on the strength of DESTINY-Breast03 efficacy and safety data, T-DXd is considered the **preferred 2L treatment** and T-DM1 is an alternative option[4,5]
  - At the previously reported DESTINY-Breast03 PFS interim analysis (data cutoff, May 21, 2021), in the T-DXd arm, the risk of disease progression or death was reduced by 72%[6]
    - mPFS by BICR was NR with T-DXd vs 6.8 months with T-DM1; HR, 0.28 (95% CI, 0.22-0.37); *P* < 0.001

1L, first-line; 2L, second-line; 2L+, second-line and beyond; BICR, blinded independent central review; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; mPFS, median progression-free survival; NR, not reached; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

1. Swain SM et al. *N Engl J Med.* 2015;372(8):724-734. 2. Perez J et al. *Expert Opin Biol Ther*. 2021;21:811-24. 3. Verma S et al. *N Engl J Med*. 2012;367:1783-91. 4. Gennari A et al. *Ann Oncol.* 2021;32:1475-1495. 5. FDA Press Release. FDA grants regular approval to fam-trastuzumab deruxtecan-nxki for breast cancer. May 4, 2022. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-regular-approval-fam-trastuzumab-deruxtecan-nxki-breast-cancer. 6. Cortes J et al. *N Engl J Med.* 2022;386:1143-1154.

Updated OS Analysis of DESTINY-Breast03

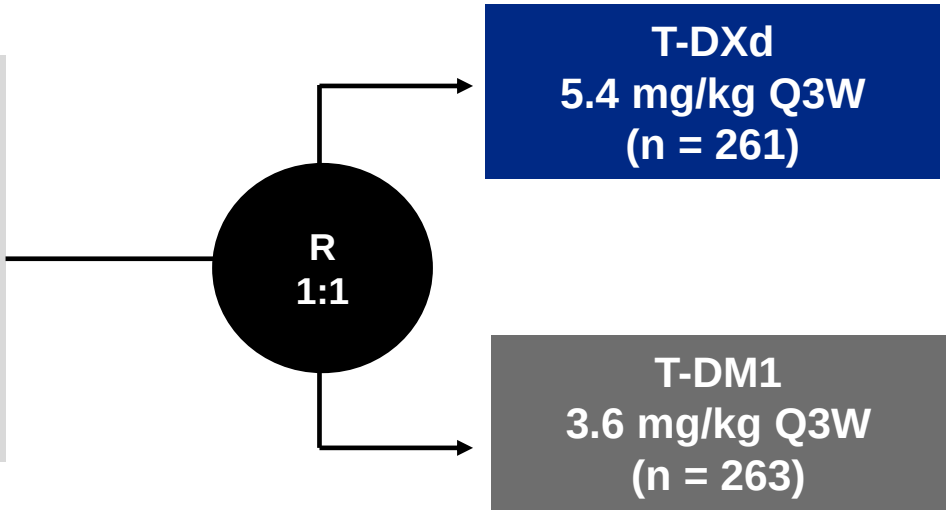
Randomized, open-label, multicenter study (NCT03529110)

Patients (N = 524)

- Unresectable or metastatic HER2-positive[a] breast cancer
- Previously treated with trastuzumab and a taxane in metastatic or (neo)adjuvant setting with recurrence within 6 months of therapy[b]

Stratification factors

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



Primary endpoint

- PFS (BICR)

Key secondary endpoint

- OS[c]

Secondary endpoints

- ORR (BICR and investigator)
- DoR (BICR)
- Safety

The prespecified OS interim analysis was planned with 153 events.[d] At the time of data cutoff (July 25, 2022), 169 OS events were observed and the *P* value to achieve statistical significance was 0.013

BICR, blinded independent central review; DoR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]HER2 IHC 3+ or IHC 2+/ISH+ based on central confirmation. [b]Progression during or within 6 months after completing adjuvant therapy involving trastuzumab and a taxane. [c]80% powered at 2-sided significance level of 5%. [d]Information fraction of 61%, with a *P* value boundary to reach statistical significance of 0.008. The *P* value was recalculated based on the actual OS events at the data cutoff.

Patient Disposition

	T-DXd n = 261	T-DM1 n = 263
Patients randomized, n (%)	261	263
Randomized but not treated	4 (1.5)	2 (0.8)
Treatment status,[a] n (%)		
Ongoing treatment	75 (29.2)	18 (6.9)
Treatment discontinuation	182 (70.8)	243 (93.1)
Primary reason for discontinuation,[a] n (%)		
Progressive disease	94 (36.6%)	178 (68.2%)
Adverse event	54 (21.0%)	21 (8.0%)
Clinical progression	5 (1.9%)	14 (5.4%)
Death	4 (1.6%)	4 (1.5%)
Withdrawal by patient	17 (6.6%)	12 (4.6%)
Physician decision	2 (0.8%)	8 (3.1%)
Other	6 (2.3%)	6 (2.3%)

Median study follow-up

- **T-DXd arm: 28.4 months (range, 0.0-46.9 months)**
- **T-DM1 arm: 26.5 months (range, 0.0-45.0 months)**

T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]Percentage calculated using the number of treated patients as denominator.

Baseline Characteristics

	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 (%)	260 (99.6)	262 (99.6)
Region, n (%)		
Europe	54 (20.7)	50 (19.0)
Asia	149 (57.1)	160 (60.8)
North America	17 (6.5)	17 (6.5)
Rest of World	41 (15.7)	36 (13.7)
HER2 status (IHC[a]), n (%)		
3+	234 (89.7)	232 (88.2)
2+	25 (9.6)	30 (11.4)
1+ | Not evaluable	1 (0.4) | 1 (0.4)	0 | 1 (0.4)
ECOG PS, n (%)		
0	154 (59.0)	175 (66.5)
1	106 (40.6)	87 (33.1)
Missing	1 (0.4)	1 (0.4)
Positive hormone receptor status, n (%)	131 (50.2)	134 (51.0)
Baseline brain metastases, n (%)	43 (16.5)	39 (14.8)
History of visceral disease, n (%)	184 (70.5)	185 (70.3)

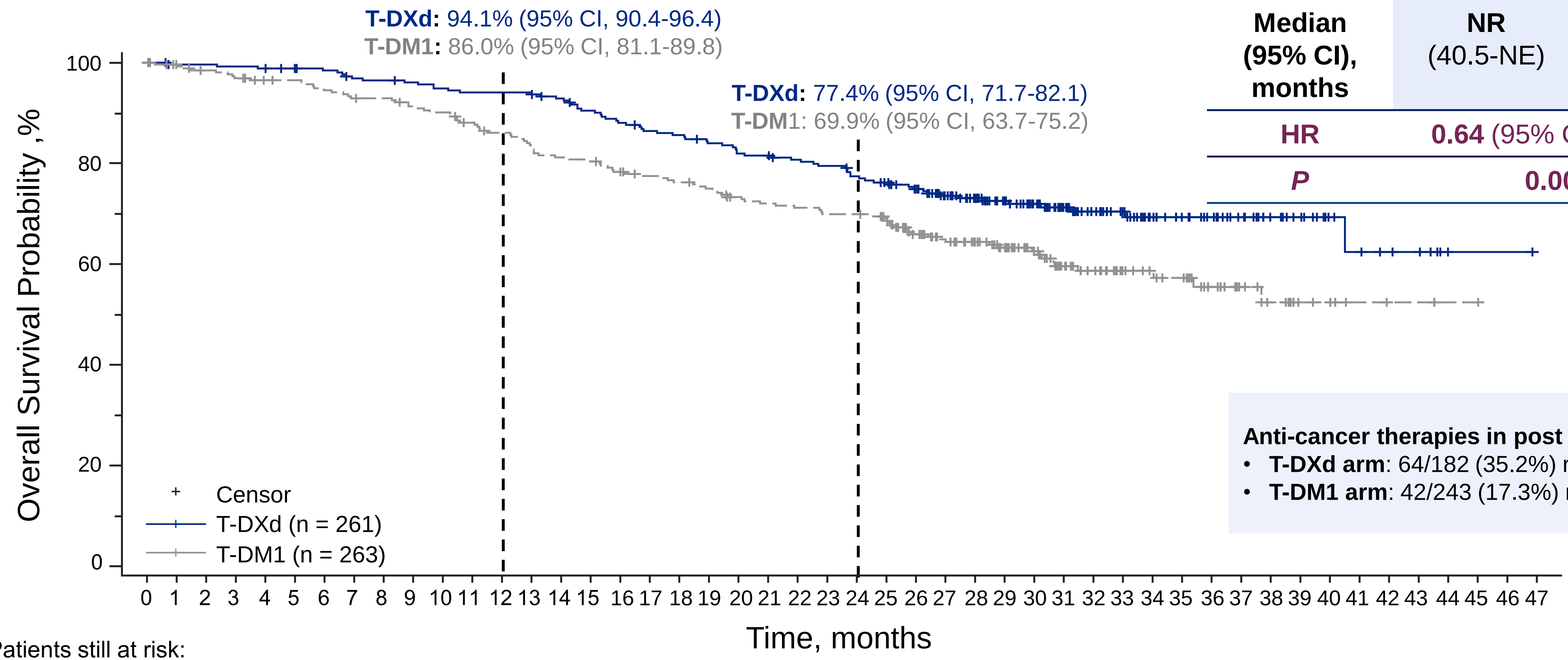
ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]HER2-status as evaluated by central laboratory.

Prior Therapies

	T-DXd n = 261	T-DM1 n = 263
Any prior systemic cancer therapy,[a,b] n (%)	260 (99.6)	262 (99.6)
Trastuzumab	260 (99.6)	262 (99.6)
Pertuzumab	162 (62.1)	158 (60.1)
Other anti-HER2 therapy[c]	42 (16.1)	38 (14.4)
Number of prior lines of therapy in the metastatic setting, median (range)	2 (0-16)	2 (0-15)
Prior lines of therapy in the metastatic setting,[b] n (%)		
0	1 (0.4)	1 (0.4)
1	108 (41.4)	102 (38.8)
2	60 (23.0)	64 (24.3)
3	44 (16.9)	45 (17.1)
4	15 (5.7)	23 (8.7)
≥5	33 (12.6)	28 (10.6)

ADC, antibody-drug conjugate; HER2, human epidermal growth factor receptor 2; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor.
[a]2 patients (1 in each treatment arm) were randomized in error and the prior cancer systemic therapy case report form was not filled. [b]Includes regimens indicated for advanced/metastatic or early progression within 6 months of regimen for (neo)adjuvant (12 months for pertuzumab). [c]Includes anti-HER2 TKI and other anti-HER2 antibody or ADC

Key Secondary Endpoint: Overall Survival



	T-DXd	T-DM1
Median (95% CI), months	**NR** (40.5-NE)	**NR** (34.0-NE)
HR	**0.64** (95% CI, 0.47-0.87)	
P	**0.0037**[a,b]	

Anti-cancer therapies in post trial setting:
- **T-DXd arm**: 64/182 (35.2%) received T-DM1
- **T-DM1 arm**: 42/243 (17.3%) received T-DXd

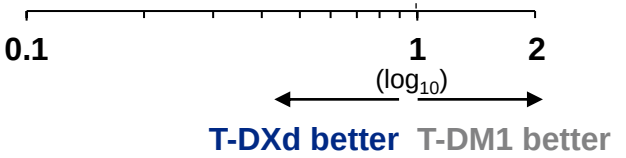
Patients still at risk:

Month	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	34	35	36	37	38	39	40	41	42	43	44	45	46	47
T-DXd	261	256	256	255	254	251	249	244	243	241	238	236	236	236	231	224	218	213	211	206	201	200	196	193	187	182	173	156	142	124	109	91	73	64	51	44	38	30	22	18	11	9	7	6	1	1	1	0
T-DM1	263	257	252	248	243	242	237	233	232	227	224	217	211	203	199	197	191	186	183	179	172	169	167	164	164	158	140	129	117	106	90	70	59	45	41	38	27	20	15	8	7	4	3	3	1	1	0	

HR, hazard ratio; mOS, median overall survival; NE, not estimable; NR, not reached; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
There were 19 patients (7.3%) treated with T-DXd and 28 patients (10.6%) treated with T-DM1 who were lost to follow-up.
[a]The *P* value for overall survival crossed the prespecified boundary (*P* = 0.013) and was statistically significant. [b]Two-sided from stratified log-rank test.

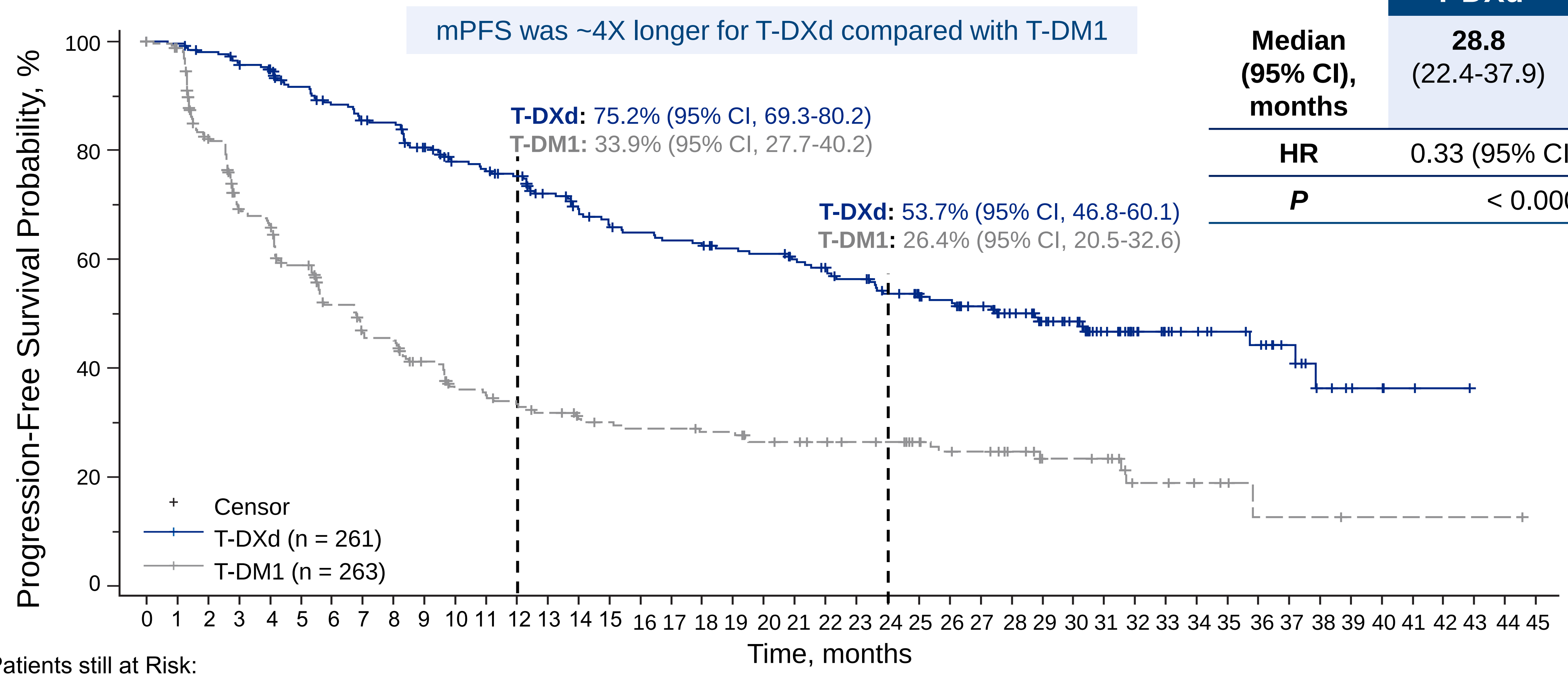
Overall Survival by Subgroups

		Number of Events		Median OS time (months, 95% CI)		Hazard Ratio for Death (95% CI)
		T-DXd	T-DM1	T-DXd	T-DM1	
All patients		72/261	97/263	NR (40.5-NE)	NR (34.0-NE)	0.64 (0.47-0.87)
Hormone receptor status	Positive (n = 272)	42/133	51/139	NR (40.5-NE)	37.7 (34.0-NE)	0.76 (0.50-1.14)
	Negative (n = 248)	30/126	45/122	NR (NE-NE)	NR (28.5-NE)	0.55 (0.35-0.87)
Prior pertuzumab	Yes (n = 320)	41/162	50/158	NR (40.5-NE)	NR (37.7-NE)	0.70 (0.46-1.06)
	No (n = 204)	31/99	47/105	NR (NE-NE)	31.5 (22.7-NE)	0.59 (0.38-0.93)
Baseline visceral disease	Yes (n = 384)	64/195	80/189	NR (40.5-NE)	35.4 (29.9-NE)	0.68 (0.49-0.95)
	No (n = 140)	8/66	17/74	NR (NE-NE)	NR (NE-NE)	0.44 (0.19-1.02)
Prior lines of systemic therapy[a]	<3 (n = 379)	44/188	57/191	NR (40.5-NE)	NR (37.7-NE)	0.70 (0.47-1.04)
	≥3 (n = 145)	28/73	40/72	NR (27.4-NE)	22.8 (16.1-31.5)	0.55 (0.34-0.89)
Baseline BM	Yes (n = 82)	17/43	22/39	NR (23.8-NE)	25.1 (12.6-NE)	0.54 (0.29-1.03)
	No (n = 442)	55/218	75/224	NR (40.5-NE)	NR (37.7-NE)	0.66 (0.47-0.94)



BM, brain metastases; NE, not estimable; NR, not reached; OS, overall survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]Prior lines of systemic therapy not including hormone therapy.

