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PD7-02 - Trastuzumab Deruxtecan in patients with Active Central Nervous System Involvement from HER2-Low Advanced Breast Cancer: The DEBBRAH Trial

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BACKGROUND

- Close to 60% of human epidermal growth factor receptor 2 (HER2)—negative advanced breast cancers (ABC) express low levels of HER2 (defined by a score of 1+ or 2+ by immunohistochemistry and negative status by in situ hybridization) [1,2]. Currently, these HER2-low ABC patients (pts) are treated as HER2-negative pts having limited targeted treatment options [2].
- Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate containing a humanized monoclonal anti-HER2 antibody linked to a potent topoisomerase I inhibitor as the cytotoxic drug [3]. Unlike other antibody-drug conjugates, T-DXd has a released payload that easily crosses the cell membrane and possesses a short half-life, leading to a potent cytotoxic effect on neighboring tumor cells with a reduced systemic exposure
- In the DESTINY-Breast04 trial, T-DXd has significantly improved the survival outcomes of HER2-low ABC pts relative to physician's choice of chemotherapy [6], which led to T-DXd approval for use by the FDA in unresectable or metastatic HER2-low BC pts [7].
- Encouraging antitumor activity of T-DXd has been also observed among HER2[+] ABC pts with active or stable brain metastases (BMs) highlighted the response of BMs to treatment and durable clinical activity of T-DXd [8-10]. Antitumor activity of T-DXd in HER2-low ABC pts with BMs is unknown.

OBJECTIVE

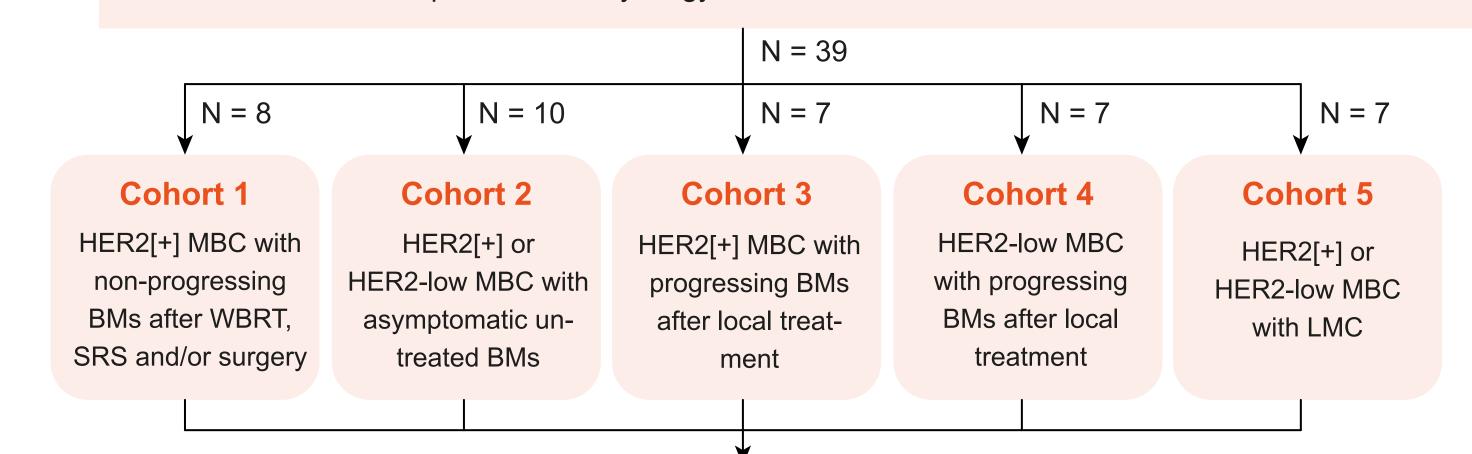
 To evaluate the efficacy and safety of T-DXd in HER2[+] and HER2-low ABC pts with BMs and/or leptomeningeal carcinomatosis (LMC). Here, we report primary results of HER2-low ABC pts who are allocated in cohorts 2 and 4.

