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French real-world safety and effectiveness of trastuzumab deruxtecan (T-DXd) in the treatment of patients with HER2+ metastatic or unresectable breast cancer (m/u BC): first results of REALITY-01 ambispective study

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BACKGROUND AND OBJECTIVES

- Despite global therapeutic advancements, there is still a medical need to improve progression-free survival (PFS), OS and quality of life (QoL) in patients (pts) with HER2+ mBC. Unfortunately, attrition rate shows that pts are at risk to not benefit from latest therapeutic options in later lines[1].
- T-DXd emerged as a promising treatment (tx) for pts with HER2+ m/u BC. This antibody-drug conjugate (ADC) is composed of an HER2-directed antibody and a topoisomerase I inhibitor linked by a cleavable tetrapeptide-based linker.
- DESTINY-Breast01 demonstrated T-DXd efficacy in pts with HER2+ mBC who were previously treated with trastuzumab emtansine (T-DM1) in terms of overall response rate (ORR) (62%), median (PFS) (19.4 months (mo)) and overall survival (OS) (29.1 mo)[2]. DESTINY-Breast02 reinforces these study's results and highlighted the favorable benefit-risk profile of T-DXd which can overcome resistance to previous ADC[3] (i.e. T-DM1) while maintaining a relatively low rate of T-DXd-related serious ADR (11.4%).
- In France, results from previous studies (DESTINY-Breast01 and 02) facilitated access of T-DXd to eligible pts before the Marketing Authorization (MA) through a Temporary Authorization for Use (Autorisation Temporaire d'Utilisation; ATU) program as monotherapy for the treatment of pts with HER2-positive m/u BC after ≥ 2 prior lines of anti-HER2 tx.
- **This REALITY-01 study aims to fill gaps with real-world data for HER2+ m/u BC pts of both cohorts (during ATU and after MA) with T-DXd tx.**

CONCLUSION

- **The safety (10.2% of T-DXd-related discontinuation), the median PFS (17.4 mo) and the ORR (49.7%) in the full analysis set are consistent with results in DESTINY-Breast01/02. In the same way, among both cohorts, only 9.5% pts had serious T-DXd-related ADRs underlying the positive benefit-risk profile of T-DXd. This shows the importance of prompt adverse events management.**
- **REALITY-01 confirm the safety and effectiveness of T-DXd in heavily pre-treated HER2+ m/u BC pts with or without mCNS and are consistent with DESTINY-Breast01/02 results.**

METHODS

Non-interventional, ambispective, longitudinal, open-label, multicenter, phase IV study

Main eligibility criteria

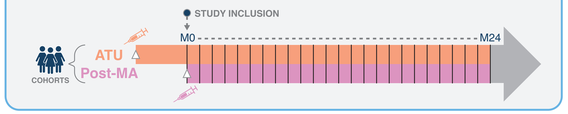
- Adult patient (age ≥ 18 years (yrs)).
- HER2+ m/u BC, with at least 1 prior anti-HER2 treatment before T-DXd, previously treated by compassionate T-DXd or previously treated or planned to be treated by T-DXd, upon the investigator's decision.
- Patient who expressed non-opposition to participate to the study.

Main exclusion criteria

- Previous participation in an interventional clinical trial with T-DXd.

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 outcomes

Safety of T-DXd in real-life conditions as per the occurrence of :

- Gastro-intestinal disorders, Interstitial Lung Disease (ILD), left ventricular dysfunction, alopecia (any grade);
- Other **grade ≥ 3** Adverse Drug Reactions (ADRs).

Secondary outcomes

- Risk factors for ADRs, description of patients' characteristics, description of T-DXd treatment over time, effectiveness of T-DXd in real-life conditions, HR-QoL.

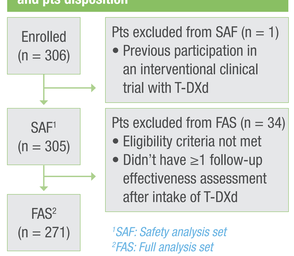
RESULTS

Patients' characteristics

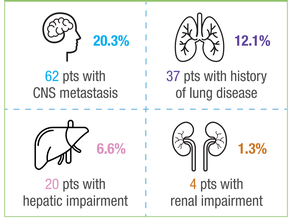
At the data cut-off, i.e. June 2023, 305 pts were enrolled (Graph 1) in 56 centers for a **median follow-up duration of 17.7 mo**.

- At the start of T-DXd initiation, median age was 59 yrs **(17.7% pts ≥70 yrs)**.
- In FAS, 51.7% of pts received **≥4 lines** before T-DXd.
- 69% (n = 187) and 15.5% (n = 42) of pts had ECOG 0-1 and ECOG 2-3 in the FAS (42 missing).

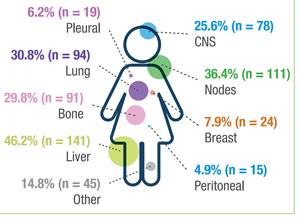
Graph 1. Flow chart of analysis sets and pts disposition



Graph 2. Subgroups of pts at the start of T-DXd (n = 305)



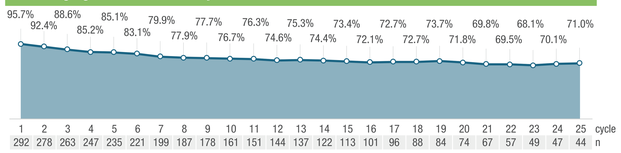
Graph 3. Metastatic sites (multiple response) at the first T-DXd cycle (n = 305)



T-DXd Treatment exposure (n = 305)

- **Median duration of T-DXd treatment was 12.5 mo** (range, 0.7-30.0).
- Median number of cycles of T-DXd received per patient was 15.0 (range, 1-39).
- 58 pts are still ongoing the treatment and 36 pts completed the study per protocol.