Updated Primary Endpoint: PFS by BICR



	T-DXd	T-DM1
Median (95% CI), months	**28.8** (22.4-37.9)	**6.8** (5.6-8.2)
HR	0.33 (95% CI, 0.26-0.43)	
P	< 0.000001[a,b]	

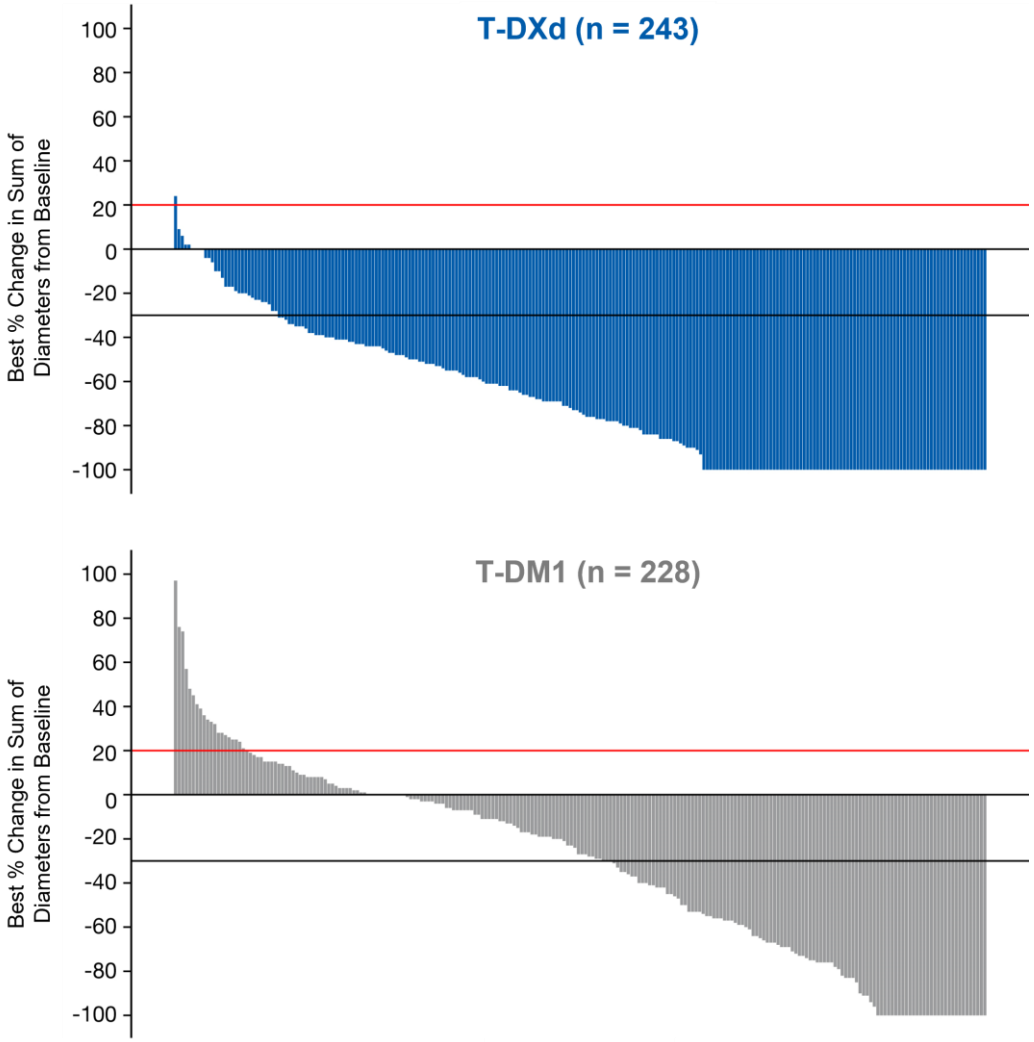
Patients still at Risk:

T-DXd	261	256	250	244	240	225	216	207	205	191	176	173	167	154	146	140	134	131	130	125	123	117	113
T-DM1	263	253	201	164	156	134	111	99	96	81	69	67	63	58	54	51	49	49	47	47	42	41	39

T-DXd	107	99	96	90	82	73	64	55	41	32	28	23	20	18	13	7	5	4	2	1	0		
T-DM1	37	36	32	28	27	22	19	15	14	8	7	6	4	2	2	2	1	1	1	1	1	1	0

BICR, blinded independent central review; HR, hazard ratio; mo, month; mPFS, median progression-free survival; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]Two-sided, from stratified log rank test. [b]Nominal *P* value.

Confirmed ORR and Other Efficacy Endpoints



	T-DXd n = 261[a]	T-DM1 n = 263[a]
Confirmed ORR by BICR		
n (%)	205 (**78.5**)	92 (**35.0**)
[95% CI]	[73.1-83.4]	[29.2-41.1]
Nominal *P* value	< 0.0001	
CR, n (%)	55 (**21.1**)	25 (**9.5**)
PR, n (%)	150 (57.5)	67 (25.5)
SD, n (%)	47 (18.0)	110 (41.8)
PD, n (%)	3 (1.1)	47 (17.9)
NE, n (%)	6 (2.3)	14 (5.3)
CBR, n (%) [95% CI]	233 (89.3) [84.9-92.8]	122 (46.4) [40.2-52.6]
Nominal *P* value	< 0.0001	
mDoR by BICR, months (95% CI)	**36.6** (22.4-NE)	**23.8** (12.6-34.7)

BICR, blinded independent central review; CBR, clinical benefit rate; CR, complete response; mDoR, median duration of response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Red line at 20% indicates progressive disease; black line at −30% indicates partial response.
[a]Only patients with measurable disease at baseline and at least 1 postbaseline target lesion assessment were included.

PFS2 and Post-Study Anticancer Treatment

	T-DXd n = 261	T-DM1 n = 263
Median PFS2 by investigator,[a] mo (95% CI)	40.5 (40.5-NE)	25.7 (18.5-34.0)
	HR, 0.47 (95% CI, 0.35-0.62)	
Patients who discontinued treatment, n (%)	182 (70.8)	243 (93.1)
Any post-study anticancer treatment,[b] n (%)	130 (71.4)	191 (78.6)
Trastuzumab	43 (23.6)	90 (37.0)
T-DXd	3 (1.6)	42 (17.3)
T-DM1	64 (35.2)	24 (9.9)
Pertuzumab	15 (8.2)	28 (11.5)
Taxane	13 (7.1)	32 (13.2)
Taxane and trastuzumab	7 (3.8)	28 (11.5)
Other anti-HER2[c]	39 (21.4)	88 (36.2)
Anti-HER2 TKI	38 (20.9)	87 (35.8)
Other anti-HER2 antibody or ADC	1 (0.5)	4 (1.6)
Hormone therapy	25 (13.7)	30 (12.3)
Other systemic therapy	75 (41.2)	147 (60.5)

ADC, antibody-drug conjugate; HR, hazard ratio; PFS2, progression-free survival on the next line of therapy; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor.
[a]From the time of randomization to second progression. [b]Patients may have received more than 1 type of post-study anticancer treatment. Denominator is the number of patients who discontinued study treatment. [c]Includes anti-HER2 TKI and other anti-HER2 antibody or ADC.

Overall Safety Summary

Type of Adverse Event, n (%)	T-DXd n = 257	T-DM1 n = 261
Any-grade TEAE	256 (99.6)	249 (95.4)
Drug related	252 (98.1)	228 (87.4)
Grade ≥3 TEAEs	145 (56.4)	135 (51.7)
Drug related	121 (47.1)	110 (42.1)
Serious TEAEs	65 (25.3)	58 (22.2)
Drug related	33 (12.8)	20 (7.7)
TEAEs associated with drug discontinuation	55 (21.4)	24 (9.2)
Drug related	51 (19.8)	17 (6.5)
TEAEs associated with dose reduction	66 (25.7)	38 (14.6)
Drug related	65 (25.3)	38 (14.6)
TEAEs associated with drug interruption	136 (52.9)	76 (29.1)
Drug related	108 (42.0)	45 (17.2)
TEAEs associated with an outcome of death	6 (2.3)	6 (2.3)
Drug related	0	0

- Median treatment duration:
  - **T-DXd**: 18.2 mo (range, 0.7-44.0)
  - **T-DM1**: 6.9 mo (range, 0.7-39.3)
- Rates of grade ≥3 TEAEs were similar between the T-DXd (56.4%) and T-DM1 (51.7%) treatment arms
- The most common drug-related TEAEs associated with discontinuation were:
  - **T-DXd**: pneumonitis (5.8%), ILD (5.1%), and pneumonia (1.9%)
  - **T-DM1**: platelet count decreased (1.5%), pneumonitis (1.1%), and thrombocytopenia (1.1%)

ILD, interstitial lung disease; mo, month; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
Relationship to study drug was determined by the treating investigator.

Most Common TEAEs in ≥20% of Patients

System Organ Class Preferred Term, n (%)	T-DXd n = 257		T-DM1 n = 261	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Blood and lymphatic system disorders				
Anemia	95 (37.0)	24 (9.3)	51 (19.5)	17 (6.5)
Platelet count decreased	64 (24.9)	20 (7.8)	114 (43.7)	52 (19.9)
White blood cell count decreased	60 (23.3)	16 (6.2)	16 (6.1)	2 (0.8)
Gastrointestinal disorders				
Nausea	198 (77.0)	18 (7.0)	79 (30.3)	1 (0.4)
Vomiting	133 (51.8)	4 (1.6)	28 (10.7)	2 (0.8)
Constipation	96 (37.4)	0	51 (19.5)	0
Diarrhea	83 (32.3)	3 (1.2)	21 (8.0)	2 (0.8)
General disorders				
Fatigue	79 (30.7)	15 (5.8)	53 (20.3)	2 (0.8)
Headache	61 (23.7)	1 (0.4)	40 (15.3)	0
Investigations				
Neutrophil count decreased	79 (30.7)	41 (16.0)	30 (11.5)	8 (3.1)
Aspartate aminotransferase increased	72 (28.0)	2 (0.8)	108 (41.4)	14 (5.4)
Alanine aminotransferase increased	59 (23.0)	4 (1.6)	83 (31.8)	12 (4.6)
Metabolism and nutrition disorders				
Decreased appetite	78 (30.4)	4 (1.6)	46 (17.6)	1 (0.4)
Weight decreased	58 (22.6)	6 (2.3)	23 (8.8)	2 (0.8)
Skin and subcutaneous tissue disorders				
Alopecia	102 (39.7)	1 (0.4)[a]	9 (3.4)	0

T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
Adverse events were managed according to the protocol. [a]Cases of alopecia reported during the study were graded based on the clinical judgement of the investigator. 1 case of alopecia was categorized as grade 3 by the investigator despite grade 3 alopecia not being recognized by the NCI Common Terminology criteria. The event outcome was reported as recovered by the investigator.

Adjudicated Drug-Related Interstitial Lung Disease/Pneumonitis

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd (n = 257)	11 (4.3)	26 (10.1)	2 (0.8)	0	0	39 (15.2)
T-DM1 (n = 261)	4 (1.5)	3 (1.1)	1 (0.4)	0	0	8 (3.1)

- Adjudicated drug-related ILD/pneumonitis rates were similar to other mBC trials with T-DXd[1,2]
- With longer treatment exposure and follow-up, the ILD/pneumonitis rate increased from 10.5% in the PFS interim analysis[3] to 15.2%
  - There were 4 additional grade 1, 8 additional grade 2, and no additional grade 3 events
- The overall incidence of grade 3 events (0.8%) was the same as in the PFS interim analysis[3]
- There were no adjudicated drug-related grade 4 or 5 events

ILD, interstitial lung disease; mBC, metastatic breast cancer; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

1. Modi S et al. *N Engl J Med* 2020; 382(7): 610-21. 2. Powell CA et al. *ESMO Open* 2022; 7(4): 100554. 3. Cortes J et al. *N Engl J Med.* 2022;386:1143-1154.

Conclusions

- **T-DXd demonstrated clinically meaningful and statistically significant improvement in OS over T-DM1, as well as continued PFS benefit, in patients previously treated with trastuzumab and a taxane**
  - T-DXd significantly reduced the risk of death by 36% (HR, 0.64)
  - mPFS with T-DXd was 4 times longer than with T-DM1 (28.8 months vs 6.8 months)
  - 78.5% of patients experienced a confirmed objective response; 1 in 5 (21.1%) experienced a CR
- **Consistent OS benefit was observed across key prespecified subgroups**
- **With a longer treatment duration, T-DXd continues to demonstrate a manageable and tolerable safety profile**
  - There were similar rates of grade ≥3 TEAEs with T-DXd and T-DM1
  - There were no grade 4 or 5 adjudicated drug-related ILD/pneumonitis events

Updated results demonstrate remarkable OS and PFS benefit with T-DXd, further supporting the use of T-DXd as the second-line standard of care in patients with HER2-positive mBC

CR, complete response; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; ILD, interstitial lung disease; mBC, metastatic breast cancer; mPFS, median progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Trastuzumab deruxtecan vs physician's choice in patients with HER2+ unresectable and/or metastatic breast cancer previously treated with trastuzumab emtansine: Primary results of the randomized phase 3 study DESTINY-Breast02

Presentation ID: GS2-01

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On behalf of the DESTINY-Breast02 investigators

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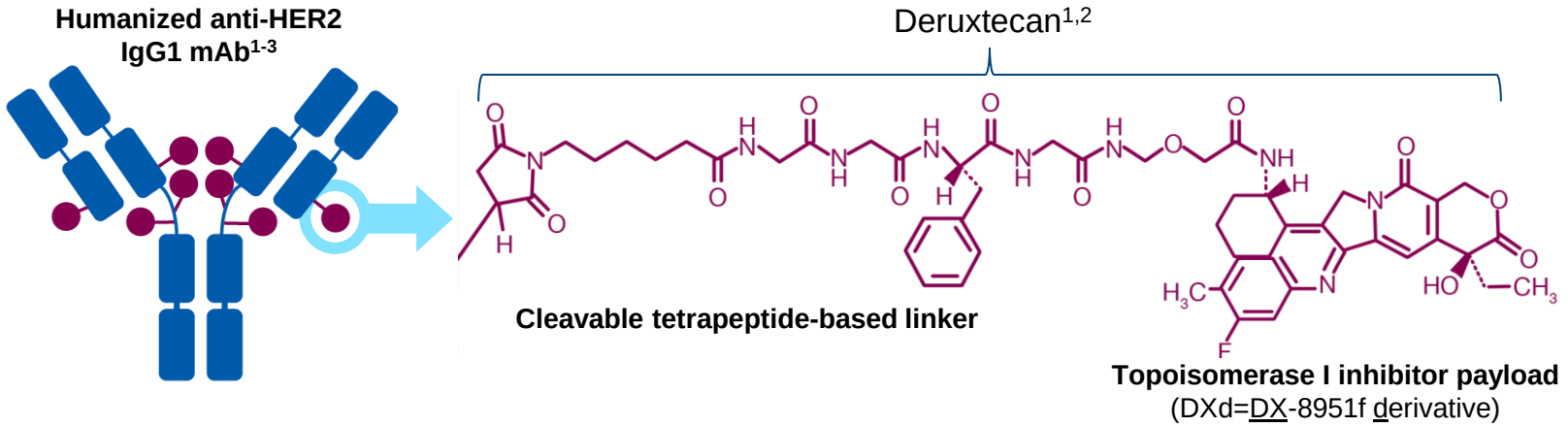
Trastuzumab Deruxtecan (T-DXd) Was Designed With 7 Key Attributes

T-DXd is an ADC composed of 3 components[1,2]:

- A humanized anti-*HER2* IgG1 mAb with the same amino acid sequence as trastuzumab, covalently linked to:
  - A topoisomerase I inhibitor payload, an exatecan derivative, via
  - A tetrapeptide-based cleavable linker



- Payload mechanism of action: topoisomerase I inhibitor[a,1,2]
- High potency of payload[a,1,2]
- High drug-to-antibody ratio ≈ 8[a,1,2]
- Payload with short systemic half-life[a,1,2]
- Stable linker payload[a,1,2]
- Tumor-selective cleavable linker[a,1,2]
- Bystander antitumor effect[a,1,4]

ADC, antibody-drug conjugate; HER2, human epidermal growth factor receptor 2; IgG1, immunoglobulin G1; mAb, monoclonal antibody; T-DXd, trastuzumab deruxtecan.
[a]The clinical relevance of these features is under investigation.
1. Nakada T et al. *Chem Pharm Bull (Tokyo).* 2019;67:173-185. 2. Ogitani Y et al. *Clin Cancer Res*. 2016;22:5097-5108. 3. Trail PA et al. *Pharmacol Ther.* 2018;181:126-142. 4. Ogitani Y et al. *Cancer Sci*. 2016;107:1039-1046.

Evolution of Treatments for HER2+ Metastatic Breast Cancer

2L+

T-DM1, EMILIA:
mPFS 9.6 months vs 6.4 months with lapatinib + capecitabine
HR, 0.65 (95% CI, 0.55-0.77; *P* < 0.001)[1]

T-DXd, DESTINY-Breast03:
mPFS not reached vs 6.8 months with T-DM1;
HR, 0.28 (95% CI, 0.22-0.37; *P* < 0.001)[2]

- Prior to DESTINY-Breast03, the EMILIA trial established T-DM1 as 2L+ standard of care[1]
- Based on the strength of the DESTINY-Breast03 trial efficacy and safety data, T-DXd is now the recommended option in the 2L setting[2]

3L+

T-DXd, DESTINY-Breast01:
mPFS = 19.4 months[3,4]

- T-DXd demonstrated robust activity in a post-TDM1 phase 2 single arm study, DESTINY-Breast01, leading to regulatory approvals globally[3-5]

DESTINY-Breast02 is a randomized, multicenter, open-label, phase 3 trial comparing the efficacy and safety of T-DXd vs TPC in patients with HER2+ mBC previously treated with T-DM1
DESTINY-Breast02 is a confirmatory trial for DESTINY-Breast01. Results of the primary analysis are presented

2L, second-line; 3L, third-line; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; mBC, metastatic breast cancer; mPFS, median progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

1. Verma S et al. *N Engl J Med*. 2012;367:1783-1791. 2. Cortés J et al. *N Engl J Med.* 2022;386:1143-1154. 3. Perez J et al. *Expert Opin Biol Ther*. 2021;21:811-824. 4. Saura C et al. Presented at ESMO 2021. Poster 279P. 5. Modi S et al. *N Engl J Med* 2020;382:610-621.