STUDY DESIGN

Figure 1. Study Design of DEBBRAH (NCT04420598)

Key elegibility criteria

- Female or male pts aged ≥18 years
- HER2[+] or HER2-low ABC pts with stable, progressing, or untreated BMs and/or LMC
- ECOG PS 0 or 1 (0–2 for cohort 5)
- Pts with HER2[+] ABC: prior taxane-based regimen and ≥1 prior line of HER2-targeted therapy in the metastatic setting
- Pts with HER2-low ABC and:
- HR[-]: ≥1 prior regimen of CT in the metastatic setting
- HR[+]: 1 prior line of ET and ≥1 prior regimen of CT in the metastatic setting
- Cohorts 2, 3, 4: Measurable brain disease on T1-weighted, gadolinium-enhanced MRI Cohort 5: LMC with positive CSF cytology results



Trastuzumab Deruxtecan (DS-8201a) 5.4 mg/kg IV, on Day 1 every 3 weeks, until PD, unacceptable toxicity, or consent withdrawal

Abbreviations: ABC, advanced breast cancer; BMs, brain metastases; CSF, Cerebrospinal fluid; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HR, hormone receptor; IV, intravenously; LMC, leptomeningeal carcinomatosis; MRI, magnetic resonance imaging; SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy.

METHODS

- This is an international, investigator-initiated, open-label, multicenter, single-arm, five-cohort, phase 2 trial (NCT04420598) (Figure 1).
- Pts will receive T-DXd until progressive disease (PD), unacceptable toxicity, or consent withdrawal.

Primary Endpoint

Cohorts 2 and 4

To assess intracranial overall response rate (ORR-IC) per RANO-BM.

Secondary Endpoints

Cohorts 2 and 4

 To assess central nervous system progression free survival (CNS-PFS), clinical benefit rate (CBR)-IC, time to response (TTR)-IC, duration of response (DOR)-IC, 12-week IC stabilization, and best percentage of change in tumor burden per RANO-BM; PFS, ORR, CBR, TTR, DOR per RECIST 1.1; overall survival (OS); and safety per NCI-CTCAE v.5.0.

Exploratory Endpoints

Cohorts 2 and 4

- To assess patient reported outcomes using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-30) and QLQ-BR23.
- To evaluate predictive and/or prognostic factors on plasma and/or tissue biopsies and/or cerebrospinal fluid (CSF) samples.

Study Assessments

- Tumor imaging of thorax and abdomen by computerized tomography scan or MRI performed at baseline, every 6 weeks for the first 6 months and, thereafter, every 9 weeks until the end of the study visit.
- Brain MRI performed at baseline, every 6 weeks for the first 6 months, and every 9 weeks thereafter, unless clinically suspected brain progression.

Stastistics

- Sample size was planned to attain an 80% power at nominal level of one-sided α of 0.05 in each cohort.
- Analysis based on the one-stage A'Hern design.
- H0: ORR-IC ≤5%; Ha: ORR-IC ≥40%.

Cohort 2

- Positive finding if ≥3 responders out of 10 pts.
- Results from cohort 2 should be considered descriptive since formal testing has to be performed in the whole cohort of pts with HER2[+] or HER2-low ABC and asymptomatic untreated BM.

Cohort 4

Positive finding if ≥2 responders out of 7 pts.

1. Recruitment And Patient Disposition

- From October 23, 2020, through February 15, 2022, 6 out of 10 pts (HER2[+] pts not included), and 7 pts were allocated into cohorts 2 and 4, respectively, across 21 hospitals in Spain and Portugal (Table 1). One patient with LMC included in cohort 4 was excluded from analysis.
- Data cutoff date: April 29, 2022
- The median follow-up was 9.5 months (range = 1.6 15.7 months)

