Poster 456P

Real-world data on effectiveness of trastuzumab deruxtecan (T-DXd) in Central Nervous System metastases (CNSm) in HER2+ previously treated metastatic breast cancer: subgroup analysis of REALITY-01 study

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Background and objectives

- Over the past decade, major therapeutic advances have significantly improved progression-free survival (PFS), overall survival (OS), and quality of life (QoL) in patients (pts) with HER2-positive metastatic breast cancer (HER2+ mBC)[1]. However, as survival improves, central nervous system metastases (CNSm), including brain metastases (BM) and leptomeningeal disease (LMD), remain a major clinical concern in this population[2-5].
- T-DXd demonstrated substantial efficacy in HER2+ mBC after ≥2 lines of treatment (tt) in the DESTINY-Breast01 (DB-01) and DESTINY-Breast02 (DB-02) trials with a favourable benefit–risk profile. In DB-01, objective response rate (ORR) was 62%, mPFS was 19.4 mo, and OS was 29.1 mo[6]. In DB-02, ORR was 74.1%, mPFS was 16.7 mo, and OS was 35.7 mo[7].
- However, patients with CNSm remain under-represented in registrational randomised clinical trials. The management of CNSm remains challenging, highlighting the need for effective systemic therapies with intracranial activity.
- Based on the results of DESTINY-Breast01, T-DXd became available in France on January 18, 2021 prior to Marketing Authorization (MA) through a Temporary Authorization for Use (Autorisation Temporaire d'Utilisation; ATU) program, allowing early access as monotherapy for eligible pts with HER2+ metastatic/unresectable (m/u) BC previously treated with ≥2 prior lines of anti-HER2 tt.
- **This subgroup analysis of REALITY-01 study (n = 306) aims to fill gaps with real-world data for HER2+ m/u BC pts including CNSm pts with BM and/or LMD only with T-DXd tt.**

Conclusions

- **REALITY-01 confirms in a real-world setting that T-DXd is safe and effective in pts with HER2+ mBC, many of whom were heavily pretreated and had poor ECOG performance status, and that these benefits are also observed in pts with CNSm.**
- **T-DXd demonstrated meaningful clinical activity in pts without and with CNSm:**
  - mPFS was comparable between pts without CNSm (**18.7 mo**) and those with CNSm (**16 mo**).
  - Two-year OS rates were 68.7% (95% CI: 61.6–74.7) and 50.9% (95% CI: 39.7–60.0), respectively.
- **In the LMD-only subgroup (n = 18),** T-DXd was initiated at full dose in all pts and showed clinically significant benefit in the majority of pts (with a low rate of treatment discontinuations), with a mPFS of 13.7 mo (95% CI: 9.7–15.4), a mOS of 21.3 mo (95% CI: 12.9–NE), and a 2-year OS rate of 41.9% (95% CI: 18.8–63.6). **This study represents one of the largest real-world cohorts of pts with LMD treated with T-DXd.**
- **In the BM-only subgroup (n = 57),** T-DXd was also initiated at full dose in all pts and showed clinically significant benefit in the majority of pts (with a low rate of treatment discontinuations), with a mPFS of 17.9 mo, and a 2-year OS rate of 51.8% (95% CI: 38.1-64.0).
- **Overall, these results support T-DXd as a standard treatment option for pretreated HER2+ mBC pts, including those with BM and/or LMD, and reinforce its role in clinical practice.**

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Methods

A non-interventional, ambispective, longitudinal, open-label, multicentre, phase IV study

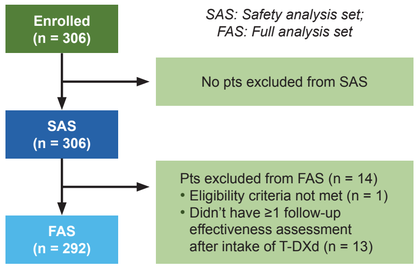
- **Main eligibility criteria:**
  - Adult patient (age ≥ 18 years (yrs)).
  - HER2+ m/u BC, with at least 1 prior anti-HER2 treatment before T-DXd, previously treated by compassionate T-DXd or previously treated or planned to be treated by T-DXd, upon the investigator's decision.
- **Dosage and duration of treatment according to the SmPC:** the recommended dosage for T-DXd was **5.4 mg/kg** administered by intravenous perfusion every 3 weeks (21-day cycle) up to disease progression and/or toxicity.
- **Primary outcome:** Safety of T-DXd in real-life conditions.
- **Secondary outcomes:** Effectiveness of T-DXd in real-life conditions according to RECIST Version 1.1 (objective response rate defined as the response across all target lesions, survival outcomes at 24 months, and duration of response), description of T-DXd treatment over time.