DESTINY-Breast02

Randomized phase 3, open-label, multicenter study (NCT03523585)

Key eligibility criteria[a]
- Centrally confirmed HER2-positive (IHC 3+ or IHC 2+/ISH+) unresectable or metastatic breast cancer
- Documented radiographic progression after most recent treatment
- Previously treated with T-DM1

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

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 406)

TPC
Per label (n = 202)
- Trastuzumab / Capecitabine
or
- Lapatinib / Capecitabine

Primary endpoint
- PFS (BICR[b])

Key secondary endpoint
- OS

Secondary endpoints
- ORR (BICR[b])
- DoR (BICR[b])
- PFS (investigator)
- Safety

Exploratory endpoints
- CBR (BICR[b])
- PFS2[c] (investigator)

At data cutoff (June 30, 2022), the median duration of follow-up[d] was:
- **21.5 months** (range, 0.1-45.6 months) in the T-DXd arm
- **18.6 months** (range, 0-45.7 months) in the TPC arm

Protocol-prespecified statistical analysis plan
- Primary analysis planned for ~372 BICR PFS events observed or 18 months from the last patient randomized, whichever came first
- Group sequential testing was used to compare OS between treatment groups hierarchically, provided PFS was significant

BICR, blinded independent central review; CBR, clinical benefit rate; DoR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; mRECIST, modified Response Evaluation Criteria in Solid Tumors version 1.1; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2; progression-free survival on the next line of therapy; Q3W, every 3 weeks; R, randomization, T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Patients with clinically inactive brain metastases and patients with treated brain metastases that were no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants could be included. [b]BICR assessed per mRECIST 1.1. [c]PFS2 was defined as the time from date of randomization to the first documented progression on the next line of therapy or death due to any cause, whichever came first. [d]Duration of follow up is defined as study duration = the date last known alive minus date of randomization plus 1.

Patient Disposition

	T-DXd n = 406	TPC n = 202
Patients Randomized, n (%)	406	202
Randomized but not treated	2 (0.5)	7 (3.5)
Treatment status, n (%)		
Ongoing treatment[a]	94 (23.3)	5 (2.6)
Treatment discontinuation[a]	310 (76.7)	190 (97.4)
Primary reason for discontinuation, n (%)		
Progressive disease[b]	174 (43.1)	141 (72.3)
Adverse event	74 (18.3)	14 (7.2)
Patient withdrawal	30 (7.4)	17 (8.7)
Clinical progression	23 (5.7)	15 (7.7)
Death	4 (1.0)	1 (0.5)
Physician decision	2 (0.5)	1 (0.5)
Lost to follow-up	1 (0.2)	0
Other	1 (0.2)	0
Protocol deviation	1 (0.2)	1 (0.5)

[a]Percentage calculated using the number of treated patients as denominator. [b]Per RECIST v1.1.
RECIST, Response Evaluation Criteria in Solid Tumors version 1.1; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Baseline Characteristics

Baseline Characteristics	T-DXd n = 406	TPC n = 202
Age, median (range), years	54.2 (22.4-88.5)	54.7 (24.7-86.5)
Age, n (%)		
<65 years | ≥65 years	321 (79.1) | 85 (20.9)	164 (81.2) | 38 (18.8)
Female, n (%)	403 (99.3)	200 (99.0)
Region, n (%)		
Asia	112 (27.6)	52 (25.7)
Europe	152 (37.4)	78 (38.6)
North America	41 (10.1)	23 (11.4)
Rest of world	101 (24.9)	49 (24.3)
HER2 status (IHC),[a] n (%)		
3+	326 (80.3)	159 (78.7)
2+ (ISH+)	79 (19.5)	41 (20.8)
2+ (ISH- or nonevaluable)	1 (0.2)	1 (0.5)
1+ (ISH+)	0	1 (0.5)
ECOG PS, n (%)		
0 | 1 | 2	228 (56.2) | 177 (43.6) | 1 (0.2)	121 (59.9) | 81 (40.1) | 0
Hormone receptor,[b] n (%)		
Positive	238 (58.6)	118 (58.4)
Negative	165 (40.6)	83 (41.1)
Brain metastases at baseline,[c] n (%)		
Yes | No	74 (18.2) | 332 (81.8)	36 (17.8) | 166 (82.2)
Visceral disease, n (%)		
Yes | No	316 (77.8) | 90 (22.2)	160 (79.2) | 42 (20.8)

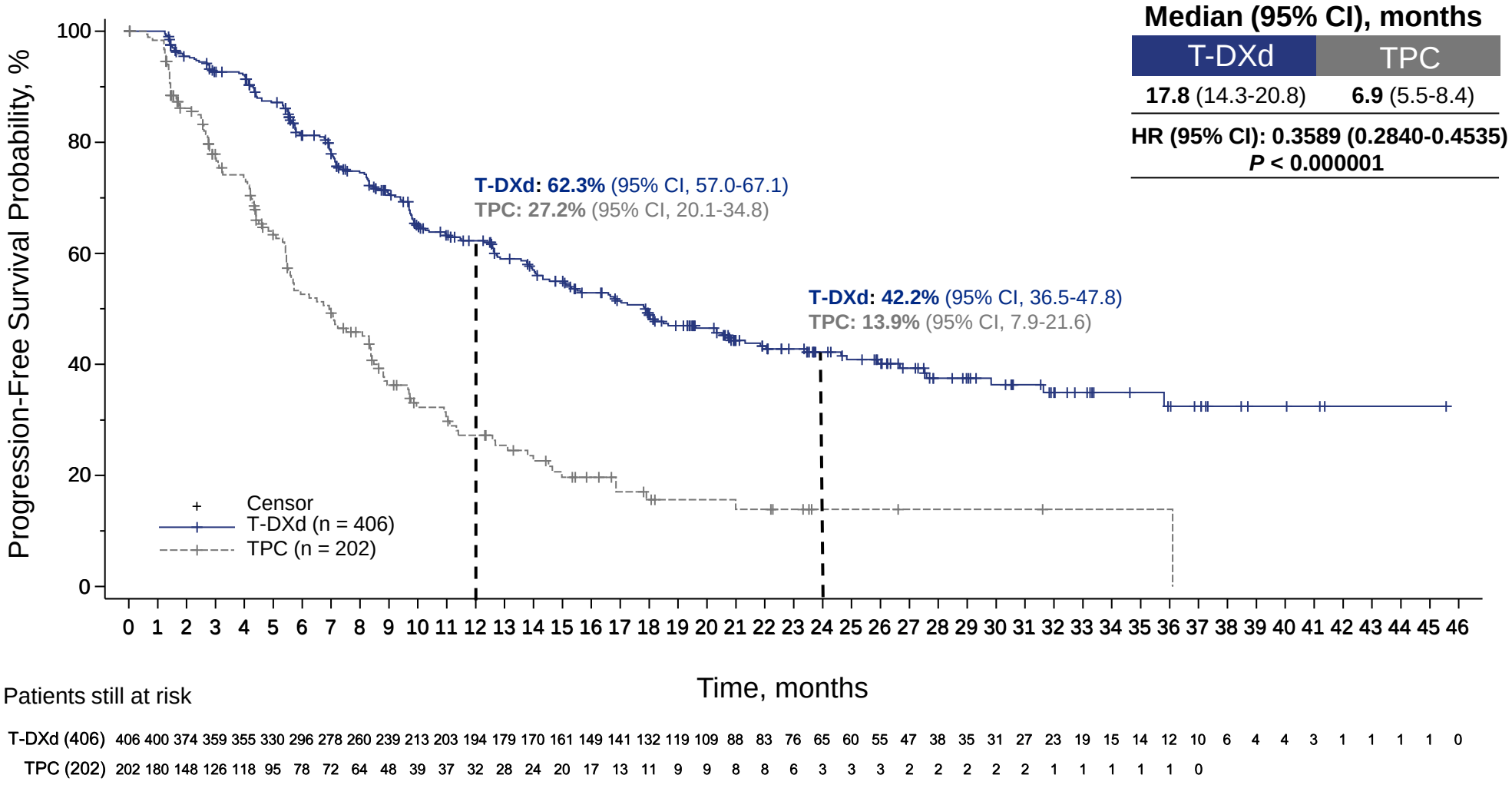
ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; ECOG PS, Eastern Cooperative Oncology Group performance status; EDC, Electronic Data Capture; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]HER2 status as evaluated by central laboratory testing. [b]3 (0.7%) patients in the T-DXd arm and 1 (0.5%) patient in the TPC arm had indeterminate hormone receptor status (neither estrogen receptors nor progesterone receptors positive and estrogen receptors indeterminate or progesterone receptors indeterminate) based on factors reported from EDC. [c]Patients with clinically inactive brain metastases and patients with treated brain metastases that were no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants could be included.

Prior Therapies

Prior Treatment	T-DXd n = 406	TPC n = 202
Prior treatment for BC, n (%)	406 (100)	202 (100)
Prior lines of therapy in the metastatic setting,[a] n (%)		
0	2 (0.5)	0
1	18 (4.4)	12 (5.9)
2	192 (47.3)	92 (45.5)
3	123 (30.3)	63 (31.2)
4	42 (10.3)	13 (6.4)
≥5	29 (7.1)	22 (10.9)
Median number of prior lines of systemic therapy in the metastatic setting,[a] (range)	2 (0-10)	2 (1-8)
Prior systemic cancer therapy, n (%)		
Trastuzumab	404 (99.5)	202 (100)
T-DM1	404 (99.5)	202 (100)
Taxane	386 (95.1)	197 (97.5)
Pertuzumab	318 (78.3)	156 (77.2)
Other systemic therapy	289 (71.2)	157 (77.7)
Hormone therapy	164 (40.4)	87 (43.1)
Anti-HER2 TKI	26 (6.4)	17 (8.4)
Other anti-HER2 therapy (except HER2 TKI)	11 (2.7)	6 (3.0)

BC, breast cancer; HER2, human epidermal growth factor receptor 2; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor; TPC, treatment of physician's choice.
[a]Includes regimens indicated for advanced/metastatic disease or rapid progression within 6 months of (neo)adjuvant (12 months for pertuzumab) therapy. Line of therapy does not include hormone therapy.

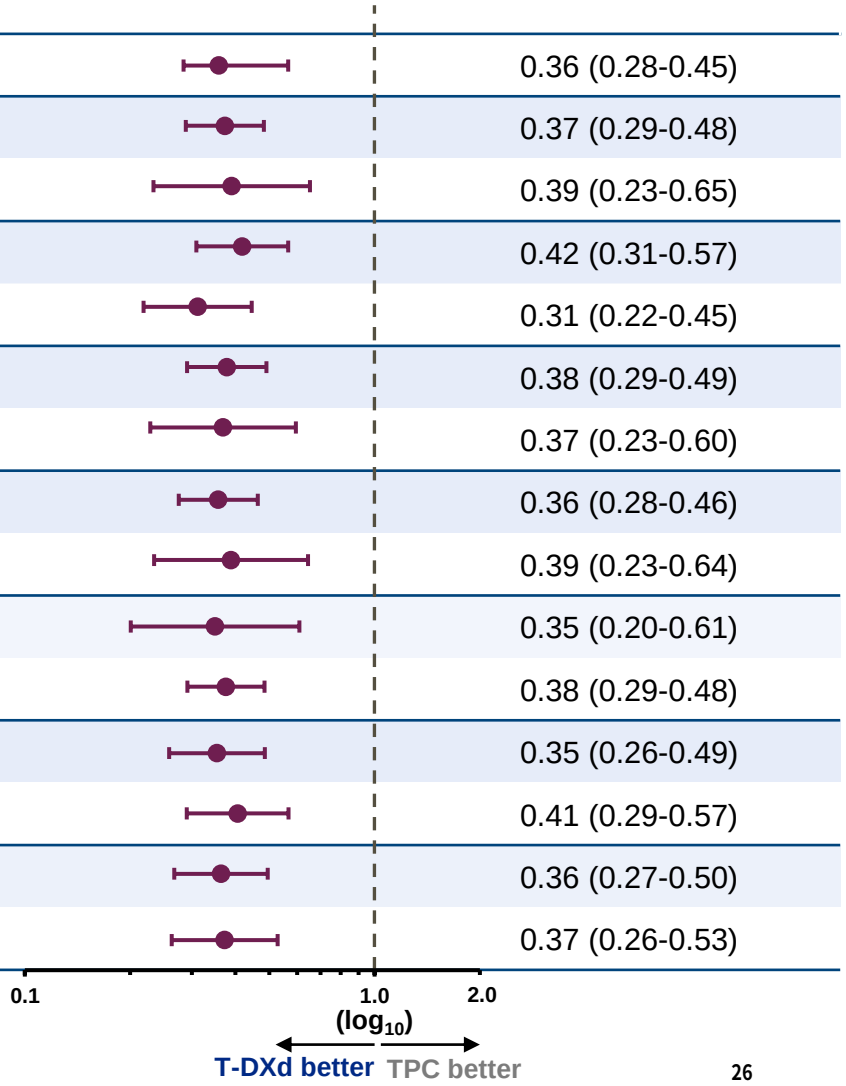
Primary Endpoint: PFS by BICR



BICR, blinded independent central review; HR, hazard ratio; mo, month; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

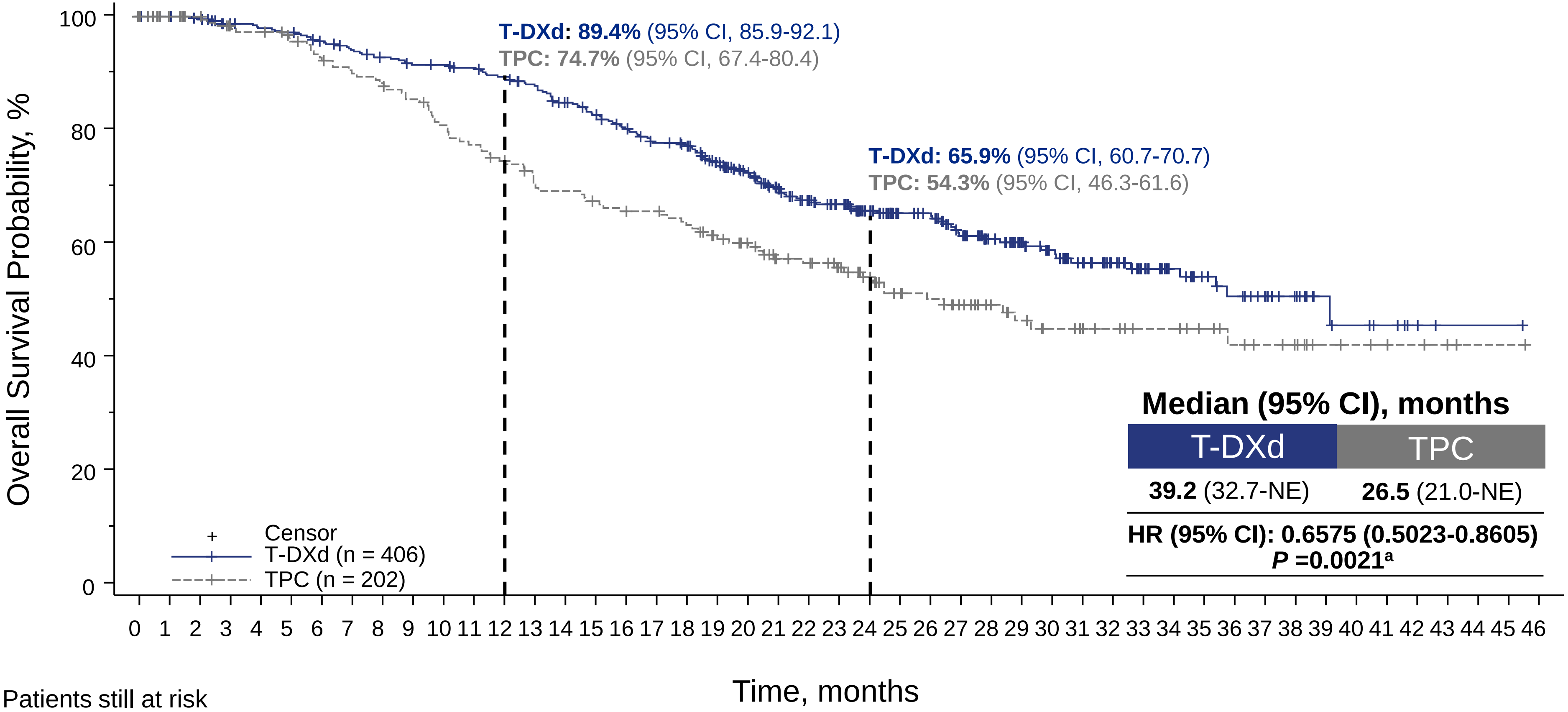
PFS in Key Subgroups

		Number of Events		Median PFS, mo (95% CI)		HR (95% CI)
		T-DXd	TPC	T-DXd	TPC	
All patients		200/406	125/202	17.8 (14.3-20.8)	6.9 (5.5-8.4)	0.36 (0.28-0.45)
Age	<65	160/321	101/164	17.9 (14.1-20.8)	7.1 (5.5-8.6)	0.37 (0.29-0.48)
	≥65	40/85	24/38	16.8 (12.7-NE)	6.7 (4.3-8.4)	0.39 (0.23-0.65)
Hormone receptor status	Positive	115/238	71/118	18.0 (15.1-21.3)	8.5 (6.5-10.0)	0.42 (0.31-0.57)
	Negative	84/165	53/83	17.0 (12.3-24.6)	5.3 (4.3-6.7)	0.31 (0.22-0.45)
Prior pertuzumab treatment[a]	Yes	155/318	95/156	17.8 (14.0-20.8)	6.2 (5.0-8.4)	0.38 (0.29-0.49)
	No	45/88	30/46	18.0 (13.9-26.7)	8.3 (5.5-12.6)	0.37 (0.23-0.60)
Visceral disease[a]	Yes	164/316	98/160	15.6 (12.8-20.3)	5.7 (5.3-7.2)	0.36 (0.28-0.46)
	No	36/90	27/42	29.8 (16.8-NE)	9.8 (6.2-12.6)	0.39 (0.23-0.64)
Baseline brain metastases	Yes	44/74	20/36	13.9 (11.1-18.0)	5.6 (3.3-8.1)	0.35 (0.20-0.61)
	No	156/332	105/166	18.7 (15.1-24.8)	7.1 (5.5-8.6)	0.38 (0.29-0.48)
Prior lines of therapy[b]	<3	105/212	66/104	16.6 (13.8-24.6)	7.0 (4.6-8.6)	0.35 (0.26-0.49)
	≥3	95/194	59/98	18.2 (14.3-22.0)	6.9 (5.5-8.8)	0.41 (0.29-0.57)
ECOG PS	0	101/228	75/121	24.6 (15.3-31.6)	8.1 (5.7-9.7)	0.36 (0.27-0.50)
	1	98/177	50/81	15.1 (11.5-18.0)	5.4 (4.3-7.5)	0.37 (0.26-0.53)



ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; mo, months; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Subgroup values are derived from baseline. [b]Lines of prior systemic therapy not including hormone therapy.