Table 1. Patient Demographic Characteristics at Baseline

Patients' Characteristics, n (%)	Cohort 2 (N = 6)	Cohort 4 (N = 6)	Overall (N = 12)
Age, median (range), years	50 (40-72)	62 (48-73)	54 (40-73)
Female, %	100%	100%	100%
ECOG PS, %			
0	5 (83.3%)	1 (16.7%)	6 (50%)
1	1 (16.7%)	5 (83.3%)	6 (50%)
Measurable systemic disease at baseline	9		
Intracranial	6 (100%)	6 (100%)	12 (100%)
Extracranial	5 (83.3%)	6 (100%)	11 (91.7%)
Number of metastatic organ sites			
1	0 (0%)	0 (0%)	0 (0%)
2	0 (0%)	0 (0%)	0 (0%)
≥3	6 (100%)	6 (100%)	12 (100%)
HER2 status (IHC, %)			,
1+	5 (83.3%)	5 (83.3%)	10 (83.3%)
2+ / ISH non-amplified	1 (16.7%)	1 (16.7%)	2 (16.7%)
Histology, %			
ER+ and/or PgR+	5 (83.3%)	4 (66.7%)	9 (75%)
ER- and PgR-	1 (16.7%)	2 (33.3%)	3 (25%)
Any prior therapy for BMs, %			
WBRT	0 (0%)	5 (83.3%)	5 (41.7%)
SRS/SRT	0 (0%)	3 (50%)	3 (25%)
Surgery	0 (0%)	1 (16.7%)	1 (8.3%)
Number of previous lines in advance dis	ease		
Median (Min; Max)	7 (4; 8)	3 (2; 4)	4 (2; 8)
Duration in months of last prior therapy			
Median (Min; Max)	4,6 (0,7; 12,6)	3,3 (1,4; 11,2)	4,2 (0,7; 12,6)
Previous systemic cancer therapy, %			
Anti-HER2 (Trastuzumab)*	0 (0%)	1 (16.7%)	1 (8.3%)
Chemotherapy	6 (100%)	6 (100%)	12 (100%)
Endocrine therapy	5 (83.3%)	4 (66.7%)	9 (75%)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; IHC, immunohistochemistry; ISH, in situ hybridization; PgR, progesterone receptor; SRS/SRT, stereotactic radiosurgery/stereotactic radiotherapy; WBRT, whole brain radiation therapy.

• n (%), number of patients (percentage based on N); N, Number of patients in the FAS population • * This patient started DEBBRAH study as IHC 2+/ISH negative. She received 3 previous lines of therapy for advanced

2. Efficacy in HER2-Low patients

disease, including trastuzumab.

- Cohort 2: ORR-IC was 66.7% (4 of 6 pts had intracranial partial response [PR]; 95% CI, 22.3–95.7) (Table 2).
- Cohort 4: ORR-IC was 33.3% meeting the primary endpoint (2 of 6 pts had intracranial PR; 95% CI, 4.3–77.7; P = .033) (Table 2).
- At data cutoff, no patient of cohort 2 and 3 (50.0%) pts of cohort 4 remained on the-

