Trastuzumab deruxtecan (T-DXd) in combination with anastrozole or fulvestrant in patients with HER2-low HR+ advanced/metastatic breast cancer: a Phase 1b, open-label, multicenter, dose-expansion study (DESTINY-Breast08)

#RF02-03

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On behalf of the DESTINY-Breast08 investigators

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Disclosures

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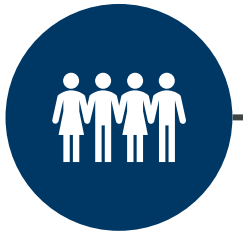
Investigating T-DXd in combination with endocrine therapies in patients with HER2-low HR+ advanced/mBC

DESTINY-Breast08: A Phase 1b, multicenter, open-label, two-part, modular study (NCT04556773)

Population for T-DXd-ET combination arms

- Locally assessed HER2-low (IHC 1+, IHC 2+/ISH−) HR+ advanced/mBC
- ≤1 prior treatment line of ET ± a targeted therapy (such as CDK4/6, mTOR, or PI3K inhibitors) for mBC allowed
- No prior chemotherapy in the metastatic setting allowed
- At least one measurable lesion per RECIST 1.1
- ECOG PS 0–1

Allocation



HR+/HR−
T-DXd + capecitabine, n=20

HR−
T-DXd + capivasertib, n=40

HR+
T-DXd + ANA, n=21
(T-DXd 5.4 mg/kg IV Q3W + anastrozole 1 mg daily*)

HR+
T-DXd + FUL, n=20
(T-DXd 5.4 mg/kg IV Q3W + fulvestrant 500 mg IM Q4W, with a 500 mg loading dose on Cycle 1, Day 15*)

Endpoints for the dose-expansion phase

- **Primary:** Safety and tolerability, including AEs, AESIs, and SAEs
- **Secondary:** ORR, PFS, DOR (all evaluated by investigator per RECIST 1.1), and OS

Part 1 dose-finding and Part 2 dose-expansion; results reported here are from the dose-expansion phase

*Patients received the RP2D from the study's dose-finding phase

AE, adverse event; AESI, adverse event of special interest; ANA, anastrozole; CDK4/6, cyclin-dependent kinases 4 and 6; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; FUL, fulvestrant; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; IM, intramuscular; ISH, in situ hybridization; IV, intravenous; mBC, metastatic breast cancer; mTOR, mammalian target of rapamycin; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; QXW, every X weeks; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; RP2D, recommended Phase 2 dose; SAE, serious adverse event; T-DXd, trastuzumab deruxtecan

André F, et al. Poster presented at ASCO 2022 (Abstract 3025)

Baseline characteristics and patient disposition

	T-DXd + ANA (N=21)	T-DXd + FUL (N=20)
Median age, years (range)	55.0 (29.0–75.0)	65.5 (31.0–73.0)
Female, n (%)	21 (100.0)	20 (100.0)
Race, n (%)		
Asian	11 (52.4)	12 (60.0)
White	10 (47.6)	7 (35.0)
Black or African	0	1 (5.0)
HER2 status, n (%)		
IHC 1+	16 (76.2)	13 (65.0)
IHC 2+/ISH−	5 (23.8)	7 (35.0)
HR status, n (%)		
ER+ and PR+	14 (66.7)	10 (50.0)
ER+ and PR−	7 (33.3)	9 (45.0)
ER+ and PR missing	0	1 (5.0)
ECOG PS, n (%)		
0	12 (57.1)	17 (85.0)
1	8 (38.1)	3 (15.0)
2	1 (4.8)	0
Received no prior line of treatment for mBC, n (%)	7 (33.3)*	6 (30.0)†
Received a prior line as first line for mBC, n (%)	14 (66.7)‡	14 (70.0)§

n (%)	T-DXd + ANA (N=21)	T-DXd + FUL (N=20)
Median duration of follow up, months (range)	20.2 (4.9–24.8)	15.2 (2.2–22.6)
Treatment ongoing	6 (28.6)	7 (35.0)
Patients who discontinued both IPs	15 (71.4)	13 (65.0)
Patients who discontinued T-DXd	15 (71.4)	16 (80.0)
AE	4 (19.0)	5 (25.0)
Subject decision	0 (0)	4 (20.0)
Objective disease progression	8 (38.1)	5 (25.0)
Subjective disease progression	3 (14.3)	2 (10.0)
Patients who discontinued ET	15 (71.4)	13 (65.0)