Key Secondary Endpoint: OS



Patients still at risk

Time, months	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
T-DXd (406)	406	404	400	390	385	382	374	366	357	352	350	346	339	331	317	306	295	282	277	257	234	215	196	183
TPC (202)	202	192	187	182	178	173	167	161	157	151	142	136	130	124	118	114	111	110	106	95	89	79	76	72

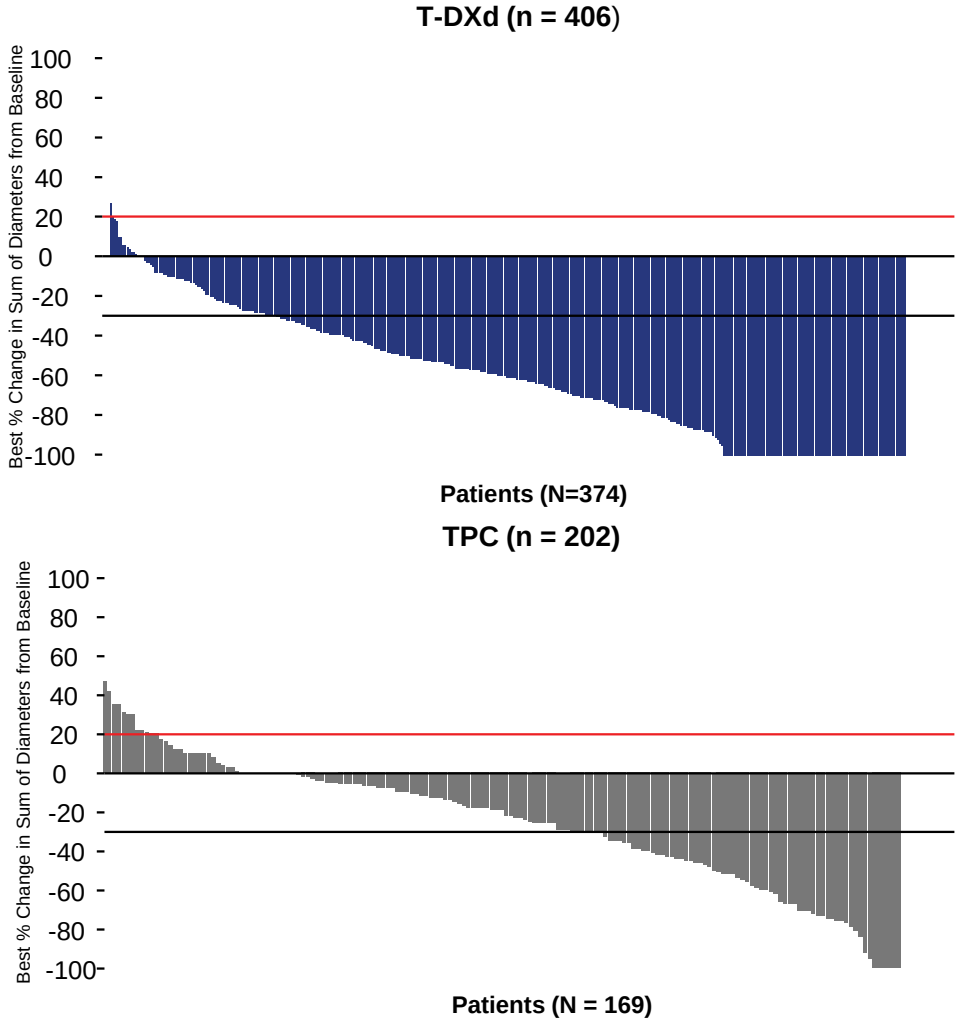
Time, months	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46
T-DXd (406)	160	144	139	122	104	93	82	72	63	51	40	34	29	25	19	10	8	6	3	1	1	1	0
TPC (202)	61	53	50	46	38	33	29	28	25	22	22	18	15	13	12	7	6	5	4	3	1	1	0

In the TPC arm

- **69.3% (140/202) of patients who discontinued therapy received a new systemic anticancer**
- **25.7% (52/202) of patients received T-DXd in the post-trial setting**

[a]The boundary for statistical significance is 0.0040. HR, hazard ratio; mo, month; NE, not estimable; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Secondary and Exploratory Efficacy Endpoints



	T-DXd n = 406	TPC n = 202
Confirmed ORR by BICR,[a] n (%)	**283 (69.7)**	**59 (29.2)**
[95% CI]	[65.0-74.1]	[23.0-36.0]
	P < 0.0001[b]	
Confirmed best overall response, n (%)		
CR	57 (14.0)	10 (5.0)
PR	226 (55.7)	49 (24.3)
SD	95 (23.4)	94 (46.5)
PD	19 (4.7)	26 (12.9)
Not evaluable	9 (2.2)	23 (11.4)
mDoR by BICR,[c] months (95% CI)	19.6 (15.9-NE)	8.3 (5.8-9.5)
CBR by BICR,[d] % (95% CI)	82.3 (78.2-85.9)	46.0 (39.0-53.2)
mPFS by investigator,[e] months (95% CI)	16.7 (14.3-19.6)	5.5 (4.4-7.0)
mPFS2,[e] months (95% CI)	35.8 (28.4-NE)	15.8 (13.5-21.0)

BICR, blinded independent central review; CBR, clinical benefit rate; CR, complete response; mDoR, median duration of response; mPFS, median progression-free survival; mPFS2; median progression-free survival on the next line of therapy; mRECIST, modified Response Evaluation Criteria in Solid Tumors version 1.1; NE, not estimable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
The line at 20% indicates progressive disease, and the line at −30% indicates a PR.
[a]Proportion of patients with confirmed CR or PR assessed by BICR per mRECIST v1.1. ORR 95% CI was calculated using the Clopper-Pearson method. [b]Two-sided. [c]BICR assessed per mRECIST v1.1. [d]Sum of CR rate, PR rate, and >6 months SD rate. [e]Median is from Kaplan-Meier analysis. CI for median is computed using the Brookmeyer-Crowley method.

Overall Safety Summary

Type of Adverse Event, n (%)	T-DXd n = 404[a]	TPC n = 195[a]
Any-grade TEAE	403 (99.8)	185 (94.9)
Drug related	394 (97.5)	180 (92.3)
Grade ≥3 TEAEs	213 (52.7)	86 (44.1)
Drug related	167 (41.3)	60 (30.8)
Serious TEAEs	103 (25.5)	46 (23.6)
Drug related	46 (11.4)	15 (7.7)
TEAEs associated with drug discontinuations	80 (19.8)	19 (9.7)
Drug related	58 (14.4)	10 (5.1)
TEAEs associated with drug interruptions	183 (45.3)	90 (46.2)
Drug related	132 (32.7)	76 (39.0)
TEAEs associated with dose reductions	102 (25.2)	89 (45.6)
Drug related	95 (23.5)	89 (45.6)
TEAEs associated with an outcome of death	11 (2.7)[b]	7 (3.6)[c]
Drug related	4 (1.0)[d]	0

Median treatment duration

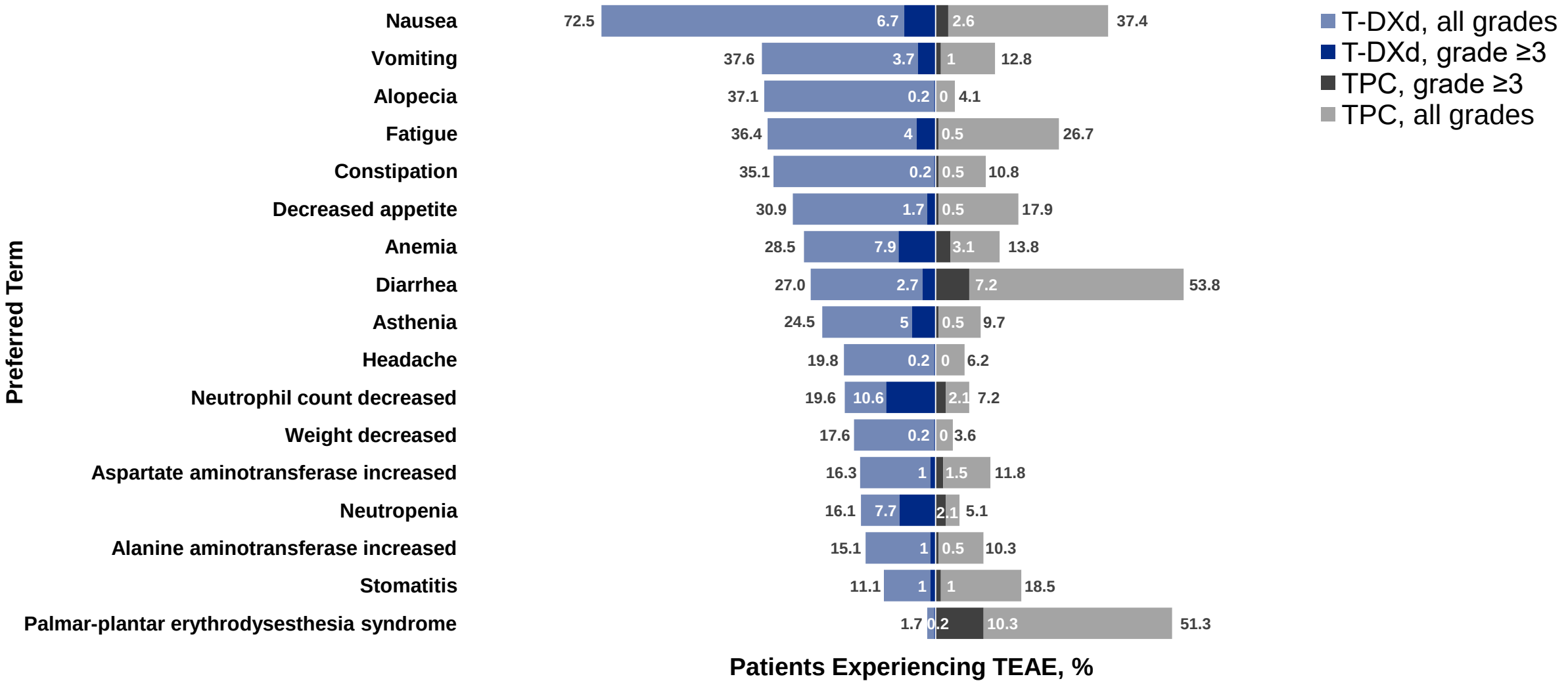
- T-DXd, 11.3 months
- TPC, ~4.5 months

Most common drug-related TEAEs associated with drug discontinuation

- T-DXd, pneumonitis (6.2%) and ILD (3.2%)
- TPC, palmar-plantar erythrodysesthesia (1.5%)

ILD, interstitial lung disease; TEAE, treatment-emergent adverse event; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]The safety analysis set includes all randomized patients who received at least 1 dose of study treatment. [b]TEAEs associated with an outcome of death included pneumonitis (n = 2), acute myeloid leukemia (n = 1), brain edema (n = 1), COVID-19 (n = 1), disease progression (n = 1), hemorrhage (n = 1), hepatitis B (n = 1), malignant pleural effusion (n = 1), pneumonia (n = 1), and vasogenic cerebral edema (n = 1). [c]TEAEs associated with an outcome of death included disease progression (n = 4), cardiac arrest (n = 1), metastases to meninges (n = 1), and pericardial effusion (n = 1). [d]Drug-related TEAEs associated with an outcome of death included pneumonitis (n = 2), acute myeloid leukemia (n = 1), and pneumonia (n = 1).

Most Common TEAEs (≥15% of Patients in Either Treatment Arm)



T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.

Adverse Events of Special Interest: ILD and LV Dysfunction

Adjudicated as Drug-related ILD[a]						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 404)	11 (2.7)	26 (6.4)	3 (0.7)	0	2 (0.5)	42 (10.4)
TPC (n = 195)	0	0	1 (0.5)	0	0	1 (0.5)

- Median time to onset of adjudicated drug-related ILD was 209.5 days (range, 41-638 days) with T-DXd

LV dysfunction[b]

- In the T-DXd arm, 18 (4.5%) patients experienced an LV dysfunction event[c]
  - 2 (0.5%) patients had a grade ≥3 event
- In the TPC arm, 3 (1.5%) patients experienced an LV dysfunction[d]
  - 1 (0.5%) patient had a grade ≥3 event

ILD, interstitial lung disease; LV, left ventricular; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]The safety analysis set includes all randomly assigned patients who received at least 1 dose of study treatment. [b]Left ventricular dysfunction included preferred terms of acute left ventricular failure, acute right ventricular failure, cardiac failure, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, chronic left ventricular failure, chronic right ventricular failure, ejection fraction decreased, left ventricular failure, right ventricular failure, ventricular failure, and left ventricular dysfunction. [c]17 ejection fraction decreased (2 grade ≥3), 1 LV dysfunction (grade 1). [d]1 ejection fraction decreased (grade 1), 2 cardiac failure (1 grade ≥3).

Conclusions

- **In DESTINY-Breast02, T-DXd demonstrated statistically significant and clinically meaningful improvement in PFS and OS vs TPC for patients with HER2+ mBC previously treated with T-DM1**
  - mPFS results showed T-DXd reduced the risk of progression or death compared with TPC (mPFS of 17.8 and 6.9 months, respectively; HR, 0.3589; 95% CI, 0.2840-0.4535; *P* < 0.000001)
  - mOS results showed T-DXd reduced the risk of death compared with TPC (mOS of 39.2 and 26.5 months, respectively; HR, 0.6575; 95% CI; 0.5023-0.8605; *P* = 0.0021)
- **The overall safety profile was consistent with the established safety of T-DXd, with no new safety signals observed**
  - Overall incidence of ILD for T-DXd in DESTINY-Breast02 was 10.4% (grade 1/2 events, 9.2%)
  - Fewer grade 5 ILD events were observed in DESTINY-Breast02 (0.5%) compared with DESTINY-Breast01 (2.7%)[1-2]

DESTINY-Breast02 confirms the favorable benefit/risk profile of T-DXd in patients with advanced HER2+ mBC, as previously demonstrated by DESTINY-Breast01

HER2, human epidermal growth factor receptor 2; HR, hazard ratio; ILD, interstitial lung disease; mBC, metastatic breast cancer; mOS, median overall survival; mPFS, median progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

1. Modi S et al. *Cancer Res*. 2021:81(4_suppl):PD3-06. 2. Saura C et al. Presented at: European Society for Medical Oncology; September 16-21, 2021. Poster 279P.

San Antonio Breast Cancer Symposium® - December 6–10, 2022

Poster PD18-11

Dose-expansion study of trastuzumab deruxtecan as monotherapy or combined with pertuzumab in patients with metastatic human epidermal growth factor receptor 2-positive (HER2+) breast cancer in DESTINY-Breast07 (DB-07)

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Objectives

- The primary objective of the dose-expansion phase of the ongoing DESTINY-Breast07 clinical trial is to assess the safety and tolerability of T-DXd as monotherapy and in combination with anticancer therapies, including pertuzumab, in patients with HER2+ metastatic breast cancer
- Secondary objectives of the dose-expansion phase are to assess the antitumor activity of T-DXd as monotherapy and in combination with other anticancer therapies and to assess the PK and immunogenicity of study drugs

Conclusions

- The safety profiles and antitumor activity of T-DXd as monotherapy or in combination with pertuzumab in the first line were consistent with those previously reported with T-DXd
  - An unconfirmed objective response was observed in 29 of 23 patients (87.0%) who received T-DXd monotherapy and in 18 of 22 (81,8%) patients who received T-DXd + pertuzumab
- This trial is ongoing, with additional T-DXd combinations being evaluated and further follow-up underway. Results reported here were based on a relatively short follow-up duration and may evolve with further follow-up
- Preclinical studies showed the potential for pertuzumab to induce greater internalization of T-DXd and inhibition of HER2-driven signaling
- These results support investigation of T-DXd monotherapy and in combination with pertuzumab in larger ongoing clinical trials (eg, DESTINY-Breast09 [NCT04784715])

Plain language summary

Why did we perform this research?