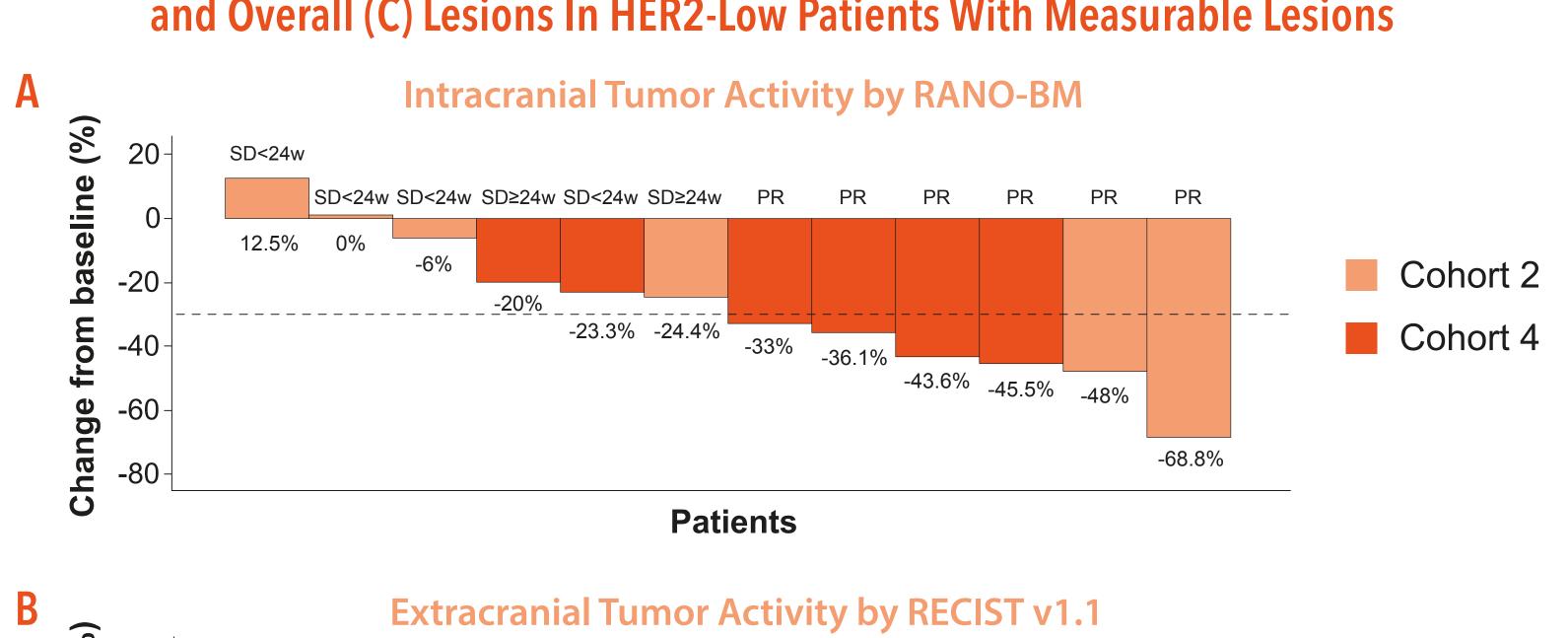
RESULTS

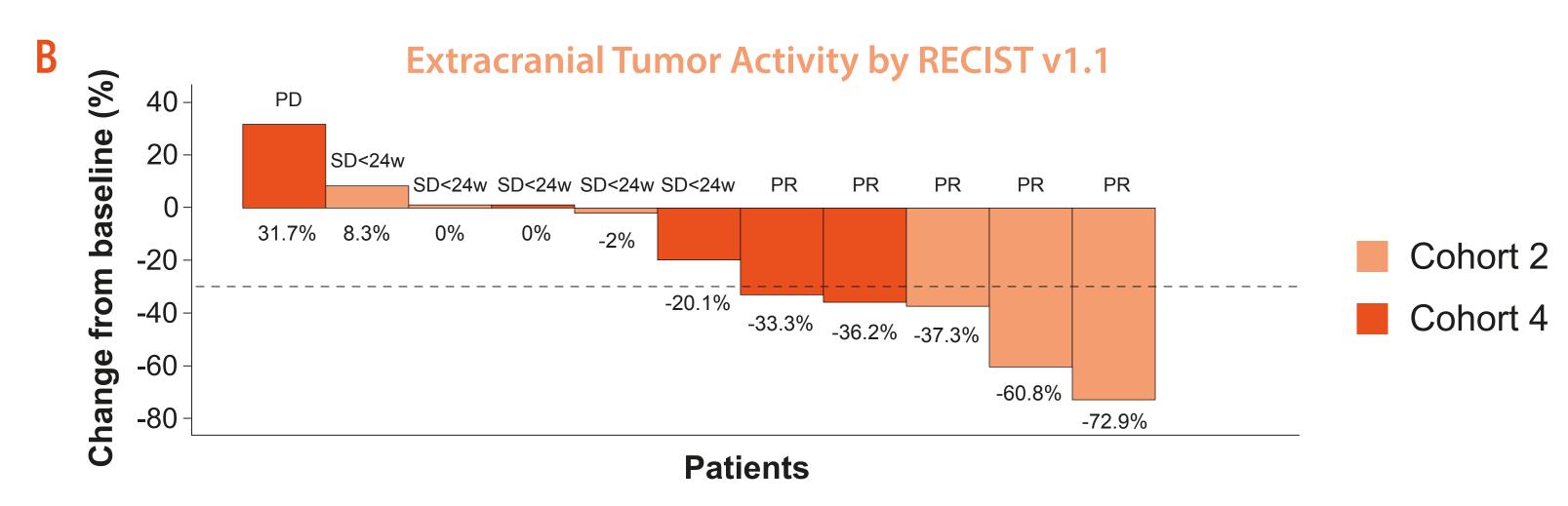
Table 2. Best Intracranial Response (RANO-BM) in HER2-Low Patients