All patients received study drug

As of August 16, 2023, **6 patients** (28.6%) **in the T-DXd + ANA arm** and **7 patients** (35.0%) **in the T-DXd + FUL arm** were **ongoing study treatment**

Disease progression was the leading reason for treatment discontinuation in both arms

*Two had received adjuvant ET, and five had de-novo mBC. †Three had received adjuvant ET, and three had de-novo mBC. ‡All patients received hormonal therapy with a targeted therapy. §11 patients received hormonal therapy with a targeted therapy, and three received hormonal therapy alone
ER, estrogen receptor; IP, investigational product; PR, progesterone receptor

Safety overview

n (%)	T-DXd + ANA (N=21)	T-DXd + FUL (N=20)
Any-grade AEs	20 (95.2)	20 (100)
Any-grade AEs occurring in ≥30% of patients in either arm		
Nausea	14 (66.7)	19 (95.0)
Alopecia	9 (42.9)	10 (50.0)
Fatigue	9 (42.9)	3 (15.0)
Anemia	7 (33.3)	5 (25.0)
COVID-19	7 (33.3)	5 (25.0)
Decreased appetite	7 (33.3)	11 (55.0)
Decreased weight	7 (33.3)	4 (20.0)
Increased AST	7 (33.3)	4 (20.0)
Neutropenia*	6 (28.6)	7 (35.0)
Vomiting	6 (28.6)	7 (35.0)
Any AEs ≥Grade 3	10 (47.6)	11 (55.0)
Any AEs ≥Grade 3 possibly related to either drug	7 (33.3)	10 (50.0)
AEs leading to dose interruptions/delays of T-DXd	12 (57.1)	8 (40.0)
AEs leading to dose reduction of T-DXd	6 (28.6)	4 (20.0)
AEs leading to discontinuation of T-DXd	4 (19.0)	6 (30.0)
Any SAEs	4 (19.0)	4 (20.0)
AEs leading to death†	1 (4.8)	0
AESIs		
Ejection fraction decreased‡	1 (4.8)	1 (5.0)
Pneumonitis (adjudicated as ILD related to any study drug)	0	5 (25.0)

- In the T-DXd + ANA arm, median actual treatment duration was 10.4 months (range 2.8–22.2) for T-DXd and 11.0 months (range 1.4–22.4) for ANA§
- In the T-DXd + FUL arm, median actual treatment duration was 6.3 months (range 1.4–21.9) for T-DXd and 8.3 months (range 1.8–22.5) for FUL§

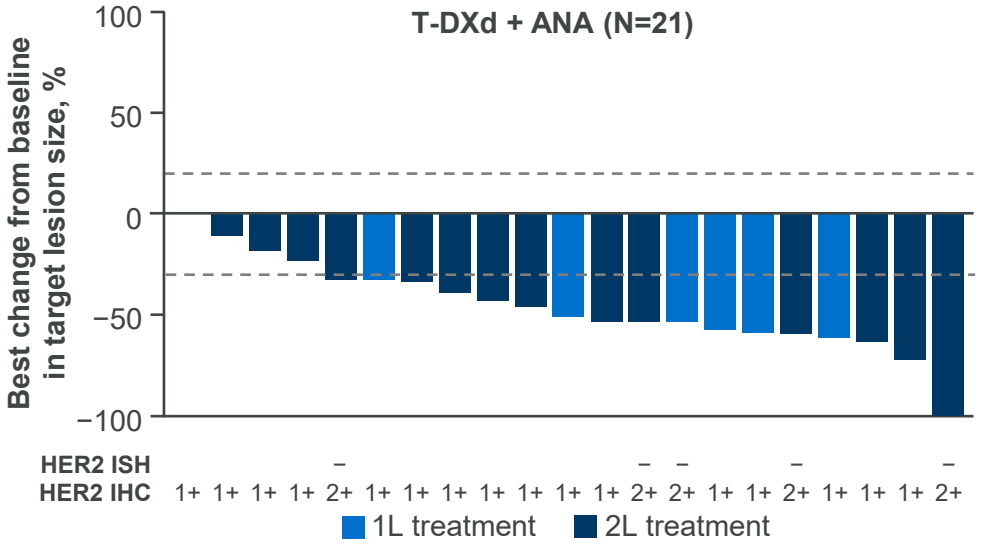
No adjudicated drug-related ILD/pneumonitis events were reported in the T-DXd + ANA arm