T-DXd is a drug used to treat HER2+ breast cancer (the cancer cells have higher than normal levels of HER2 protein) that has spread from its original site to other parts of the body (metastatic).[1,2] Currently, doctors may prescribe T-DXd only after other anticancer drugs have not been able to control the cancer.[1,2] We want to find out if T-DXd can be used to treat metastatic HER2+ breast cancer before other anticancer drugs are used. We also want to see if T-DXd can be used in combination with other anticancer drugs.

How did we perform this research?

In the ongoing DESTINY-Breast07 study, we are assessing T-DXd alone and in combination with other anticancer drugs in participants with HER2+ metastatic breast cancer who have not yet received other anticancer drugs. We are assessing how safe T-DXd alone and T-DXd combination treatments are and how effective they are at treating HER2+ metastatic breast cancer. Results presented here are from an early analysis of the data before the study has been completed.

What were the findings of this research?

23 participants were treated with T-DXd alone, and 22 participants were treated with T-DXd + pertuzumab. Most participants had side effects that either had no or mild symptoms and did not require medical treatment (mild side effects) or required limited medical treatment or limited some daily activities (moderate side effects). In most participants, T-DXd alone or T-DXd + pertuzumab helped decrease the size or number of tumors.

What are the implications of this research?

These initial results support continuing to test how well these drugs work in participants with HER2+ metastatic breast cancer.

Where can I access more information?

ClinicalTrials.gov. A Phase 1b/2 Study of T-DXd Combinations in HER2-Positive Metastatic Breast Cancer (DB-07). https://clinicaltrials.gov/ct2/show/NCT04538742

This study is sponsored by AstraZeneca Pharmaceuticals in collaboration with Daiichi Sankyo, Inc. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201).

References: 1. Enhertu (fam-trastuzumab deruxtecan-nxki). Prescribing information. Daiichi Sankyo, Inc; 2022. 2. Enhertu (trastuzumab deruxtecan). Summary of product characteristics. Daiichi Sankyo, Inc; 2022.

Poster presented at the San Antonio Breast Cancer Symposium®; December 6-10, 2022; San Antonio, TX, and virtual by Erika P. Hamilton.

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Poster presented at the San Antonio Breast Cancer Symposium®; December 6-10, 2022; San Antonio, TX, and virtual by Erika P. Hamilton.

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Introduction

- Trastuzumab deruxtecan (T-DXd) is approved in the United States and Europe for patients with unresectable or metastatic HER2+ breast cancer who received ≥1 prior anti-HER2–based regimen[1,2]
- In the phase 3 DESTINY-Breast03 trial of patients with HER2+ metastatic breast cancer, T-DXd reduced the risk of disease progression or death by 72% vs T-DM1 (hazard ratio, 0.28; 95% CI, 0.22-0.37; *P*<.001; data cutoff, May 21, 2021)[3]
- To see if T-DXd can be safely comb ined with other anticancer drugs, T-DXd monotherapy and combinations with anticancer therapies are being assessed in the ongoing, phase 1b/2, multicenter, open-label, modular DESTINY-Breast07 trial. The study consists of 2 phases: a dose-finding phase (part 1) and a dose-expansion phase (part 2)
- Results from the dose-finding phase were previously presented and showed that T-DXd 5.4 mg/kg + pertuzumab 420 mg Q3W was well tolerated in patients who received prior treatment in the metastatic setting[4]
- Here we report preliminary efficacy and additional safety follow-up results from patients who received first-line treatment in the dose-expansion phase
- Based on the distinct mechanisms of action of T-DXd and pertuzumab, we also conducted preclinical studies with these treatments in HER2-expressing cell lines to elucidate the potential synergy in their mechanisms of action

Methods

- Patients in this study had metastatic HER2+ breast cancer (NCT04538742; **Figure 1**)
- Patients received no prior therapy for advanced/metastatic breast cancer. Data are reported for the following modules:
  - Module 0: T-DXd 5.4 mg/kg Q3W
  - Module 2: T-DXd 5.4 mg/kg Q3W + pertuzumab 420 mg Q3W (pertuzumab loading dose: 840 mg)
- Data are reported with a data cutoff of July 1, 2022; recruitment is ongoing. These data are from the safety interim analysis population (patients randomized on or before October 13, 2021) with longer follow-up time

Preclinical studies

- To assess the effects of pertuzumab on T-DXd internalization, live cell imaging was performed using pH-dependent fluorescently labeled T-DXd
- To assess the effects of T-DXd, pertuzumab, or combination treatment on HER2 signaling, total and pHER2 levels and downstream substrates were evaluated by immunoblot

Figure 1. Study design (dose-expansion phase)[a-c]

Population

Modules 0-5

- HER2+ (IHC 3+, IHC 2+/ISH+) advanced/unresectable or metastatic breast cancer
- No prior lines of therapy for advanced or metastatic breast cancer
- Either no brain metastases or previously treated stable brain metastases

Randomized →
- Module 0: T-DXd monotherapy (n=75)[d]
- Module 1: T-DXd + durvalumab (n=75)
- Module 2: T-DXd + pertuzumab (n=50)
- Module 3: T-DXd + paclitaxel (n≈40 to 50)
- Module 4: T-DXd + durvalumab + paclitaxel (n≈40 to 50)
- Module 5: T-DXd + tucatinib (n≈35)

Endpoints for the dose-expansion phase

- **Primary:** AEs, serious AEs, and laboratory findings
- **Secondary:** ORR and PFS per RECIST version 1.1, PFS2, DOR, OS, PK, and antidrug antibodies to study drugs

[a] The dose-expansion phase is using the recommended phase 2 doses determined in the dose-finding phase.
[b] Continuation of study drugs is allowed after local therapy for isolated central nervous system progression.
[c] The dose-expansion phase contains 2 additional modules: modules 6 (T-DXd + tucatinib) and 7 (T-DXd monotherapy). Patients randomized to these modules have HER2+ advanced/unresectable or metastatic breast cancer, have received ≤1 prior line of therapy for advanced or metastatic breast cancer, and have untreated brain metastases not needing local therapy or brain metastases previously treated with local therapy that have progressed since prior local therapy.
[d] Patients in module 0 are receiving the approved T-DXd dose for HER2+ breast cancer.

Results

Patients

- In this population, 23 patients were randomized to the T-DXd monotherapy module, and 22 were randomized to the T-DXd + pertuzumab module (**Tables 1** and **2**)
- In the T-DXd monotherapy module, the median actual treatment duration was 9.1 (range, 0.7-13.2) months
- In the T-DXd + pertuzumab module, the median actual treatment duration was 9.2 (range, 0.9-13.5) months with T-DXd and 9.2 (range, 0.9-13.5) months with pertuzumab
- The median duration of follow-up was 11.0 months in the T-DXd monotherapy module and 10.0 months in the T-DXd + pertuzumab module

Table 1. Patient disposition

n (%)	T-DXd monotherapy N=23[a]	T-DXd + pertuzumab N=22[a]
Treatment ongoing	17 (73.9)	16 (72.7)
Treatment discontinued	6 (26.1)	6 (27.3)[b]
AE	2 (8.7)	3 (13.6)
Withdrawn by patient	2 (8.7)	1 (4.5)
Objective disease progression	1 (4.3)	2 (9.1)
Lost to follow-up	1 (4.3)	0

[a] All patients received study drug.
[b] Discontinued T-DXd and pertuzumab.

Table 2. Patient demographics and disease characteristics

	T-DXd monotherapy N=23	T-DXd + pertuzumab N=22
Age, mean (range), years[a]	53.4 (34-80)	53.2 (33-75)
Female, n (%)	23 (100.0)	22 (100.0)
Race, n (%)		
White	16 (69.6)	14 (63.6)
Asian	7 (30.4)	8 (36.4)
HER2 status, n (%)		
IHC 3+[b]	17 (73.9)	19 (86.4)
IHC 2+/ISH+	5 (21.7)	2 (9.1)
Missing[c]	1 (4.3)	1 (4.5)
Hormone receptor status, n (%)[d]		
ER− and PR−	11 (47.8)	9 (40.9)
ER+ and PR−	4 (17.4)	4 (18.2)
ER− and PR+	0	1 (4.5)
ER+ and PR+	8 (34.8)	8 (36.4)
ECOG performance status, n (%)		
0	17 (73.9)	16 (72.7)
1	6 (26.1)	6 (27.3)

[a] Age calculated at randomization.
[b] Includes IHC 3+ and IHC 3+/ISH+.
[c] After the data cutoff, both patients with missing IHC scores were determined to be IHC 3+.
[d] ER+ and PR+ correspond to >1% expression or positive; ER− and PR− correspond to <1% expression or negative.

Safety

- No grade ≥3 AEs of nausea or vomiting were reported (**Table 3**)
- One patient in each module died due to disease progression (T-DXd monotherapy) and disease under study (T-DXd + pertuzumab)
- Adjudicated drug-related ILD/pneumonitis was reported in 1 patient (4.3%) with T-DXd monotherapy and no patients with T-DXd + pertuzumab

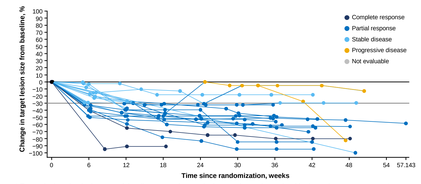
Table 3. Safety results

n (%)	T-DXd monotherapy N=23	T-DXd + pertuzumab N=22
Any-grade AEs	23 (100.0)	22 (100.0)
Any-grade AEs (≥20% in either module)		
Nausea	17 (73.9)	14 (63.6)
Alopecia	11 (47.8)	8 (36.4)
Vomiting	8 (34.8)	9 (40.9)
Diarrhea	6 (26.1)	14 (63.6)
Anemia	5 (21.7)	8 (36.4)
COVID-19	4 (17.4)	9 (40.9)
Fatigue	4 (17.4)	8 (36.4)
Neutropenia	4 (17.4)	7 (31.8)
Decreased appetite	4 (17.4)	6 (27.3)
Aspartate aminotransferase increased	4 (17.4)	5 (22.7)
Asthenia	4 (17.4)	5 (22.7)
Alanine aminotransferase increased	3 (13.0)	5 (22.7)
Weight decreased	2 (8.7)	5 (22.7)
Constipation	1 (4.3)	5 (22.7)
Grade ≥3 AEs	7 (30.4)	9 (40.9)
Grade ≥3 AEs in >1 patient in either module		
Neutropenia	2 (8.7)	4 (18.2)
Anemia	0	3 (13.6)
Diarrhea	0	2 (9.1)
Serious AEs	2 (8.7)	3 (13.6)
AEs of special interest		
Adjudicated drug-related ILD/pneumonitis	1 (4.3)[a]	0
Left ventricular dysfunction	2 (8.7)[b]	0
Deaths	1 (4.3)[c]	1 (4.5)[d]

[a] ILD/pneumonitis was possibly related to T-DXd (as assessed by the ILD adjudication committee), was grade 2, and led to discontinuation of T-DXd.
[b] Left ventricular dysfunction was possibly related to T-DXd (as assessed by the investigator), was grade 2 in both patients, and led to T-DXd interruption in 1 patient.
[c] Death was due to disease progression (assessed by brain magnetic resonance imaging).
[d] Death was due to disease under study (per autopsy report).

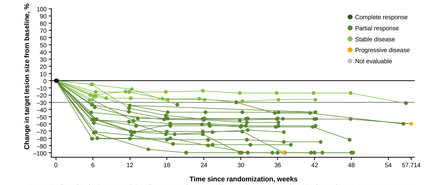
Antitumor activity

Figure 2. Percent change in target lesion size over time with T-DXd monotherapy[a,b]



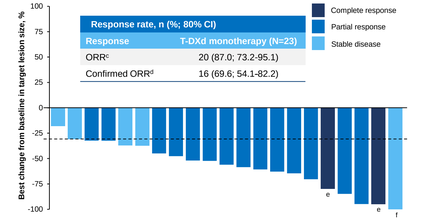
[a] Target lesion size is the sum of the diameters of target lesions and was determined by investigator assessment per RECIST 1.1.
[b] Data are being reviewed for the 2 patients who continued receiving treatment on study after experiencing disease progression.

Figure 3. Percent change in target lesion size over time with T-DXd + pertuzumab[a]



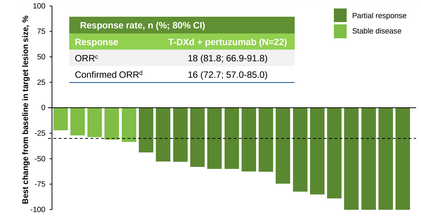
[a] Target lesion size is the sum of the diameters of target lesions and was determined by investigator assessment per RECIST 1.1.

Figure 4. Best percent change in target lesion size with T-DXd monotherapy[a,b]



[a] Best change in target lesion size is the maximum reduction from baseline (or minimum increase from baseline in the absence of a reduction). Target lesion size is the sum of diameters of target lesions and was determined by investigator assessment per RECIST 1.1. Dashed horizontal line indicates 30% reduction. The color of each bar indicates the RECIST 1.1 response as assessed by investigators.
[b] Data are reported for patients who had ≥1 postbaseline computed tomography scan.
[c] Includes unconfirmed responses.
[d] Confirmation of investigator-assessed CR or PR per RECIST 1.1 was required after ≥4 weeks.
[e] For 2 patients with RECIST 1.1 CR and best change of <100%, the target lesion was a lymph node. Lymph nodes <10 mm diameter qualify as a CR even if the reduction is <100%.
[f] For 1 patient with 100% reduction in target lesion, the unconfirmed BOR was PR (due to non-CR response in non-target lesion) but due to lack of confirmed assessment ≥4 weeks later, the BOR was recorded as SD.
Note: in these footnotes, CR, PR, and SD denote complete response, partial response, and stable disease, respectively.

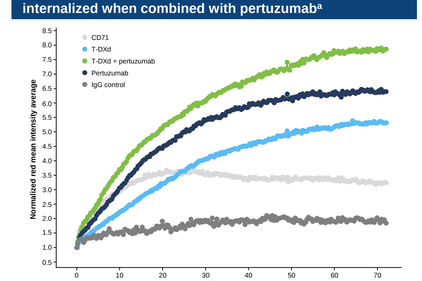
Figure 5. Best percent change in target lesion size with T-DXd + pertuzumab[a,b]



[a] Best change in target lesion size is the maximum reduction from baseline (or minimum increase from baseline in the absence of a reduction). Target lesion size is the sum of diameters of target lesions and was determined by investigator assessment per RECIST 1.1. Dashed horizontal line indicates 30% reduction. The color of each bar indicates the RECIST 1.1 response as assessed by investigators.
[b] Data are reported for patients who had ≥1 postbaseline computed tomography scan.
[c] Includes unconfirmed responses.
[d] Confirmation of investigator-assessed complete or partial response per RECIST 1.1 was required after ≥4 weeks.

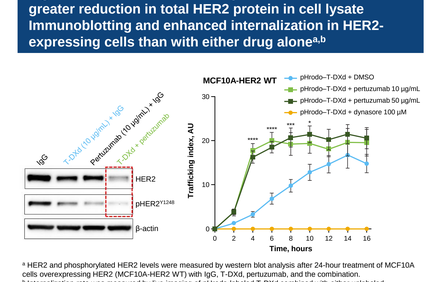
Preclinical studies

Figure 6. T-DXd was more rapidly and effectively internalized when combined with pertuzumab[a]



[a] Internalization rate was measured by pHrodo with labeled T-DXd, pertuzumab, IgG nontargeting control, and CD71 positive control. Combination arm is combination of labeled T-DXd and unlabeled pertuzumab.

Figure 7. T-DXd combined with pertuzumab showed a greater reduction in total HER2 protein in cell lysate Immunoblotting and enhanced internalization in HER2-expressing cells than with either drug alone[a,b]



[a] HER2 and phosphorylated HER2 levels were measured by western blot analysis after 24-hour treatment of MCF10A cells overexpressing HER2 (MCF10A-HER2 WT) with IgG, T-DXd, pertuzumab, and the combination.
[b] Internalization rate was measured by live imaging of pHrodo-labeled T-DXd combined with either unlabeled pertuzumab or with the endocytosis inhibitor dynasore.

Disclosures

Erika P. Hamilton reports consulting or advisory fees from Arcus, Arvinas, AstraZeneca, Black Diamond, Boehringer Ingelheim, CytomX, Daiichi Sankyo, Dantari, Deciphera Pharmaceuticals, Eisai, Greenwich LifeSciences, H3 Biomedicine, iTeos, Janssen, Lilly, Loxo, Merck, Mersana, Novartis, Orum Therapeutics, Pfizer, Propella Therapeutics, Puma Biotechnology, Relay Therapeutics, Seagen, Silverback Therapeutics, and Roche/Genentech and research funding to her institution from AbbVie, Acerta Pharma, Acrutar Biotechnology, ADC Therapeutics, AKESOBIO Australia, Amgen, Arqvive, ArQule, Artios, Arvinas, AstraZeneca, AtlasMedx, Black Diamond, Bliss BioPharmaceuticals, Boehringer Ingelheim, Cascadian Therapeutics, Clovis, Compugen, Cullen-Florence, Curis, CytomX, Daiichi Sankyo, Dana-Farber Cancer Institute, Dantari, Deciphera, Duality Biologics, eFFECTOR Therapeutics, Ellipses Pharma, Elucida Oncology, EMD Serono, Fochon, FujiFilm, G1 Therapeutics, H3 Biomedicine, Harpoon, Hutchinson MediPharma, Immunogen, Immunomedics, Incyte, Infinity Pharmaceuticals, inventisBio, Jacobio, Karyopharm, Leap Therapeutics, Lilly, Lycera, Mabspace Biosciences, Macrogenics, Medimmune, Merck, Mersana, Merus, Millennium, Molecular Templates, Myraid Genetic Laboratories, Novartis, Nucana, Olema, OncoMed, Orconova Therapeutics, ORIC Pharmaceuticals, Orinove, Pfizer, PharmaMar, Pieris Pharmaceuticals, Pionyr Immunotherapeutics, Plexxikon, Radius Health, Regeneron, Relay Therapeutics, Repertoire Immune Medicine, Rgenix, Roche/Genentech, Seagen, Sermonix Pharmaceuticals, Shattuck Labs, Silverback, StemCentRx, Sutro, Syndax, Syros, Taiho, Taplmmune, Tesaro, Tolmar, Torque Therapeutics, Treadwell Therapeutics, Verastem, Vincerx Pharma, Zenith Epigenetics, and Zymeworks.