Overall Response, n (%) CR 0 (0.0%) 0 (0.0%) 0 (0.0%) PR 4 (66.7%) 2 (33.3%) 6 (50.0%) SD ≥ 24w 1 (16.7%) 1 (16.7%) 2 (16.7%) SD < 24w	Tumor response, n (%)	Cohort 2 (N = 6)	Cohort 4 (N = 6)	Overall (N = 12)
PR $4 (66.7\%)$ $2 (33.3\%)$ $6 (50.0\%)$ SD $\geq 24w$ $1 (16.7\%)$ $1 (16.7\%)$ $2 (16.7\%)$ SD < 24w $1 (16.7\%)$ $3 (50.0\%)$ $4 (33.3\%)$ PD $0 (0.0\%)$ $0 (0.0\%)$ $0 (0.0\%)$ ORR-IC, n (%) $4 (66.7\%)$ $2 (33.3\%)$ $6 (50.0\%)$ CBR-IC, n (%) $5 (83.3\%)$ $3 (50.0\%)$ $8 (66.7\%)$	Overall Response, n (%)			
$SD \ge 24w$ 1 (16.7%) 1 (16.7%) 2 (16.7%) SD < 24w 1 (16.7%) 3 (50.0%) 4 (33.3%) PD 0 (0.0%) 0 (0.0%) 0 (0.0%) ORR-IC, n (%) 4 (66.7%) 2 (33.3%) 6 (50.0%) ORR-IC, n (%) 5 (83.3%) 3 (50.0%) 8 (66.7%)	CR	0 (0.0%)	0 (0.0%)	0 (0.0%)
SD < 24w	PR	4 (66.7%)	2 (33.3%)	6 (50.0%)
OD 0 (0.0%) 0 (0.0%) 0 (0.0%) ORR-IC, n (%) 4 (66.7%) 2 (33.3%) 6 (50.0%) CBR-IC, n (%) 5 (83.3%) 3 (50.0%) 8 (66.7%)	SD ≥ 24w	1 (16.7%)	1 (16.7%)	2 (16.7%)
ORR-IC, n (%) 4 (66.7%) 2 (33.3%) 6 (50.0%) CBR-IC, n (%) 5 (83.3%) 3 (50.0%) 8 (66.7%)	SD < 24w	1 (16.7%)	3 (50.0%)	4 (33.3%)
CBR-IC, n (%) 5 (83.3%) 3 (50.0%) 8 (66.7%)	PD	0 (0.0%)	0 (0.0%)	0 (0.0%)
	ORR-IC, n (%)	4 (66.7%)	2 (33.3%)	6 (50.0%)
DoR-IC, Median (Min; Max) 3.6 (2.0; 7.1) 7.8 (7.3; 8.3) 5.8 (2.0; 8.3)	CBR-IC, n (%)	5 (83.3%)	3 (50.0%)	8 (66.7%)
	DoR-IC, Median (Min; Max)	3.6 (2.0; 7.1)	7.8 (7.3; 8.3)	5.8 (2.0; 8.3)

- Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease. ORR: CR + PR; CBR: CR + PR + SD ≥ 24w; w, weeks.
- n (%), number of patients (percentage based on N); N, Number of patients in the FAS population

Figure 2. Waterfall Plots Of Best Response Based On Intracranial (A), Extracranial (B), and Overall (C) Lesions In HER2-Low Patients With Measurable Lesions