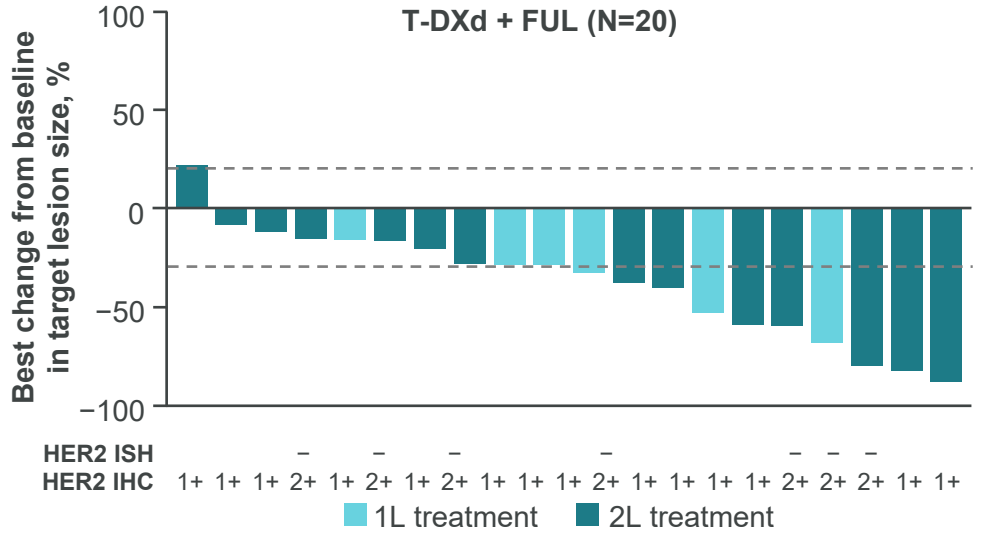
- **All adjudicated drug-related ILD/pneumonitis** events in the **T-DXd + FUL** arm **were Grade 2**; at DCO, two cases had resolved, one was resolving, and two were not resolved
- Four of the five patients with adjudicated drug-related ILD had at least one of the following potential risk factors: advanced age (>65 years, n=3), moderate renal impairment at baseline (n=1), prior thoracic radiation (n=1), and time since initial diagnosis >4 years (n=3)

*Grouped term including neutropenia and decreased neutrophil count events. †Reported by investigator as related to disease and drug-induced pneumonitis; however, the ILD was not considered to be drug-induced by adjudication. ‡Both cases Grade 2 and resolved at DCO. §Total treatment duration, excluding drug interruptions and delays
AST, aspartate aminotransferase; DCO, data cutoff; ILD, interstitial lung disease

Response rates and duration of response

	T-DXd + ANA (N=21)	T-DXd + FUL (N=20)
Confirmed ORR, % (95% CI)	71.4 (47.8, 88.7)	40.0 (19.1, 64.0)
Unconfirmed ORR, % (95% CI)	76.2 (52.8, 91.8)	50.0 (27.2, 72.8)
Median DOR, months (95% CI)*	9.8 (6.7, NE)	NE (4.1, NE)

