Poster PS5-03-05

First-line datopotamab deruxtecan (Dato-DXd) vs chemotherapy in patients with locally recurrent inoperable or metastatic triple negative breast cancer (TNBC) for whom immunotherapy was not an option: Additional safety analyses from the TROPION-Breast02 study

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Objective

- To provide details of the safety profile of Dato-DXd in the TROPION-Breast02 study, including analyses of exposure-adjusted safety and AEs of special interest (oral mucositis/stomatitis; ocular surface events; ILD/pneumonitis).

Conclusions

- In TROPION-Breast02, patients were on treatment for more than twice as long in the Dato-DXd vs ICC arm. Absolute incidence rates of grade ≥3 and serious TRAEs were similar, and discontinuations were lower, with Dato-DXd vs ICC; exposure-adjusted rates of TRAEs were lower with Dato-DXd vs ICC.
- Treatment-related AESIs with Dato-DXd were mainly grade 1/2 and rarely led to treatment discontinuation, and grade ≥2 events were mostly resolved to grade ≤1 at DCO.
- These data further support Dato-DXd as the new first-line standard of care for patients with locally recurrent inoperable or metastatic TNBC for whom immunotherapy is not an option.

Plain language summary

Why did we perform this research?

- Datopotamab deruxtecan (Dato-DXd) is a type of drug called an "antibody-drug conjugate" that consists of an antibody (Dato) and an anticancer drug (DXd), joined via a linker.
- The TROPION-Breast02 study looked at how well Dato-DXd worked, compared with chemotherapy, as initial (first-line) treatment for people with triple-negative breast cancer (TNBC), with a tumor that had grown back in the same place that it started (locally recurrent) and could not be operated on (inoperable), or that had spread from its original site (metastatic), and for whom immunotherapy (treatment that helps the immune system kill cancer cells) was not an option.
- In TROPION-Breast02, people who received Dato-DXd lived longer overall, and lived longer without their disease growing, spreading, or getting worse, compared with people who received chemotherapy.
- This analysis aimed to understand more details of the side effects seen with Dato-DXd in TROPION-Breast02.

How did we perform this research?

- The number of people with side effects was divided by the total time on treatment then multiplied by 100 to calculate exposure-adjusted incidence rates.
- Details of side effects of special interest to researchers were assessed, including oral mucositis/stomatitis (sores or inflammation in the mouth), ocular surface events (side effects that affect or damage the surface of the eye), and interstitial lung disease (ILD)/pneumonitis (inflammation or scarring of the lung).

What were the findings of this research?

- People given Dato-DXd stayed on treatment for over twice as long as people given chemotherapy (8.5 vs 4.1 months), and when adjusted for the time on treatment, the rates of side effects, and side effects that led to stopping treatment, were lower with Dato-DXd compared with chemotherapy.
- Treatment-related side effects of special interest with Dato-DXd were mainly mild or moderate, rarely led to stopping treatment, and moderate or severe events had mostly reduced to mild severity or completely disappeared at the time of analysis.

What are the implications of this research?

- These data on side effects support the use of Dato-DXd as a new first-line treatment for people with locally recurrent inoperable or metastatic TNBC for whom immunotherapy is not an option.

Poster

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Introduction

- The phase 3 TROPION-Breast02 study (NCT05374512) met both dual primary endpoints: first-line Dato-DXd demonstrated statistically significant and clinically meaningful improvements in OS and PFS compared with ICC in patients with locally recurrent inoperable or metastatic TNBC for whom immunotherapy was not an option:[1]
  - Median OS 23.7 vs 18.7 months; HR 0.79 (95% CI 0.64–0.98); P=0.0291
  - Median PFS by BICR 10.8 vs 5.6 months; HR 0.57 (95% CI 0.47–0.69); P<0.0001.
- In TROPION-Breast02, the Dato-DXd safety profile was manageable and generally consistent with the known profile.[1]

Methods

- Full details of the study design (Figure 1) and primary results have been published previously.[1]
- EAIRs of AEs, derived from a post-hoc analysis, were expressed as subject rate (per 100 patient years), calculated as number of patients with AEs divided by the total duration of treatment across all patients, multiplied by 100.
- AESIs for Dato-DXd included oral mucositis/stomatitis, ocular surface events, and ILD/pneumonitis.
  - An independent adjudication committee reviewed all cases of potential ILD/pneumonitis to assess whether the event was a true case, and if so, if it was drug-related.

Figure 1. TROPION-Breast02 design: Randomised, phase 3, open-label, global study

Key inclusion criteria:

- Patients with histologically or cytologically documented locally recurrent inoperable or metastatic TNBC
- No prior chemotherapy or targeted systemic therapy in the locally recurrent inoperable or metastatic setting
- Immunotherapy not an option
- ECOG PS 0 or 1
- No minimum DFI

1:1

Dato-DXd 6 mg/kg IV Day 1 Q3W **(n=323)**

Investigator's choice of chemotherapy (ICC)* Paclitaxel, nab-paclitaxel, capecitabine, eribulin mesylate/eribulin, carboplatin **(n=321)**

Endpoints

Dual primary:
- OS
- PFS by BICR per RECIST v1.1

Secondary included:
- PFS (investigator assessed), ORR, DoR
- Safety

Randomisation stratified by: Geographic region (US/Canada/Europe vs other geographic regions); PD-L1 status (high [CPS ≥10] vs low [CPS <10]); DFI history (*de novo* vs prior DFI 0–12 months vs prior DFI >12 months)

*If no prior taxane, or prior taxane in the (neo)adjuvant setting and DFI >12 months: paclitaxel 80 mg/m² IV, D1, 8, 15, Q3W, or nab-paclitaxel 100 mg/m² IV, D1, 8, 15, Q4W; if prior taxane and DFI 0–12 months: capecitabine 1000 or 1250 mg/m² orally twice daily, D1–14, Q3W (dose determined by standard institutional practice), or eribulin mesylate 1.4 mg/m² / eribulin 1.23 mg/m² IV, Day 1, 8, Q3W, or carboplatin AUC 6 IV, D1, Q3W.