Results

Patients' characteristics at T-DXd initiation

- At the data cut-off (November 2024), 50 centres recruited 306 pts, **with a median follow-up duration of 23.3 mo**.
- Among them, **29.1% (n = 89) had CNSm at T-DXd initiation**. Of these pts:
  - 20.2% (n = 18) had LMD only,
  - 64.0% (n = 57) had BM only,
  - 12.4% (n = 11) had both,
  - 3 pts had CNSm of undetermined location.
- Among the 89 pts with CNSm, CNS radiotherapy was delivered as stereotactic radiosurgery in 18.0% (n = 16), and as whole-brain radiotherapy in 3.4% (n = 3), while 78.7% (n = 70) did not receive radiotherapy. CNSm surgery was performed in 6.7% pts (n = 6). Among the 28 pts included with LMD, 10.7% (n = 3) received intrathecal treatment for LMD.
- At T-DXd initiation, 29.2% (n = 26) of pts with CNSm presented CNSm-related symptoms (intracranial pressure, neurological disorders, others) (1 missing data).
- **The recommended T-DXd dose of 5.4 mg/kg was administered to 95.8% (n = 203) of pts without CNSm, 100.0% (n = 18) with LMD only, 100.0% (n = 57) with BM only, and 90.9% (n = 10) with LMD and BM.** Data were missing for 0.3% (n = 1) of pts.

Figure 1. Flow chart of analysis sets and patient disposition



SAS: Safety analysis set; FAS: Full analysis set

	Number of pts by CNSm status			Number of pts by CNSm location		
	No	Yes	Missing	LMD only	BM only	LMD + BM
SAS (n = 306)	212	89	5	18	57	11
FAS (n = 292)	200	88	4	18	57	10

Table 1. Patient characteristics at T-DXd initiation in subgroups

	Total (SAS)	CNSm[1]		CNSm location[2]		
		No	Yes	LMD only	BM only	LMD + BM
Number of patients	**306**	212	89	18	57	11
Age						
Median age, yrs (min–max)	59 (27–90)	61 (29–89)	54 (27–90)	53 (27–79)	54 (31–90)	55 (28–67)
≥70 yr, n (%)	58 (19.0)	45 (21.2)	10 (11.2)	2 (11.1)	8 (14.0)	0
ECOG status, n (%)						
0–1	207 (67.6)	155 (73.1)	49 (55.0)	7 (38.9)	35 (61.4)	7 (63.6)
2–3	52 (17.0)	23 (10.9)	29 (32.5)	10 (55.5)	14 (24.6)	3 (27.3)
Missing	47 (15.4)	34 (16.0)	11 (12.5)	1 (5.6)	8 (14.0)	1 (9.1)
Lines of anti-cancer systemic treatment for metastatic or locally advanced disease, n (%)						
≥4	159 (52.0)	105 (49.5)	52 (58.4)	10 (55.6)	35 (61.4)	6 (54.5)
Missing	1 (0.3)	0	0	0	1 (1.8)	0
Mean time between date of first T-DXd cycle and date of metastases/advanced disease diagnosis, mo (min–max)	56.1 (2.2–250.9)	57.0 (4.6–250.9)	54.9 (2.2–198.6)	42.1 (10–111)	61.5 (2–199)	47.5 (7–127)

[1]5 missing data; [2]3 patients with CNS metastases of undetermined location.

Safety and tolerability (SAS; n = 306)

- **Median duration of T-DXd treatment was 11.9 mo** (range, 0.7–26.7).

Table 2. Occurrence of T-DXd-related ADRs in subgroups

	Total (SAS)	CNSm		CNSm location		
		No	Yes	LMD only	BM only	LMD + BM
Number of patients	**306**	212	89	18	57	11
Any ADR, n (%)	**261 (85.3)**	**183 (86.3)**	**73 (82.0)**	**12 (66.7)**	**49 (86.0)**	**10 (90.9)**
Associated with dose reduction	50 (16.3)	32 (15.1)	17 (19.1)	2 (11.1)	12 (21.1)	3 (27.3)
Associated with study drug interruption	72 (23.5)	48 (22.6)	23 (25.8)	4 (22.2)	14 (24.6)	5 (45.5)
Associated with study drug discontinuation	34 (11.1)	22 (10.4)	12 (13.5)	2 (11.1)	10 (17.5)	0
Associated with an outcome of death	4 (1.3)	2 (0.9)	2 (2.2)	1 (5.6)	1 (1.8)	0
Any grade ≥3 ADR, n (%)	**115 (37.6)**	**73 (34.4)**	**40 (44.9)**	**8 (44.4)**	**28 (49.1)**	**4 (36.4)**
Any Serious ADR, n (%)	**30 (9.8)**	**15 (7.1)**	**15 (16.9)**	**4 (22.2)**	**9 (15.8)**	**2 (18.2)**