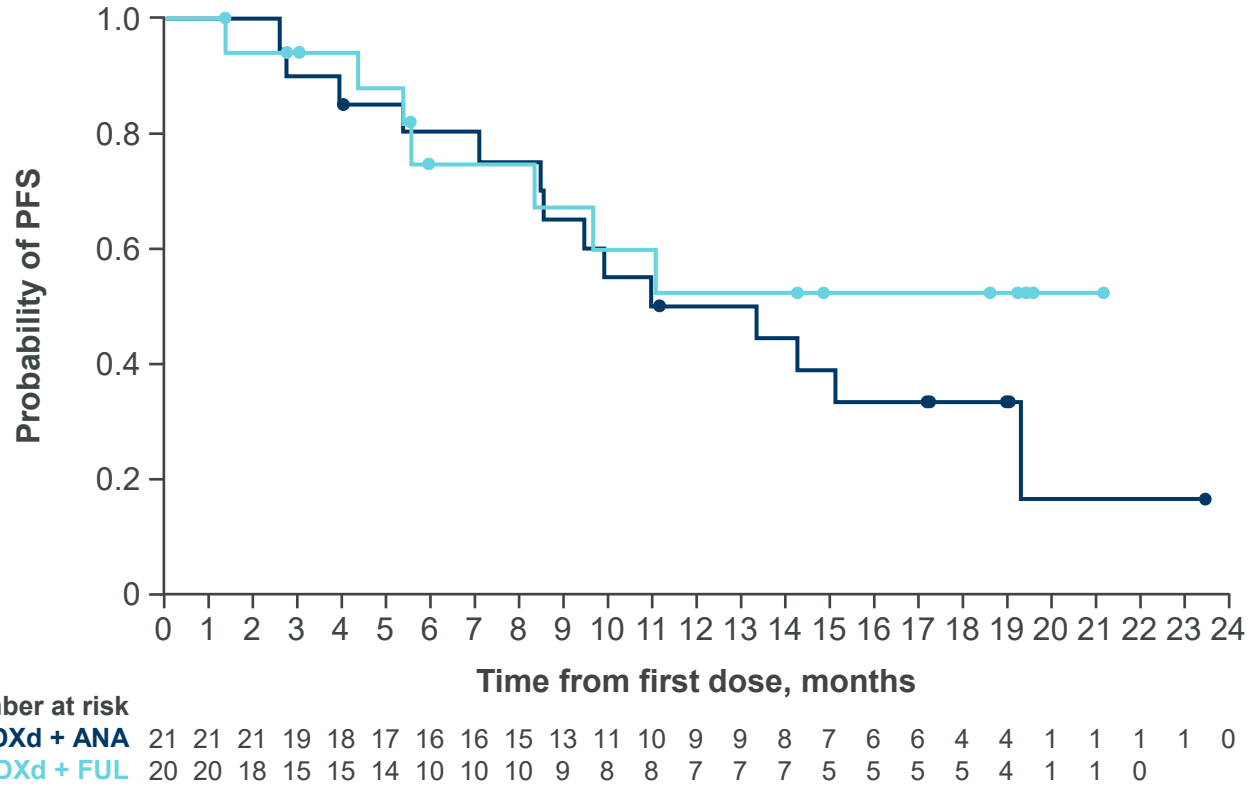




- **Efficacy results need to be interpreted with caution owing to the small datasets**
  - **Of note, 15% of patients in the T-DXd + FUL arm withdrew consent and discontinued study treatment before disease progression**

*NE signifies that median DOR was not reached for these patients at the time of DCO
Median DOR calculated using Kaplan-Meier technique. Target lesion size is the sum of diameters of target lesions, assessed by investigator per RECIST 1.1.
Best change in target lesion is the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction.
Dotted reference lines at −30% and 20% indicate thresholds for partial response and progressive disease, respectively
1L, first line; 2L, second line; CI, confidence interval; NE, not evaluable

Progression-free survival



	T-DXd + ANA (N=21)	T-DXd + FUL (N=20)
Total PFS events, n (%)	14 (66.7)	7 (35.0)
Median PFS, months (95% CI)*	13.4 (8.5, 19.4)	NE (5.6, NE)
PFS rate at 6 months, % (95% CI)	80.7 (56.3, 92.3)	75.3 (46.4, 90.0)
PFS rate at 12 months, % (95% CI)	50.4 (27.5, 69.5)	52.7 (25.0, 74.4)

*NE signifies that median PFS was not reached for these patients at the time of DCO
PFS was assessed by investigator per RECIST 1.1

Conclusions

- **Safety profiles for T-DXd + ET combinations were generally consistent or comparable to the known safety profile of both agents**
- **T-DXd in combination with anastrozole or fulvestrant was active in chemotherapy-naïve patients with HER2-low HR+ mBC, demonstrating encouraging antitumor activity**
  - Confirmed ORR was 71.4% (95% CI 47.8, 88.7) in the T-DXd + ANA arm and 40% (95% CI 19.1, 64.0) in the T-DXd + FUL arm
  - Median DOR was 9.8 months (95% CI 6.7, NE) in the T-DXd + ANA arm and NE (95% CI 4.1, NE) in the T-DXd + FUL arm*
  - Median PFS was 13.4 months (95% CI 8.5, 19.4) in the T-DXd + ANA arm and NE (95% CI 5.6, NE) in the T-DXd + FUL arm*
- **Small datasets limit the interpretation of the efficacy results; further research to evaluate T-DXd in combination with endocrine therapies is warranted**

*NE signifies that median DOR/PFS was not reached for these patients at the time of DCO

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