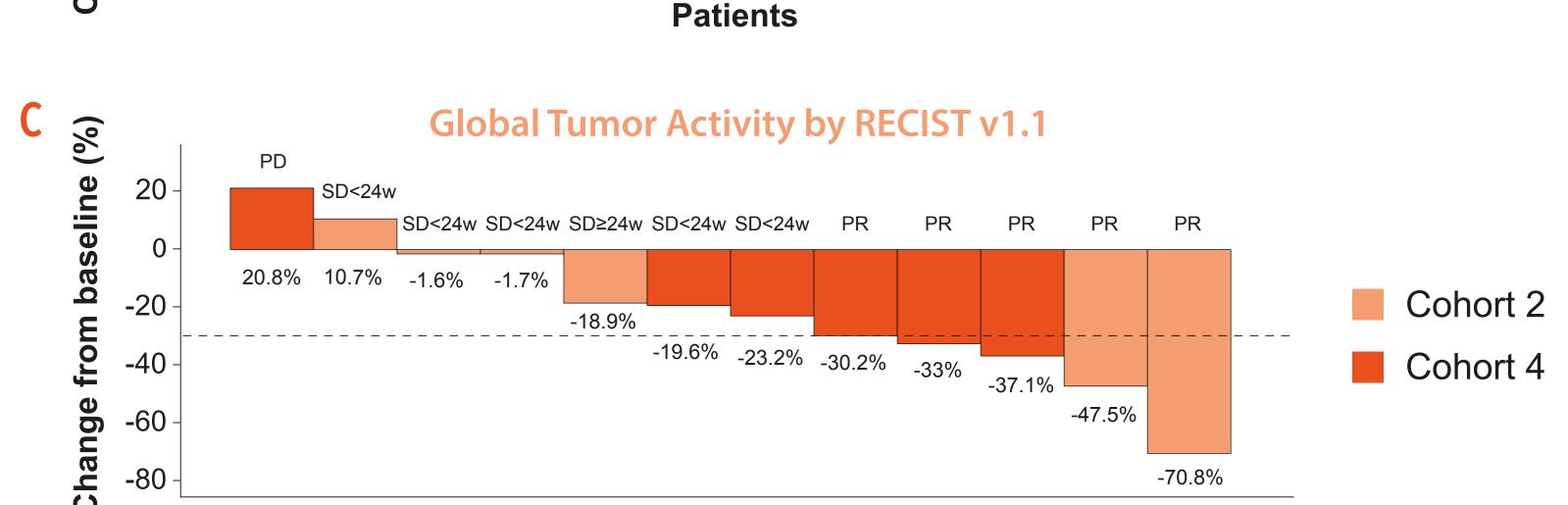


Table 3. Overall Response in HER2-Low Patients

Patients

Tumor response, n (%)	Cohort 2 (N = 6)	Cohort 4 (N = 6)	Overall (N = 12)
ORR, n (%)	3 (50.0%)	2 (33.3%)	5 (41.7%)
CBR, n (%)	3 (50.0%)	3 (50.0%)	6 (50.0%)
DoR, Median (Min; Max)	4.5 (3.5; 7.1)	5.8 (5.5; 6.1)	5.5 (3.5; 7.1)
PFS	5.67 months (95% CI:4.7-NA) (Events: 9/12)		

- **Abbreviations:** 95% CI, 95% of confidence interval; NA, not achieved
- n (%), number of patients (percentage based on N); N, Number of patients in the FAS population

3. Safety in HER2-Low Patients

- The most common treatment emergent adverse events (TEAEs) of any grade (G) were fatigue (58.3%; 8.3% G≥3) and nausea (50.0%; 0% G≥3). Two (16.7%; 0% G≥3) cases of interstitial lung disease/pneumonitis were reported (Table 4).
- Serious unrelated TEAEs occurred in 2 (16.7%) of 12 pts; 1 case of general pain (G3) and 1 case of venous embolism (G5) that led to death.
- No treatment-related deaths were reported.

Table 4. Related TEAEs Occurring In ≥15% of HER2-Low Patients

System Organ Class Preferred term, n (%)	Overall (Overall (N = 12)	
System Organ Glass i referred term, if (70)	Any grade	Grade 3	
ANY	10 (83.3%)	2 (16.7%)	
HEMATOLOGICAL	3 (25.0%)	1 (8.3%)	
Anemia	2 (16.7%)	0 (0%)	
Neutropenia	2 (16.7%)	0 (0%)	
NON-HEMATOLOGICAL	10 (83.3%)	1 (8.3%)	
Fatigue	7 (58.3%)	1 (8.3%)	
Nausea	6 (50.0%)	0 (0%)	
Vomiting	4 (33.3%)	0 (0%)	
Gamma-glutamyltransferase increased	2 (16.7%)	0 (0%)	
Interstitial lung disease/pneumonitis	2 (16.7%)	0 (0%)	
Diarrhea	2 (16.7%)	0 (0%)	

• At data cutoff, 12 patients who were enrolled in the two cohorts, received at least one dose of studydrug and were included in the

CONCLUSIONS

- . T-DXd showed a preliminary antitumor activity in pretreated HER2-low ABC pts with asymptomatic untreated or progressing BMs after local treatment.
- 2. Further investigation is needed in larger cohorts to validate the substantial response of BMs to T-DXd in this population.

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