Graph 4. Number and proportion of pts (n = 305) receiving the recommended dose of 5.4 mg/kg at each treatment cycle



Safety and tolerability (n = 305)

- **ADRs of interest were reported in 78.7% (240) pts** (95% CI [73.7;83.1]), of whom 12.9% (31) discontinued T-DXd tx.
- **Median time to first T-DXd related ADR** of interest was **27.0 days** (95% CI [22.0;44.0]). Out of a total of 843 T-DXd-related ADRs, 4.3% (36) were serious, meaning 1% (3) resulted in death (ILD/pneumonitis).
- 14.1% (43) pts (95% CI [10.4;18.5]) experienced T-DXd related ILD/pneumonitis, of whom 30.2% (13), (95% CI [2.3;7.2]) discontinued T-DXd tx.

Table 1. Pts with ILD related to T-DXd administration (n=305)

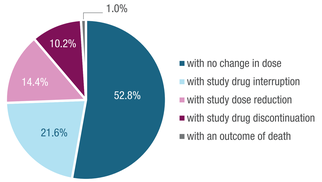
	n(%)
Any ILD	**43 (14.1)**
1	14 (4.6)
2	16 (5.2)
3	7 (2.3)
4	0
5	3 (1.0)

Table 2. Summary of T-DXd-related ADRs (n = 305)

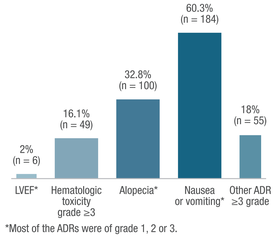
	n(%)
Any ADR, n(%) [95% CI]	**240 (78.7) [73.7;83.1]**
Any Serious ADR, n (%)	**29 (9.5)**
Any grade ≥3 ADR, n (%)	**103 (33.8)**
Haematotoxicity	49 (16.1)
Gastrointestinal disorders	19 (6.2)
Asthenia and fatigue	16 (5,2)
Respiratory, thoracic and mediastinal disorders	12 (3.9)
Metabolism and nutrition disorders	12 (3.9)
Nervous system disorders	6 (2.0)
Infections and infestations	5 (1.6)
General physical health deterioration	4 (1.3)
Cardiac disorders	3 (1.0)
Reproductive system and breast disorders	2 (0.7)
Ejection fraction decreased	2 (0.7)

Grade ≥ 3 ADRs which occurred in 1 patient each: Gamma-GT increased, Weight decreased, Skin and subcutaneous tissue disorders, Eye inflammation, Hyperbilirubinaemia, Frostbite, Bone pain, Embolism, Oedema peripheral, Pain.

Graph 5. Treatment continuity associated with any T-DXd-related ADRs (n = 305)



Graph 6. Proportion of patients with ADRs, (n = 305)



*Most of the ADRs were of grade 1, 2 or 3.

Effectiveness (n = 271)

- **Median PFS was 17.4 mo** (95% CI [15.6;19.6]). Median OS was not reached.
- **Among the 271 pts, 185 had at least one on-treatment assessment and ORR was 49.7%** (95% CI [42.3;57.2]), including 24.9% (n = 46) of CR.

Graph 7. PFS and OS

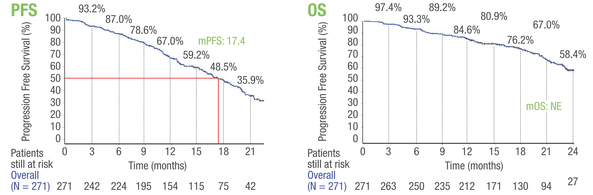


Table 3. Best Overall Response Rate and Objective Response Rate

	Total (n = 271)
Best Overall Response, n (%)	
Complete Response (CR)	46 (24.9)
Partial Response (PR)	46 (24.9)
Stable Disease (SD)	61 (33.0)
Progressive Disease (PD)	6 (3.2)
Not Evaluable (NE)	26 (14.1)
Objective Response Rate (ORR, CR+PR)	
n/N (%)	92/185 (49.7)
95% CI	(42.3;57.2)
Duration of response of CR or PR** (months)	
Pts with CR/PR	106
Median (95% CI)	14.5 (9.8;NE)

**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 vdate (i.e. date of last imaging).

Focus on mCNS (n = 271)

- At T-DXd initiation, 60 pts had mCNS, of which 35% (21) were symptomatic as active brain metastasis.
- mCNS location was parenchymal in 73.8% (48) cases and leptomeningeal in 26.2% (17) cases, (4 missing).
- Among the mCNS pts who underwent at least one on-treatment CNS assessment (n = 42), 52.4% pts (22) achieved complete or partial CNS response (CR, PR).

Table 4. Best Overall Response Rate in mCNS pts

	Total (n = 42)
Best Overall Response, n (%)	
Complete Response (CR)	8 (19.1)
Partial Response (PR)	14 (33.3)
Stable Disease (SD)	19 (45.2)
Progressive Disease (PD)	1 (2.4)

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Conflict of interest
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