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ESPERANZA: Results from an external comparator study of trastuzumab deruxtecan in HER2 IHC3+ Solid Tumors

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Objective

- To evaluate the comparative effectiveness of T-DXd versus RW SoC in patients with HER2 IHC 3+ locally advanced unresectable or metastatic solid tumors with 1+ prior LoT using an external control arm study design with a target trial emulation approach.

Conclusions

- RW SoC outcomes indicate an unmet need in the previously treated HER2 IHC 3+ solid tumors, with mOS of 7 months.
- The >10-month improvement in mOS and >5-month improvement in mPFS with T-DXd versus RW SoC demonstrates its clinical value and supports its role as the first tumor-agnostic treatment option for previously treated patients with HER2 IHC 3+ solid tumors.

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Introduction

- HER2 overexpression, an actionable biomarker across multiple solid tumors, is linked with a biologically aggressive phenotype.[1-3]
- T-DXd is a HER2-directed ADC[4], approved by the FDA, EMA and others for previously treated HER2 (IHC 3+) solid tumors based on clinically meaningful antitumor activity demonstrated in the DESTINY-Lung01 (NCT02564900), DESTINY-CRC02 (NCT04744831), DESTINY-PanTumor02 (NCT04482309) single arm trials.[5-7]
- The comparative effectiveness of T-DXd in select tumor types versus RW SoC was not assessed in these trials.

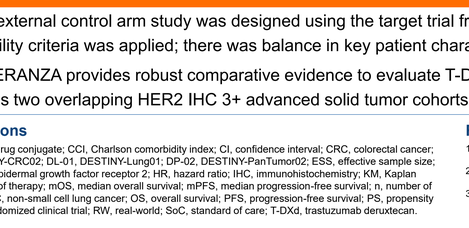
Methods

- **ESPERANZA** (NCT06973161) is an external control arm study comparing T-DXd with RW SoC, conducted using a target trial emulation framework, in the approved tumor-agnostic indication.
- **Data Source:** T-DXd-treated patients from the single-arm reference trials DL-01, DC-02, and DP-02 were included.[4,5,6] Included RW SoC-treated patients were drawn from 23 RW clinical sites and data sources across nine countries in Europe (Denmark, France, Italy, Spain, Portugal, Germany and UK) and North America (USA and Canada).
- **Index date**: T-DXd patients were indexed at start of treatment in the trial, while RW SoC patients were indexed at an eligible line of therapy (2L+), selected at random to mirror LoT distribution in the trial.
- **Key eligibility criteria for RW SoC**
  - Included: Adults with HER2 IHC3+ locally advanced, unresectable, or metastatic solid tumors and ≥1 prior systemic anticancer therapy between Jan 2017-Dec 2022 to align with the recruitment period for the 3 single arm trials. [5-7]
  - Excluded: patients with use of T-DXd or DXd-ADC at or prior to index date.
- **Study cohorts**: Tumor-agnostic (patients with biliary tract, bladder, cervical, CRC, endometrial, epithelial ovarian, NSCLC, pancreatic, or other solid tumors) and pan-tumor cohorts (all cancers in tumor agnostic cohort, except CRC and NSCLC).
- **Outcome measures:** OS was the primary outcome, and PFS was a secondary outcome.
- **Statistical analyses:** The target sample size (N=384) for this study was not met. Results were not interpreted within a hypothesis-testing framework. Consistent with this approach, p-values are not reported.
  - Potential confounders which included tumor type, age, prior LoTs, tumor stage, and CCI, were identified through a literature review and clinician validation and adjusted for using standardized mortality ratio propensity score weighting to balance the RW SoC and T-DXd arms. Outcomes were analyzed using weighted KM curves and Cox proportional hazards models.

Results

Study Participation

Figure 1. Patient identification for tumor-agnostic cohort (RW SoC)



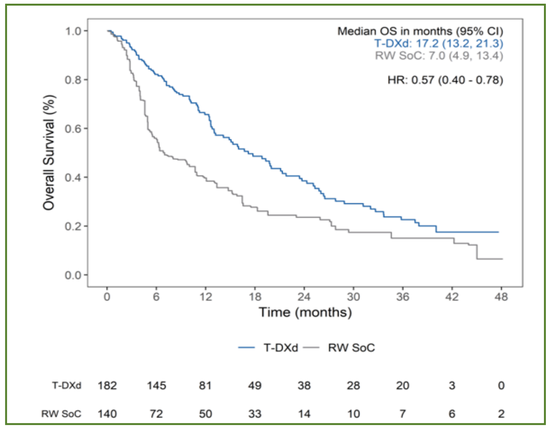
- The tumor-agnostic cohort comprised 322 patients (T-DXd, n=182; RW SoC, n=140) (Figure 1), while the pan-tumor cohort (a sub-cohort of the tumor agnostic cohort) comprised 197 patients (T-DXd, n=101; RW SoC, n=96).