Acknowledgments

We thank the patients who are participating in this study as well as their families and caregivers.

This study is sponsored by AstraZeneca Pharmaceuticals in collaboration with Daiichi Sankyo, Inc. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201).

Medical writing support was provided by Christopher Edwards, PhD, CMPP (ArticulateScience, LLC), and was funded by AstraZeneca.

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Abbreviations

AE, adverse event; AU, arbitrary units; BOR, best overall response; CD71, cluster of differentiation 71; DMSO, dimethyl sulfoxide; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HER2+, HER2-positive; IgG, immunoglobulin G; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival after next-line treatment; pHER2, phosphorylated HER2; pHER2^{Y1248}, HER2 phosphorylated at tyrosine 1248; PK, pharmacokinetics; PR, progesterone receptor; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; WT, wild type.

DESTINY-Breast07

San Antonio Breast Cancer Symposium® - December 6-10, 2022
Poster PD11-08

Trastuzumab Deruxtecan (T-DXd) + Durvalumab (D) as First-line (1L) Treatment for Unresectable Locally Advanced/Metastatic Hormone Receptor-negative (HR–), HER2-low Breast Cancer: Updated Results from BEGONIA, a Phase 1b/2 Study

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*Current affiliation: Merck Sharpe & Dohme LLC, Rahway, New Jersey

Introduction

- Patients with HR–, HER2-low (immunohistochemistry [IHC] score 1+ or IHC 2+ and negative in situ hybridization [ISH]) advanced/metastatic breast cancer (a/mBC) have poor prognosis (median progression-free survival [PFS] of 5.9 months[1]).[1,2]
- Combining immune checkpoint inhibitors with 1L chemotherapy modestly improves outcomes but only in programmed cell death ligand-1 (PD-L1)–high triple-negative a/mBC, emphasizing a critical unmet need for patients with PD-L1–low disease and for further improving outcomes in PD-L1–high disease.[3,4]
- BEGONIA (NCT03742102) is an ongoing 2-part, open-label platform study, evaluating safety and efficacy of durvalumab, an anti–PD-L1 antibody, combined with other novel therapies in 1L triple-negative a/mBC, including HR–, HER2-low disease.[5]
- T-DXd is an antibody-drug conjugate consisting of a HER2-targeting antibody and topoisomerase I inhibitor payload that showed 50% objective response rate (ORR) and median PFS of 8.5 months in patients with previously treated HR–, HER2-low mBC (NCT03734029).[6]
- Early data from BEGONIA Arm 6 of T-DXd in combination with durvalumab were presented at ASCO 2021 (n=11) and showed promising responses.[5]

Objective

- To report an update on safety, tolerability, and efficacy results as well as data from additional patients of the T-DXd + durvalumab combination in BEGONIA.

Methods

- The first 6 patients treated with T-DXd + durvalumab were evaluated for dose-limiting toxicities (DLTs), no DLTs were observed, and additional patients were enrolled in Part 1 (previously reported[6]); Part 1 ORR evaluation confirmed proceeding to the Part 2 expansion.
- Tumors were assessed per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 every 6 weeks for the first 48 weeks, then every 12 weeks thereafter.
- Confirmed response was assessed for patients who had the opportunity for ≥2 on-treatment disease assessments, progressed, or died.
- PD-L1 was assessed using the VENTANA PD-L1 (SP263) Assay; expression was defined as the percentage of the tumor area populated by tumor cells or immune cells with membranous staining (tumor area positivity [TAP]).
- A sample was considered PD-L1 high if it demonstrated ≥10% TAP PD-L1 expression.
- HER2 expression was assessed locally by IHC and ISH, which may have been determined by fluorescence or dual ISH methods.

Poster

Plain language summary

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BEGONIA Study Design

Eligibility criteria

- Unresectable locally advanced or metastatic Stage IV TNBC
- No prior treatment for Stage IV disease
- ≥12 months since taxane therapy for early-stage disease
- Eastern Cooperative Oncology Group performance status of 0–1
- Measurable disease per RECIST v1.1
- No autoimmune, inflammatory illnesses
- Adequate organ and marrow function

Additional criteria for T-DXd + durvalumab arm

- HER2-low tumor expression (per local testing; IHC 2+/ISH– or IHC 1+) and hormone receptor-negative tumors
- No ongoing pulmonary disorders

Treatment arms[a]

Arm 1: D + Paclitaxel (P)

Arm 2: D + P + Capivasertib

Arm 5: D + P + Oleclumab

Arm 7: D + Datopotamab Deruxtecan

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Arm 6: T-DXd + durvalumab (D)
T-DXd: 5.4 mg/kg IV Q3W
Durvalumab: 1120 mg IV Q3W
Treatment arm discussed in this presentation

Part 1

Arms 2–7 only: Safety run-in (up to 6 patients) → Simon 2-stage evaluation of ORR to precede initiation of Part 2 for each novel treatment arm. If expansion criteria are met, then novel treatment arm may proceed to Part 2

Primary endpoints	Safety and tolerability
Secondary endpoints	ORR, DoR, PFS, OS
Exploratory endpoint	Association of PD-L1 and HER2 expression with treatment response

Part 2 Expansion

Enrollment of additional 27 patients in the novel treatment arm

Primary endpoint	ORR
Secondary endpoints	PFS, DoR, PFS6, OS

[a]Arms 3 and 4, D + P + selumetinib and D + P + danvatirsen, were removed from the protocol prior to enrolling patients.

Results and Interpretation

- As of the data cutoff of July 22, 2022, 58 patients received T-DXd + durvalumab in Parts 1 and 2, with 28 receiving ongoing treatment (**Table 1**).
  - Ten discontinued T-DXd + durvalumab because of an adverse event (AE), 19 discontinued due to progression, and 4 for other reasons (more than 1 reason may have been reported).
- Median (range) follow-up time was 13.4 (1–25) months.

Table 1. Patient and disease characteristics

Characteristic	N=58
Age, median (range), years	54 (29–81)
Race, n (%)	
White	39 (67.2)
Asian	16 (27.6)
Black/African American	2 (3.4)
Other	1 (1.7)
No prior treatment, n (%)	16 (27.6)
Prior treatments for early-stage disease, n (%)	
Radiotherapy	35 (60.3)
Cytotoxic chemotherapy	37 (63.8)
Taxane	32 (55.2)
Anthracycline	37 (63.8)
Platinum compound	12 (20.7)
Hormonal therapy	16 (27.6)
Targeted therapy	1 (1.7)
Visceral metastases[a], n (%)	39 (67.2)
Lymph node metastases, n (%)	36 (62.1)
PD-L1 expression, n (%)	
High (TAP ≥10%)	7 (12.1)
Low (TAP <10%)	45 (77.6)
Missing	6 (10.3)
HER2 expression, local testing, n (%)	
IHC 1+	37 (63.8)
IHC 2+ / ISH–	21 (36.2)

[a]Defined as liver/hepatic and/or respiratory metastases.

Table 2. Safety summary

	N=58
Any Grade AE, n (%)	57 (98.3)
Common AEs (≥20% patients, any grade)	
Nausea	45 (77.6)
Fatigue	30 (51.7)
Neutropenia	18 (31.0)
Vomiting	17 (29.3)
Alopecia	16 (27.6)
Decreased appetite	15 (25.9)
Anemia, constipation	14 (24.1) each
Asthenia, diarrhea	12 (20.7) each
Any Grade 3/4 AE	25 (43.1)
Any serious AE	12 (20.7)
Any treatment-related AE[a]	55 (94.8)
Grade 3/4	20 (34.5)
Any durvalumab AESI	43 (74.1)
Any T-DXd AESI	13 (22.4)
AE leading to T-DXd + D discontinuation	10 (17.2)
AE leading to dose interruption	32 (55.2)
AE leading to death[b]	2 (3.4)
Durvalumab dose delay	26 (44.8)
T-DXd dose delay	24 (41.4)
T-DXd dose reduction	6 (10.3)

AESI, adverse event of special interest.
[a]Per investigator assessment. [b]1 patient died due to cardiac failure unrelated to treatment and 1 patient died due to COVID-associated pneumonitis, which was adjudicated as treatment-related.

- No DLTs were observed.
- Common AEs were mainly gastrointestinal and hematologic (**Table 2**).
- Grade 3/4 AEs were mainly hematologic; the most common were neutropenia (13 [22.4%]) and anemia (5 [8.6%]).
- Durvalumab AESIs occurring in ≥10% of patients were diarrhea, hypothyroidism, interstitial lung disease (ILD)/pneumonitis, and rash; most cases were Grade 1/2.
- T-DXd AESIs occurring in ≥10% of patients were ILD/pneumonitis; most cases were Grade 1/2.
- The adjudication committee confirmed 8 cases of treatment-related ILD/pneumonitis: Grade 1 (n=3), Grade 2 (n=3), Grade 3 (n=1), and Grade 5 (n=1; COVID-associated pneumonitis).
  - 2 additional cases are pending review.

Table 3. Response and survival outcomes

	N=58
Confirmed ORR, n (%)	33 (56.9)
95% CI	43.2–69.8
CR	1 (1.7)
PR	32 (55.2)
Unconfirmed ORR, n (%)	35 (60.3)
95% CI	46.6–73.0
Median PFS (95% CI), months	12.6 (8.3–NC)

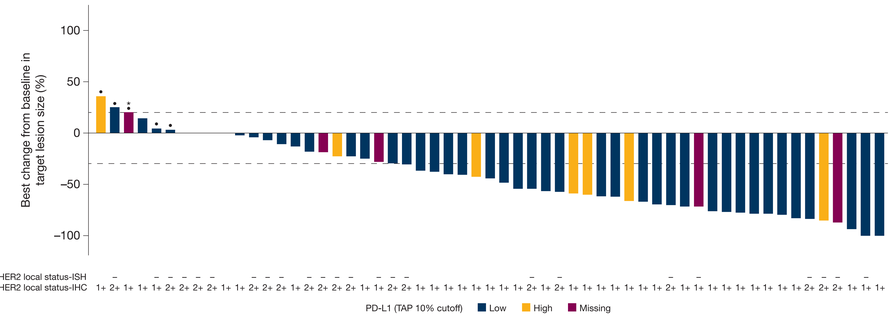
CR, complete response; NC, not calculated; PR, partial response.

- With T-DXd + durvalumab treatment, 56.9% of patients had a confirmed tumor response (**Table 3, Figure 1**).
- Responses were durable, with 69.7% of patients having ongoing response at the data cutoff (**Figure 2**).
- Responses were observed in PD-L1–low and PD-L1–high tumors (**Figure 1**).

Table 4. ORR based on HER2 status

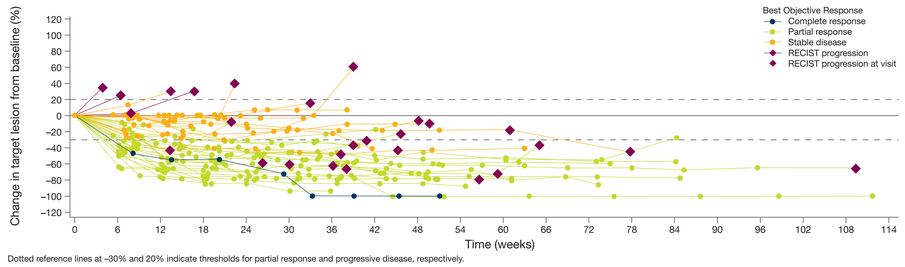
HER2 status, local testing	IHC 1+ n=37	IHC 2+/ISH– n=21
Confirmed ORR, n (%)	25 (67.6)	8 (38.1)
95% CI	50.2–82.0	18.1–61.6
Unconfirmed ORR, n (%)	26 (70.3)	9 (42.9)
95% CI	53.0–84.1	21.8–66.0

Figure 1. Best change from baseline of target lesion size



Dotted reference lines at −30% and 20% indicate thresholds for partial response and progressive disease, respectively.
[a]If the best percentage change from baseline of target lesions cannot be calculated due to progression, withdrawal, or death, the value is imputed at +20%. "•" Patients with progressive disease as best overall response.

Figure 2. Change from baseline in sum of target lesions over time



Dotted reference lines at −30% and 20% indicate thresholds for partial response and progressive disease, respectively.

Conclusions

- For patients with HR–, HER2-low a/mBC, T-DXd in combination with durvalumab in the 1L setting shows a tolerable and manageable safety profile consistent with the known profile of individual agents.
- These updated results further demonstrate promising efficacy (response rate, durability of response, and PFS) of T-DXd + durvalumab in 1L HR–, HER2-low mBC.
  - Responses were observed in patients with HER2 IHC 1+ and IHC 2+/ISH– as well as with PD-L1–high and PD-L1–low tumors.
- Results for T-DXd + durvalumab in the 1L setting from BEGONIA, as well as previously reported Phase 3 results of T-DXd alone in the second-line or greater setting, support additional studies of these treatments in 1L HR–, HER2-low mBC.

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Acknowledgments

This study was funded by AstraZeneca and Daiichi Sankyo. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201). The authors would like to thank the patients, their families and caregivers, and all investigators involved in this study. Medical writing support, which was in accordance with Good Publication Practice (GPP3) guidelines, was provided by Nicole Seneca, PhD, of Parexel and was funded by AstraZeneca.

PD13-08

Phase 1 TROPION-PanTumor01 Study Evaluating Datopotamab Deruxtecan (Dato-DXd) in Unresectable or Metastatic Hormone Receptor–Positive/HER2-Negative Breast Cancer

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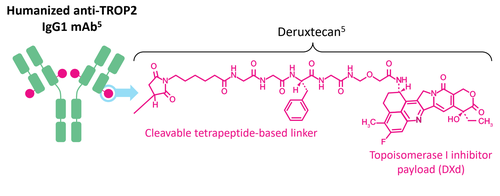
Introduction

- Available treatment options for patients with HR+/HER2− breast cancer who have progressed on or after endocrine therapy have shown limited efficacy[1]
- TROP2 is highly expressed in various tumor types, including breast cancer, and high membrane expression levels may be a marker of poor prognosis in patients with breast cancer[2-4]
- Datopotamab deruxtecan (Dato-DXd) is an antibody-drug conjugate consisting of a humanized anti-TROP2 IgG1 monoclonal antibody covalently linked to a highly potent topoisomerase I inhibitor payload via a stable, tumor-selective, tetrapeptide-based cleavable linker



7 Key Attributes

Payload mechanism of action: topoisomerase I inhibitor[5-7,a]
High potency of payload[5-7,a]
Optimized drug to antibody ratio ≈4[5,a,b]
Payload with short systemic half-life[5-7,a,b]
Stable linker-payload[5-7,a]
Tumor-selective cleavable linker[5-7,a]
Bystander antitumor effect[6,8,a]

[a]The clinical relevance of these features is under investigation. [b]Based on animal data.

- TROPION-PanTumor01 (NCT03401385) is evaluating the safety and efficacy of Dato-DXd in advanced/metastatic breast cancer, NSCLC, and other tumor types[9-11]
  - Based on clinical results and exposure-response analyses, 6 mg/kg was selected for dose expansion across the clinical development program, which includes different tumor types and the following trials: the phase 3 TROPION-Lung01, phase 1 TROPION-Lung02, phase 3 TROPION-Lung07, phase 3 TROPION-Lung08, phase 3 TROPION-Breast01, and phase 3 TROPION-Breast02 trials[10,12-18]
- Here we present the first reported results in patients with unresectable or metastatic HR+/HER2− breast cancer (data cutoff: July 22, 2022)

Objectives

- To assess the safety and tolerability of Dato-DXd at the recommended dose for expansion
- To assess the efficacy of Dato-DXd in patients with advanced HR+/HER2− breast cancer

Conclusions

- In heavily pretreated patients with HR+/HER2− breast cancer, Dato-DXd showed highly encouraging and durable efficacy
  - Confirmed ORR and DCR by BICR were 27% and 85%, respectively; median DOR was not evaluable
  - Median PFS by BICR was 8.3 months (95% CI, 5.5-11.1 months)
- Dato-DXd demonstrated a manageable safety profile with no new safety signals
  - TEAEs were primarily grade 1 or 2, with stomatitis and nausea being the most common
  - No cases of grade ≥3 diarrhea or febrile neutropenia were observed
  - Enhanced management guidelines for stomatitis were initiated after patients enrolled in this study
- Further studies of Dato-DXd in breast cancer are warranted
  - A phase 3, randomized trial, TROPION-Breast01 (NCT05104866), that compares Dato-DXd vs chemotherapy as 2L therapy for metastatic HR+/HER2− breast cancer is currently underway

Poster presented at: 2022 SABCS Annual Meeting; December 6-10, 2022; San Antonio, TX.