Effectiveness (FAS; n = 292)

- **mPFS was 18.7 mo (95% CI: 15.2–21.4) for pts without CNSm and 16.0 mo** (95% CI: 12.9–19.5) **for pts with CNSm.**
- Among pts with LMD only, **mPFS was 13.7 mo** (95% CI: 9.7–15.4).
- The 2-year OS rate was 68.7% (95% CI: 61.6–74.7) in pts without CNSm and 50.9% (95% CI: 39.7–60.0) in pts with CNSm.
- In pts with only LMD, **mOS was 21.3 mo** (95% CI: 12.9–NE) and **the 2-year OS rate was 41.9%** (95% CI: 18.8–63.6).
- **The median time to first CNS event or death was 25.7 mo (95% CI, 23.7–NE) in pts without CNSm at T-DXd initiation.**

Figure 2. PFS in subgroups (with or without CNSm)

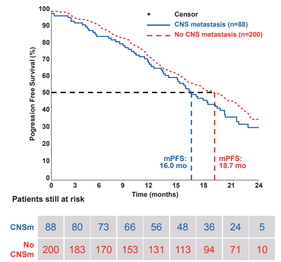


Figure 3. PFS in subgroups by CNSm location (LMD only, BM only, LMD + BM)

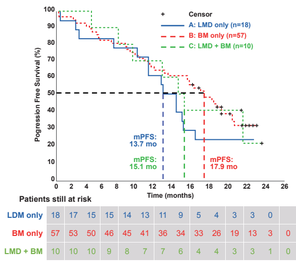


Figure 4. OS in subgroups by CNSm location (LMD only, BM only, LMD + BM)

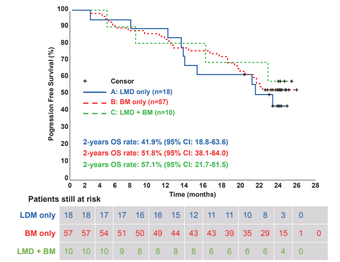


Table 3. Best overall response rate, objective response rate and duration of response in subgroups

	Total (FAS)	CNSm[3]		CNSm location[4]		
		No	Yes	LMD only	BM only	LMD + BM
Number of patients	**292**	200	88	18	57	10
Subjects with at least one on-treatment assessment, n (%)	194 (66.4)	136 (68.0)	54 (61.4)	8 (44.4)	35 (61.4)	9 (81.8)
Best Overall Response, n (%)						
Complete Response (CR)	50 (25.8)	33 (24.3)	14 (25.9)	3 (37.5)	9 (25.7)	2 (22.2)
Partial Response (PR)	45 (23.2)	34 (25.0)	11 (20.4)	1 (12.5)	9 (25.7)	1 (11.1)
Stable Disease (SD)	62 (32.0)	47 (34.6)	15 (27.8)	2 (25.0)	7 (20.0)	6 (66.7)
Progressive Disease (PD)	8 (4.1)	6 (4.4)	2 (3.7)	1 (12.5)	1 (2.9)	0
Not Evaluable (NE)	29 (14.9)	16 (11.8)	12 (22.2)	1 (12.5)	9 (25.7)	0
Duration of response[5] of CR or PR, mo	13.4	13.3	14.1	NE	17.3	10.4
Median (95% CI)	(9.0–17.4)	(8.7–17.4)	(8.1–NE)	(5.4–NE)	(8.1–NE)	(3.2–NE)

[3]4 missing data; [4]3 patients with CNS metastases of undetermined location; [5]Censoring rules: if pts lost to follow-up, censor date will be last contact date available; if pts who have non-CNS progression or not known to have died at the end of study or at the date of cut-off, censor date will be the last disease evaluation date (i.e. date of last imaging).

Abbreviations

ADR: adverse drug reaction; ATU: Autorisation Temporaire d'Utilisation (Temporary Authorization for Use); BC: breast cancer; BM: brain metastases; CNSm: central nervous system metastases; CR: complete response; DoR: duration of response; ECOG: Eastern Cooperative Oncology Group; FAS: full analysis set; HR: hazard ratio; LMD: leptomeningeal disease; MA: Marketing Authorization; mo: month; m/u: metastatic or unresectable; NE: not estimable; ORR: objective response rate; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PR: partial response; pts: patients; QoL: quality of life; SAS: safety analysis set; SD: stable disease; SmPC: Summary of Product Characteristics; T-DXd: trastuzumab deruxtecan; tt: treatment.

Disclosures

First Author: AstraZeneca, Invited Speaker, Institutional; Daiichii Sankyo, Invited Speaker, Institutional; Lilly, Invited Speaker, Institutional; Novartis, Invited Speaker, Institutional; Pfizer, Invited Speaker, Institutional; Seagen, Coordinating PI, Institutional, No financial interest.

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