Baseline Characteristics

- The RW SoC cohort included the same nine tumor types represented in the referent trials, supporting a clinically relevant comparison with T-DXd.
- Before weighting, T-DXd patients had received more prior LoT than RW SoC patients (median prior LoT: 2 vs 1), and chemotherapy-based regimens represented the most common RW SoC treatments (chemotherapy alone: 30.7%; chemotherapy plus non-anti-HER2 targeted therapy: 15.0%; chemotherapy plus anti-HER2 therapy: 12.1%).
- Following weighting, both cohorts were balanced for the selected baseline confounders, with remaining imbalances limited to a few non-adjusted characteristics, including ECOG performance.
- After weighting, most common treatments in RW SoC arm (ESS=60) were chemotherapy-based (chemotherapy alone: 33.0%; chemotherapy plus non-anti-HER2 targeted therapy: 16.2%; chemotherapy plus anti-HER2 therapy: 7.8%).

Overall Survival Outcomes

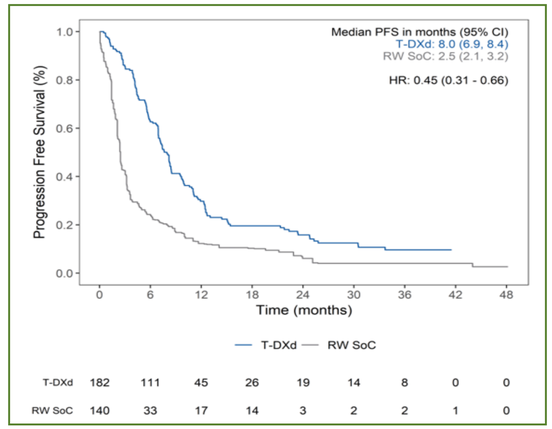
Figure 2. Weighted KM curve of OS in tumor-agnostic cohort



- After weighting, mOS was 17.2 months for T-DXd vs. 7.0 months for RW SoC (HR: 0.57; 95% CI: 0.40, 0.78) in the tumor-agnostic cohort (Figure 2).
- Similar findings were observed in the pan-tumor cohort, with longer weighted mOS for T-DXd than RW SoC (17.7 [95% CI: 12.6, 21.8 months] vs 5.5 months [95% CI: 4.1, 11.8 months]; HR=0.57; 95% CI: 0.40, 0.84).

Progression-free Survival* Outcomes

Figure 3. Weighted KM curve of PFS in tumor-agnostic cohort



- After weighting, T-DXd improved mPFS versus RW SoC (8.0 vs. 2.5 months; HR=0.45; 95% CI: 0.31, 0.66) in the tumor-agnostic cohort (Figure 3).
- Similar findings were observed in the pan-tumor cohort, with longer weighted mPFS for T-DXd than RW SoC (8.3 [95% CI: 7.0,12.3 months] vs 3.0 months [95% CI: 1.8, 3.3]; HR=0.39; 95% CI: 0.27, 0.55).

***PFS definitions:** T-DXd: Time from index line to date of objective disease progression or death before receiving another anti-cancer therapy. RW SoC: Time from index line to earliest of date of tumor progression (if captured), treatment discontinuation (due to progression), subsequent anti-cancer therapy or death.

Discussion

- This external control arm study was designed using the target trial framework to emulate an ideal RCT. Conclusions should be considered in line with the limitations of RW data. However, these are trial-aligned RW patients where key trial eligibility criteria was applied; there was balance in key patient characteristics after PS weighting; and data quality was good with no missing data in the covariates used for weighting.
- ESPERANZA provides robust comparative evidence to evaluate T-DXd clinical effectiveness versus RW SoC where a randomized controlled trial was not feasible. Clinically meaningful improvements in both OS and PFS were consistent across two overlapping HER2 IHC 3+ advanced solid tumor cohorts.

Abbreviations

ADC, antibody-drug conjugate; CCI, Charlson comorbidity index; CI, confidence interval; CRC, colorectal cancer; DC-02, DESTINY-CRC02; DL-01, DESTINY-Lung01; DP-02, DESTINY-PanTumor02; ESS, effective sample size; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IHC, immunohistochemistry; KM, Kaplan Meier; LoT, line of therapy; mOS, median overall survival; mPFS, median progression-free survival; n, number of patients; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; PS, propensity score; RCT, randomized clinical trial; RW, real-world; SoC, standard of care; T-DXd, trastuzumab deruxtecan.

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