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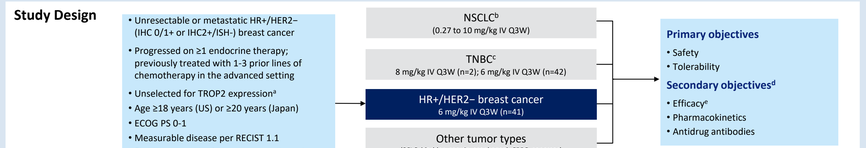
Methods

- TROPION-PanTumor01 (NCT03401385) is a phase 1, multicenter, open-label, 2-part, dose-escalation and -expansion study evaluating Dato-DXd in previously treated patients with solid tumors
- The primary objectives were safety and tolerability
- Tumor responses, including ORR (CR + PR) and DCR (CR + PR + SD), were assessed by BICR per RECIST version 1.1

Study Design



[a] Pretreatment tumor tissue was required for retrospective analysis of TROP2 expression. [b] Results from the NSCLC cohort have been previously reported.[10,12] [c] Includes patients treated in the dose-escalation and dose-expansion portions. [d] Exploratory objectives include analyses of biomarkers associated with response. [e] Response assessments are based on RECIST 1.1.

Results

- As of the July 22, 2022, data cutoff, 41 patients had received Dato-DXd 6 mg/kg, and 5 patients had treatment ongoing (median study duration, 13.7 months [range, 9-16 months]); the primary cause of treatment discontinuation was disease progression (71%, including PD or clinical progression)
  - In this heavily pretreated patient population, with a median of 5 prior regimens (range, 3-10) for metastatic disease; 95% of patients had prior CDK4/6 inhibitors in the adjuvant or metastatic setting (**Table 1**)
- All-cause TEAEs were observed in 100% (any grade) and 41% (grade ≥3) of patients (**Tables 2** and **3**)
  - The most common TEAEs (any grade, grade ≥3; **Table 3**) were stomatitis (83%, 10%), nausea (56%, 0%), and fatigue (46%, 2%); of the 15 patients (37%) with alopecia, 17% had grade 1 and 20% had grade 2
  - Cases of stomatitis were primarily grade 1 or 2 (37% each)
  - Three patients (7%) experienced neutropenia, 5% had grade 1 and 2% had grade 2
  - Two patients had pneumonitis (grade 2 and 3), and 1 was adjudicated as having grade 3 drug-related interstitial lung disease
  - One patient died due to dyspnea, which was not considered to be treatment related
- Confirmed responses by BICR were observed in 11 patients (27%; **Table 4** and **Figure 2**)
- Responses were durable (**Figures 3** and **4**); median progression-free survival was 8.3 months (95% CI, 5.5-11.1 months)
- Median overall survival was not reached, with 59% of patients alive for >1 year

Table 1. Baseline Characteristics

Patient characteristics	N=41
Age, median (range), years	57 (33-75)
Country, n (%)	
US/Japan	35 (85)/6 (15)
ECOG PS, n (%)	
0/1	20 (49)/21 (51)
De novo metastatic disease, n (%)	
Yes	21 (51)
No	20 (49)
Brain metastases, n (%)	6 (15)
Median time from initial treatment for metastatic disease to the first dose, median (range), months	42.7 (10.2-131.1)
Prior therapies in the adjuvant or metastatic setting	
(Neo)adjuvant chemotherapy	15 (37)
Prior therapies in metastatic setting, median (range), n	5 (3-10)
Prior chemotherapy regimens in metastatic setting, median (range), n	2 (1-6)
Endocrine therapy in metastatic setting ≥6 months	33 (80)
CDK4/6 inhibitors	39 (95)
≤12 months	19 (46)
>12 months	20 (49)
Capecitabine	34 (83)
Taxanes	24 (59)
Anthracyclines	22 (54)
mTOR inhibitors	12 (29)
PI3K inhibitors[a]	8 (20)
Topo I inhibitor–based ADC	0

[a] One patient received a dual mTOR/PI3K inhibitor.

Table 2. Safety Summary

Patients, n (%)	N=41 Any grade	Grade ≥3
TEAEs	41 (100)	17 (41)
Treatment-related TEAEs	41 (100)	9 (22)
Dose adjustments due to AEs		
Dose reductions[a]	5 (12)	
Treatment interruptions[b]	15 (37)	
Treatment discontinuations[c]	5 (12)	
Serious TEAEs	6 (15)	
Treatment related[d]	1 (2)	

[a] Dose reductions occurred in 5 patients due to stomatitis (n=4), fatigue (n=1), keratitis (n=1), and decreased appetite (n=1). [b] >1 AE per patient; [c] Fifteen patients had treatment delayed due to stomatitis (n=7), retinopathy (n=1), dysphagia (n=1), nausea (n=1), fatigue (n=2), malaise (n=1), COVID-19 (n=1), cellulitis (n=1), otitis media (n=1), urinary tract infection (n=1), fall (n=1), decreased lymphocyte count (n=1), and nasal congestion (n=1). >1 AE per patient; [d] Five patients discontinued treatment due to keratitis (n=1), keratopathy (n=1), stomatitis (n=1), and pneumonitis (n=2); [d]Treatment-related serious TEAE was pneumonitis.

Table 3. All-Cause TEAEs Observed in ≥15% of Patients

TEAEs, n (%)[a]	N=41 Any grade	Grade ≥3
Any TEAE	**41 (100)**	**17 (41)**
Stomatitis	34 (83)	4 (10)
Nausea	23 (56)	0
Fatigue	19 (46)	1 (2)
Alopecia	15 (37)	NA
Headache	12 (29)	0
Constipation	11 (27)	0
Vomiting	10 (24)	0
Dry eye	10 (24)	0
Anemia	7 (17)	3 (7)
Dyspnea	7 (17)	1 (2)
Diarrhea	7 (17)	0
Decreased appetite	7 (17)	0
Rash	7 (17)	0
Cataract[a]	6 (15)	0
Decreased lymphocyte count	6 (15)	6 (15)
Cough	6 (15)	0
Hypokalemia	6 (15)	0

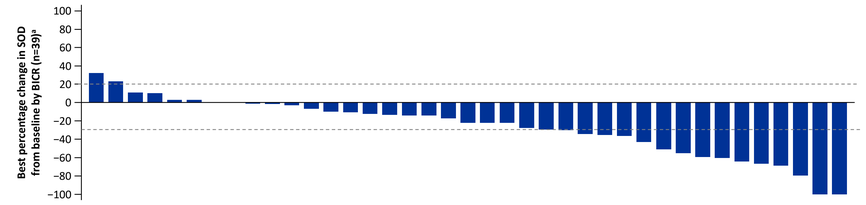
[a] All 6 cases (5 grade 1 and 1 grade 2) were reported as not related to study drug.

Table 4. Best Overall Response by BICR

Patients, n (%)[a]	N=41
Objective response rate	11 (27)
Partial response	11 (27)
Non-CR/non-PD	1 (2)
Stable disease	23 (56)
Not evaluable	1 (2)
Disease control rate	35 (85)
Clinical benefit rate[b]	18 (44)
Progressive disease	5 (12)
Duration of response, median (95% CI), months	NE (4.4-NE)

[a] Postbaseline tumor assessments were not available for 1 patient at data cutoff. One patient was not confirmed to have a target lesion per BICR and had a best overall response of non-CR/non-PD. [b] CR + PR + SD for ≥6 months.

Figure 2. Antitumor Responses by BICR



[a] Postbaseline tumor assessments were not available for 1 patient at data cutoff. One patient was not confirmed to have a target lesion per BICR and therefore had a best overall response of non-CR/non-PD.

Figure 3. Tumor Responses Were Durable

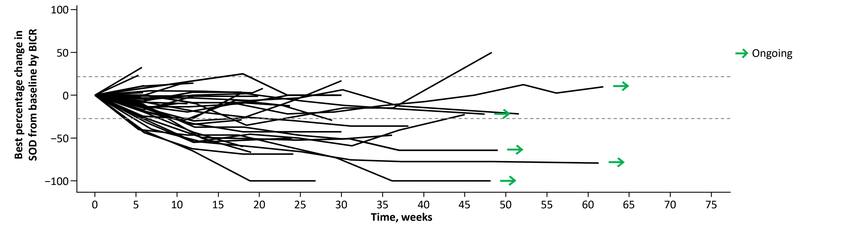
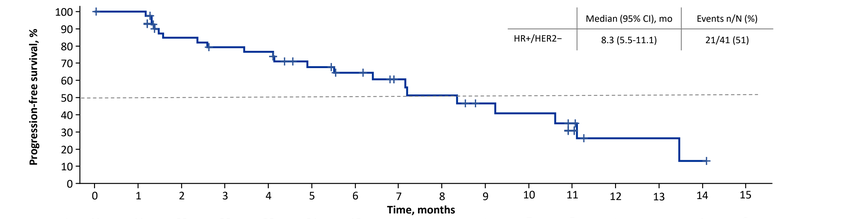


Figure 4. Progression-Free Survival by BICR



	Median (95% CI), mo	Events n/N (%)
HR+/HER2−	8.3 (5.5-11.1)	21/41 (51)

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Abbreviations

2L, second line; ADC, antibody-drug conjugate; AE, adverse event; BICR, blinded independent central review; CDK4/6, cyclin dependent kinases 4/6; CR, complete response; CRPC, castration-resistant prostate cancer; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IgG1, immunoglobulin G1; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenous; mTOR, mechanistic target of rapamycin kinase; NA, not available; NE, not evaluable; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PI3Ki, phosphatidyl 3-kinase inhibitor; PR, partial response; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SCLC, small-cell lung cancer; SD, stable disease; SOD, sum of diameters; TEAE, treatment-emergent adverse event; TNBC, triple-negative breast cancer; Topo I, topoisomerase I; TROP2, trophoblast cell-surface antigen 2.

Acknowledgments

We thank the patients, their families, and their caregivers for their participation and the study staff for their contributions.
This study is sponsored by Daiichi Sankyo, Inc. In July 2020, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for datopotamab deruxtecan (Dato-DXd).
Medical writing support was provided by Allison Lytle, PhD, of ArticulateScience, LLC, and was funded by Daiichi Sankyo, Inc. Editorial support was provided in accordance with Good Publication Practice guidelines (ismpp.org/gpp-2022).

Funding

This study is sponsored by Daiichi Sankyo, Inc.

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P6-10-03

Datopotamab Deruxtecan (Dato-DXd) in Advanced Triple-Negative Breast Cancer (TNBC): Updated Results From the Phase 1 TROPION-PanTumor01 Study

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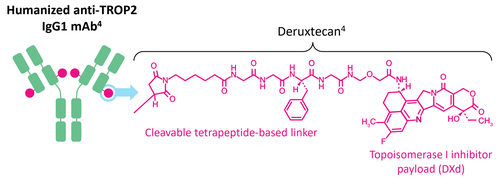
Introduction

- Effective treatment options are limited for patients with advanced or metastatic TNBC who have progressed or are refractory to standard treatments
- TROP2 is highly expressed in various tumor types, including breast cancer, and high membrane expression levels may be a marker of poor prognosis in patients with breast cancer[1-3]
- Datopotamab deruxtecan (Dato-DXd) is an antibody-drug conjugate consisting of a humanized anti-TROP2 IgG1 monoclonal antibody covalently linked to a highly potent topoisomerase I inhibitor payload via a stable, tumor-selective, tetrapeptide-based cleavable linker



The 7 Key Attributes

Payload mechanism of action: topoisomerase I inhibitor[4-6,a]
High potency of payload[4-6,a]
Optimized drug to antibody ratio ≈4[4,a,b]
Payload with short systemic half-life[4-6,a,b]
Stable linker-payload[4-6,a]
Tumor-selective cleavable linker[4-6,a]
Bystander antitumor effect[6,7,a]

[a]The clinical relevance of these features is under investigation. [b]Based on animal data.

- TROPION-PanTumor01 (NCT03401385) is evaluating the safety and efficacy of Dato-DXd in advanced/metastatic breast cancer, NSCLC, and other tumor types[8-10]
  - Based on clinical results and exposure-response analyses, 6 mg/kg was selected for expansion across the clinical development program, which includes different tumor types and the following ongoing trials: the phase 3 TROPION-Lung01, phase 1 TROPION-Lung02, phase 3 TROPION-Lung07, phase 3 TROPION-Lung08, phase 3 TROPION-Breast01, and the phase 3 TROPION-Breast02[8,11-17]
- Here we present the updated results for patients with advanced TNBC (data cutoff: July 22, 2022)

Objectives

- To assess the safety and tolerability of Dato-DXd at the recommended dose for expansion
- To assess the efficacy of Dato-DXd in patients with advanced TNBC

Abbreviations

1L, first line; ADC, antibody-drug conjugate; AE, adverse event; BICR, blinded independent central review; BL, baseline; CR, complete response; CRPC, castration-resistant prostate cancer; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IgG1, immunoglobulin G1; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, in situ hybridization; IV, intravenous; NA, not available; NE, not evaluable; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PARPi, poly-ADP ribose polymerase inhibitor; PD, progressive disease; PFS, progression-free survival; PR, partial response; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SCLC, small cell lung cancer; SD, stable disease; SOD, sum of diameters; TEAE, treatment-emergent adverse event; TNBC, triple-negative breast cancer; Topo I, topoisomerase I, TROP2, trophoblast cell-surface antigen 2.

Funding

This study is sponsored by Daiichi Sankyo, Inc.

Acknowledgments

- We thank the patients, their families, and their caregivers for their participation and the study staff for their contributions
- This study is sponsored by Daiichi Sankyo, Inc. In July 2020, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for datopotamab deruxtecan (Dato-DXd)
- Medical writing support was provided by Allison Lytle, PhD, of ArticulateScience, LLC, and was funded by Daiichi Sankyo, Inc. Editorial support was provided in accordance with Good Publication Practice guidelines (ismpp.org/gpp-2022)

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Poster presented at: 2022 SABCS Annual Meeting; December 6-10, 2022; San Antonio, TX.

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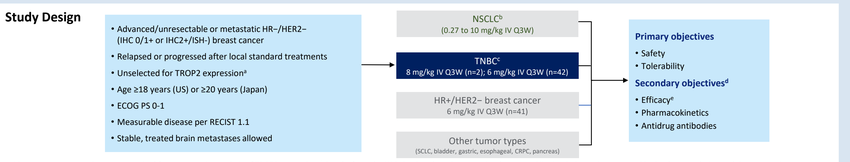
Methods

- TROPION-PanTumor01 (NCT03401385) is a phase 1, multicenter, open-label, 2-part, dose-escalation and -expansion study evaluating Dato-DXd in previously treated patients with solid tumors
- The primary objectives were safety and tolerability
- Tumor responses, including ORR (CR+ PR) and DCR (CR + PR + SD), were assessed by BICR per RECIST version 1.1

Study Design



[a]Pretreatment tumor tissue was required for retrospective analysis of TROP2 expression. [b]Results from the NSCLC cohort have been previously reported.[8,11] [c]Includes patients treated in the dose-escalation and dose-expansion portions. [d]Exploratory objectives include analyses of biomarkers associated with response. [e]Response assessments are based on RECIST 1.1.

Results

- As of the July 22, 2022, data cutoff, 44 patients had received Dato-DXd and 3 patients had treatment ongoing (median study duration, 19.3 months [range, 15-25 months]); the primary cause of treatment discontinuation was disease progression (86%, including PD or clinical progression)
  - Patients were heavily pretreated, with a median of 3 prior regimens (range, 1-10) in the advanced setting (**Table 1**)
- All cause TEAEs were observed in 100% (any grade) and 52% (grade ≥3) of patients (**Tables 2 and 3**)
  - The most common TEAEs (any grade, grade ≥3; **Table 3**) were stomatitis (73%, 11%), nausea (66%, 2%), and vomiting (39%, 5%)
  - Of the 16 patients (36%) who experienced alopecia, 23% had grade 1 and 14% had grade 2
  - One patient experienced grade 3 decreased neutrophil count
  - No cases of ILD, febrile neutropenia, or grade ≥3 diarrhea were reported
  - No treatment-related deaths were observed
- Antitumor responses were observed in the majority of patients (**Figure 2**), with an ORR of 32% in all patients and 44% in patients who were treatment naive to Topo I inhibitor–based ADC therapies and had measurable disease at baseline (**Table 4**)
  - A median DOR of 16.8 months in each patient group and a median survival of 13.5 months in all treated patients and 14.3 months in Topo I inhibitor–naive patients were observed (**Figures 3 and 4**)

Table 1. Baseline Characteristics

Patient characteristics	N=44
Age, median (range), years	53 (32-82)
Country, n (%)	
US	31 (70)
Japan	13 (30)
ECOG PS, n (%)	
0	18 (41)
1	26 (59)
De novo metastatic disease, n (%)	
Yes	14 (32)
No	30 (68)
Brain metastases, n (%)	5 (11)
Prior therapies in metastatic setting, median (range), n	3 (1-10)
Previous systemic treatment, n (%)	
Taxanes	41 (93)
Anthracyclines	33 (75)
Capecitabine	27 (61)
Platinum-based chemotherapy	23 (52)
Immunotherapy	20 (45)
Topo I inhibitor–based ADC[a]	14 (32)
PARPi	8 (18)

[a]Sacituzumab govitecan, n=11; trastuzumab deruxtecan, n=2; patritumab deruxtecan, n=1.

Table 2. Safety Summary

Patients, n (%)	N=44	
	Any grade	Grade ≥3
TEAEs	44 (100)	23 (52)
Treatment-related TEAEs	43 (98)	11 (25)
Dose adjustments due to AEs		
Dose reductions[a]	7 (16)	
Treatment interruptions[b]	12 (27)	
Treatment discontinuations[c]	1 (2)	
Serious TEAEs	9 (20)	
Treatment related[d]	2 (5)	

[a]Dose reductions occurred in 7 patients due to stomatitis (n=2), fatigue (n=2), dry eye (n=1), retinal exudates (n=1), and dysgeusia (n=1); [b]Twelve patients had treatment delayed due to stomatitis (n=7), dry eye (n=1), blurred vision (n=1), bronchitis (n=1), skin infection (n=1), musculoskeletal chest pain (n=1), dysgeusia (n=1), chronic obstructive pulmonary disease (n=1), dermatitis acneiform (n=1), and dyspnea (n=1), >1 AE per patient; [c]One patient discontinued treatment due to grade 1 pneumonitis (which was centrally adjudicated as not ILD); [d]Treatment-related serious TEAEs included nausea, upper gastrointestinal hemorrhage, and vomiting, >1 AE per patient.

Table 3. All-Cause TEAEs Observed in ≥15% of Patients

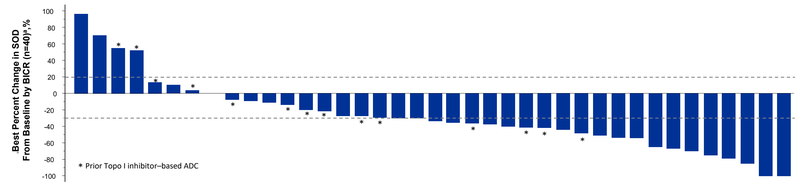
TEAEs, n (%)	N=44	
	Any grade	Grade ≥3
Any TEAE	44 (100)	23 (52)
Stomatitis	32 (73)	5 (11)
Nausea	29 (66)	1 (2)
Vomiting	17 (39)	2 (5)
Alopecia	16 (36)	NA
Fatigue	15 (34)	3 (7)
Headache	11 (25)	0
Constipation	10 (23)	0
Decreased neutrophil count	9 (20)	1 (2)
Pyrexia	8 (18)	0
Cough	8 (18)	0
Decreased lymphocyte count	8 (18)	3 (7)
Anemia	7 (16)	1 (2)
Decreased appetite	7 (16)	0
Hypokalemia	7 (16)	0
Diarrhea	7 (16)	0
Rash	7 (16)	0
Dry eye	7 (16)	0

Table 4. Best Overall Response by BICR

Patients, n (%)[a]	All patients N=44	Topo I inhibitor–naive patients with measurable disease at BL n=27
Objective response rate	14 (32)	12 (44)
Complete response	1 (2)	1 (4)
Partial response	13 (30)	11 (41)
Non-CR/non-PD	3 (7)	0
Stable disease	18 (41)	10 (37)
Not evaluable	1 (2)	1 (4)
Disease control rate	35 (80)	22 (81)
Clinical benefit rate (CR + PR + SD ≥ 6mo)	17 (39)	13 (48)
Progressive disease	8 (18)	4 (15)
Duration of response, median (95% CI), mo	16.8 (5.6-NE)	16.8 (5.6-NE)

[a]Postbaseline tumor assessments were not available for 1 patient at data cutoff. Three patients were not confirmed to have a target lesion per BICR and had a best overall response of non-CR/non-PD.

Figure 2. Antitumor Tumor Responses by BICR



[a]Postbaseline tumor assessments were not available for 1 patient at data cutoff. Three patients were not confirmed to have a target lesion per BICR and therefore had a best overall response of non-CR/non-PD.

Figure 3. Progression-Free Survival by BICR

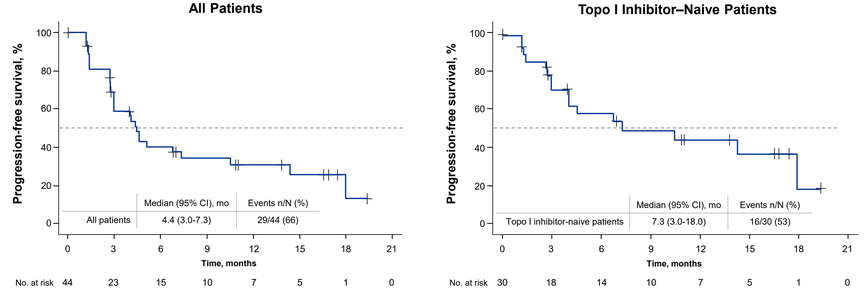
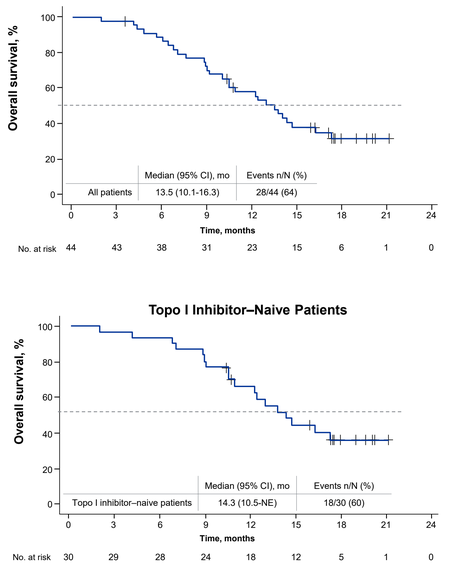


Figure 4. Overall Survival



Conclusions

- In heavily pretreated patients with advanced TNBC, Dato-DXd showed highly encouraging and durable responses
  - ORR by BICR was 32% in all patients and 44% in Topo I inhibitor–naive patients with measurable disease at baseline; median DOR was 16.8 months in both groups
  - Median PFS was 4.4 months (95% CI, 3.0-7.3 months) in all patients and 7.3 months (95% CI, 3.0-18.0 months) in Topo I inhibitor–naive patients
  - Median OS was 13.5 months (95% CI, 10.1-16.3 months) in all patients and 14.3 months (95% CI, 10.5-NE) in Topo I inhibitor–naive patients
- Dato-DXd demonstrated a manageable safety profile, and no new safety signals were observed
  - Grade 1 or 2 nausea and stomatitis were the most frequent TEAEs
  - Neutropenia and diarrhea (≤20%) were uncommon
- Enhanced management guidelines for stomatitis were initiated after patients enrolled in this study
- Further studies of Dato-DXd in TNBC are warranted
  - Dato-DXd is being evaluated as 1L therapy compared with chemotherapy in the phase 3 TROPION-Breast02 (NCT05374512) trial
  - BEGONIA is a phase 1b/2 trial evaluating the efficacy and safety of Dato-DXd in combination with durvalumab

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San Antonio Breast Cancer Symposium® - December 6-10, 2022
Poster PD11-09

Datopotamab Deruxtecan (Dato-DXd) + Durvalumab (D) as First-line (1L) Treatment for Unresectable Locally Advanced/Metastatic Triple-negative Breast Cancer (a/mTNBC): Updated Results from BEGONIA, a Phase 1b/2 Study

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Introduction

- Patients with a/mTNBC have limited treatment options and a poor prognosis (objective response rate [ORR] of 37%, median duration of response of 6.5 months, and median overall survival [OS] of 15.5 months with 1L chemotherapy).[1]
- Combining immune checkpoint inhibitors with 1L chemotherapy modestly improves outcomes but only in programmed cell death ligand-1 (PD-L1)–high a/mTNBC, emphasizing a critical unmet need for patients with PD-L1–low disease and for further improving outcomes in PD-L1–high disease.[2,3]
- BEGONIA (NCT03742102) is an ongoing 2-part, open-label platform study, evaluating safety and efficacy of durvalumab, an anti–PD-L1 antibody, combined with other novel therapies in 1L a/mTNBC, including Dato-DXd.[4]
- Dato-DXd is an antibody-drug conjugate consisting of a humanized anti-TROP2 antibody covalently linked to a highly potent topoisomerase I inhibitor payload via a stable, tumor-selective, tetrapeptide-based cleavable linker.[5,6]
- Early data from BEGONIA Arm 7 of durvalumab in combination with Dato-DXd were presented at ESMO Breast 2022 (n=29) and showed promising responses.[7]

Objective

- To report an update on safety, tolerability, and efficacy results as well as data from additional patients of the Dato-DXd + durvalumab combination in BEGONIA.

Methods

- The first 6 patients treated with Dato-DXd + durvalumab were evaluated for dose-limiting toxicities (DLTs), no DLTs were observed, and additional patients were enrolled in Part 1 (previously reported[7]); Part 1 ORR evaluation confirmed proceeding to the Part 2 expansion.
- Tumors were assessed per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 every 6 weeks for the first 48 weeks, then every 12 weeks thereafter.
- PD-L1 was assessed using the VENTANA PD-L1 (SP263) Assay, and expression was defined as the percentage of the tumor area populated by tumor or immune cells with membranous staining (tumor area positivity [TAP]).
- A sample was considered PD-L1 high if it demonstrated ≥10% TAP PD-L1 expression.
- Confirmed response was assessed for patients who had the opportunity for ≥2 on-treatment disease assessments, progressed, or died; unconfirmed response was assessed for patients who had the opportunity for ≥1 on-treatment disease assessment.

Poster

Plain Language Summary

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BEGONIA Study Design

Eligibility criteria

- Unresectable, locally advanced, or metastatic Stage IV TNBC
- No prior treatment for Stage IV disease.
- ≥12 months since taxane therapy for early-stage disease
- Measurable disease per RECIST v1.1
- Eastern Cooperative Oncology Group performance status of 0–1
- No autoimmune, inflammatory illnesses
- Adequate organ and marrow function

Additional criteria for Dato-DXd + durvalumab arm

- No prior treatment with immune checkpoint inhibitors or TOPO I-based antibody-drug conjugates

Treatment arms[a]

Arm 1: D + Paclitaxel (P)

Arm 2: D + P + Capivasertib

Arm 5: D + P + Oleclumab

Arm 6: D + Trastuzumab deruxtecan

Poster PD11-08

Arm 7: Dato-DXd + durvalumab (D)

Dato-DXd: 6 mg/kg IV Q3W

Durvalumab: 1120 mg IV Q3W

Treatment arm discussed in this presentation

Part 1

Arms 2–7 only: Safety run-in (up to 6 patients) → Simon 2-stage evaluation of ORR to precede initiation of Part 2 for each novel treatment arm. If expansion criteria are met, then novel treatment arm may proceed to Part 2

Primary endpoints	Safety and tolerability
Secondary endpoints	ORR, DoR, PFS, OS

Part 2 Expansion

Enrollment of additional 27 patients in the novel treatment arm

Primary endpoint	ORR
Secondary endpoints	PFS, DoR, PFS6, OS

Exploratory endpoint	Association of PD-L1 expression with treatment response

[a]Arms 3 and 4, D + P + selumetinib and D + P + danvatirsen, were removed from the protocol prior to enrolling patients.

Results and Interpretation

- As of the data cutoff of July 22, 2022, 61 patients received Dato-DXd + durvalumab in Parts 1 and 2, with 45 receiving ongoing treatment (**Table 1**).
  - Four discontinued Dato-DXd + durvalumab because of an adverse event (AE), 13 discontinued due to progression, and 1 patient decided to stop treatment (more than1 reason may have been reported).
- Median (range) follow-up time was 7.2 (1–14) months.

Table 1. Patient and disease characteristics

Characteristic	N=61
Age, median (range), years	53 (31–74)
Race, n (%)	
White	38 (62.3)
Asian	15 (24.6)
Black/African American	4 (6.6)
Other	4 (6.6)
No prior treatment, n (%)	25 (41.0)
Prior treatments for early-stage disease, n (%)	
Radiotherapy	30 (49.2)
Cytotoxic chemotherapy	32 (52.5)
Taxane	25 (41.0)
Anthracycline	28 (45.9)
Platinum compound	9 (14.8)
Hormonal therapy	9 (14.8)
Targeted therapy	3 (4.9)
Visceral metastases[a], n (%)	35 (57.4)
Lymph node metastases, n (%)	41 (67.2)
PD-L1 expression, n (%)	
High (TAP ≥10%)	7 (11.5)
Low (TAP <10%)	53 (86.9)
Missing	1 (1.6)

[a]Defined as liver/hepatic and/or respiratory metastases.

- No DLTs were reported.
- Common AEs were mostly gastrointestinal (**Table 2**).
- 11 patients (18.0%) underwent Dato-DXd dose reduction due to an AE, 7 (11.5%) of those were associated with stomatitis.
- Of the neutropenic (2 [3.3%]) events reported, none were Grade 3 or 4; diarrhea was reported for 8 (13.1%) patients, with 1 Grade 3 event and no Grade 4 events.
- The adjudication committee confirmed 2 (3.3%) patients had Grade 1 interstitial lung disease/pneumonitis.
- Durvalumab AEs of special interest (AESIs) occurring in ≥10% of patients were rash, diarrhea, and hypothyroidism; most were Grade 1/2 events.
- Dato-DXd AESIs occurring in ≥10% of patients were predominantly Grade 1/2 events and included stomatitis, rash, pruritus, and dry eye.

Table 2. Safety summary

	N=61
Any Grade AE, n (%)	60 (98.4)
Common AEs (≥20% patients, any grade)	
Nausea	35 (57.4)
Stomatitis	34 (55.7)
Alopecia	28 (45.9)
Fatigue, constipation	24 (39.3) each
Rash	17 (27.9)
Vomiting	13 (21.3)
Any Grade 3/4 AE	25 (41.0)
Any serious AE	10 (16.4)
Any treatment-related AE[a]	57 (93.4)
Grade 3/4	21 (34.4)
Any durvalumab AESI	46 (75.4)
Any Dato-DXd AESI	49 (80.3)
AE leading to Dato-DXd + D discontinuation	4 (6.6)
AE leading to dose interruption	27 (44.3)
AE leading to death[b]	1 (1.6)
Durvalumab dose delay	25 (41.0)
Dato-DXd dose delay	23 (37.7)
Dato-DXd dose reduction	12 (19.7)

[a]Per investigator assessment.
[b]Patient died due to dehydration, unrelated to treatment.

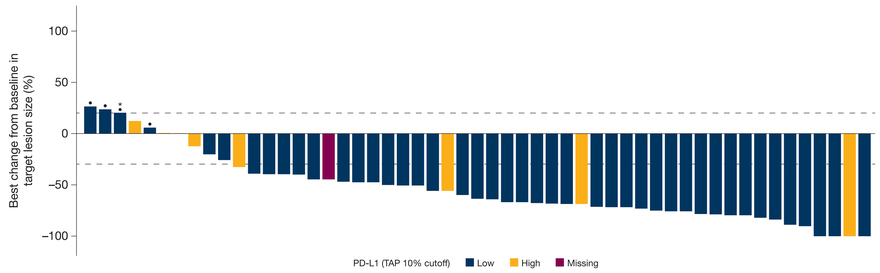
Table 3. Response and survival outcomes

	N=61
Follow-up, median (range), months	7.2 (1–14)
Confirmed ORR	
Evaluable patients, n	53
ORR, n (%)	39 (73.6)
95% CI	59.7–84.7
CR, n (%)	4 (7.5)
PR, n (%)	35 (66.0)
Unconfirmed ORR	
Evaluable patients, n	60
ORR, n (%)	48 (80.0)
95% CI	67.7–89.2

CR, complete response; PR, partial response.

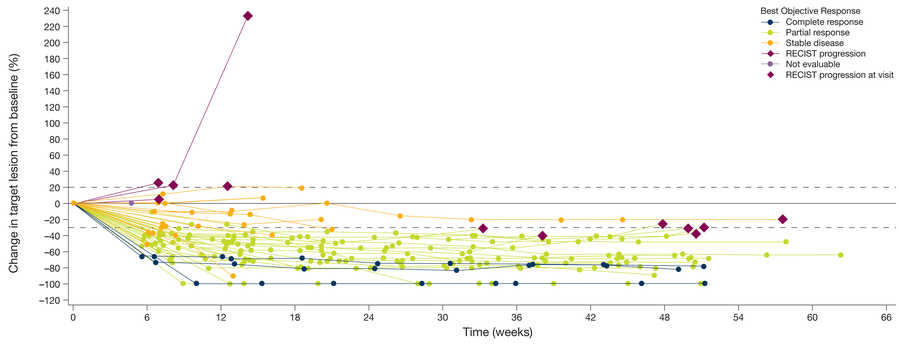
- With Dato-DXd + durvalumab treatment, 73.6% of patients had a confirmed tumor response (**Table 3, Figure 1**).
- Responses were durable, with 82% of patients remaining in response at the data cutoff (**Figure 2**).
- Responses were observed in PD-L1–low and PD-L1–high tumors (**Figure 1**).

Figure 1. Best change from baseline of target lesion size



n = 53.
Dotted reference lines at –30% and 20% indicate thresholds for partial response and progressive disease, respectively.
*If the best percentage change from baseline of target lesions cannot be calculated due to progression, withdrawal, or death, the value is imputed at +20%. "•" Patients with progressive disease as best overall response.

Figure 2. Change from baseline in sum of target lesions over time



Dotted reference lines at –30% and 20% indicate thresholds for partial response and progressive disease, respectively.

Conclusions

- In this updated analysis with a median of 7 months follow-up, the combination of Dato-DXd + durvalumab in 1L a/mTNBC demonstrated a tolerable and manageable safety profile.
- A compelling high response rate, with 4 patients having complete response, was observed with Dato-DXd + durvalumab.
- Although subgroups were small, responses were observed in PD-L1–high and PD-L1–low tumors.
- While maturity is low, response durability is promising; longer follow-up will further inform efficacy results, including PFS.
- Further investigation of Dato-DXd + durvalumab is warranted in this patient population.

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Acknowledgments

This study was funded by AstraZeneca and Daiichi Sankyo. In July 2020, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for datopotamab deruxtecan (Dato-DXd; DS-1062). The authors would like to thank the patients, their families and caregivers, and all investigators involved in this study. Medical writing support, which was in accordance with Good Publication Practice (GPP3) guidelines, was provided by Nicole Seneca, PhD, of Parexel and was funded by AstraZeneca.