Key toxicity management guidelines for patients receiving Dato-DXd

- **Daily use of prophylaxis with a steroid-containing mouthwash highly recommended** (e.g., dexamethasone oral solution 4 times daily or similar mouthwash regimen using an alternative steroid advocated by institutional/local guidelines).
  - In the absence of steroid-containing mouthwash, daily use of inert, bland mouth rinses (e.g., non-alcoholic/bicarbonate-containing mouthwash, 4–6 times daily) recommended.
- **Prophylactic cryotherapy** (ice chips or ice water held in the mouth throughout the infusion) also suggested.
- Daily use of **artificial tears** and **avoidance of contact lenses** recommended.

Ophthalmological assessment requirements

Dato-DXd arm	At baseline; every 3 cycles while on treatment; as clinically indicated for any ocular symptoms; at end of treatment
ICC arm	At baseline; as clinically indicated for any ocular symptoms; at end of treatment

Results and interpretation

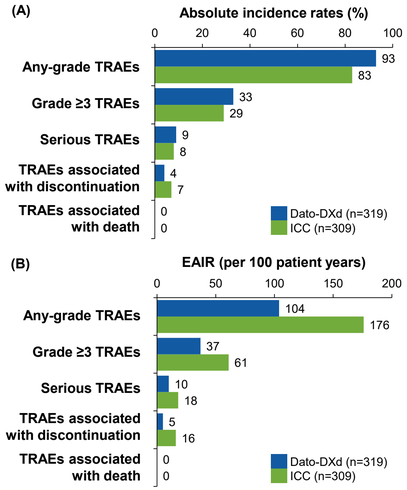
Patients and exposure

- At DCO (25 August 2025), 319 patients had received Dato-DXd and 309 had received ICC.
- Median total treatment duration (range) was 8.5 months (0.7–38.0) in the Dato-DXd arm and 4.1 months (0.1–32.0) in the ICC arm. 35.1% of patients in the Dato-DXd arm vs 9.4% in the ICC arm had total exposure >12 months.

Absolute and exposure-adjusted incidence of TRAEs

- Despite more than double the median duration of treatment in the Dato-DXd arm, absolute incidence rates of grade ≥3 TRAEs and serious TRAEs were similar, and discontinuations were lower, with Dato-DXd vs ICC (Figure 2A). There were no treatment-related deaths in TROPION-Breast02.
- Exposure-adjusted rates of any-grade TRAEs, grade ≥3 TRAEs, serious TRAEs, and TRAEs associated with discontinuation were lower with Dato-DXd vs ICC (Figure 2B).

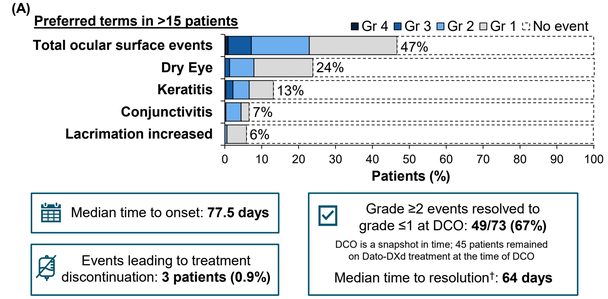
Figure 2. (A) Absolute incidence rates of TRAEs and (B) exposure-adjusted incidence rates of TRAEs

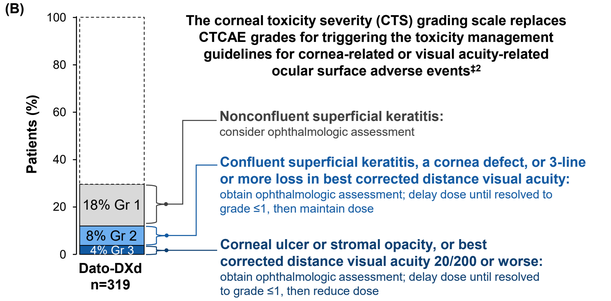


Treatment-related AESIs for Dato-DXd

- In the Dato-DXd arm, treatment-related ocular surface events were reported in 149 patients (47%)[1] (Figure 3), and treatment-related oral mucositis/stomatitis in 192 patients (60%)[1] (Figure 4).
- Adjudicated drug-related ILD/pneumonitis was reported in 9 patients (2.8%) in the Dato-DXd arm – grade 1 in 1 patient (0.3%), grade 2 in 7 patients (2.2%), and grade 5 in 1 patient (0.3%).[1]
  - The grade 5 event was characterized by the investigator as grade 3 pneumonitis, with death assessed as related to breast cancer.
  - Median time to onset was 259 days; 4/9 events had resolved at DCO, with median time to resolution of 112.5 days; events led to treatment discontinuation in 3 patients (0.9%).

Figure 3. Treatment-related ocular surface events* (A) by CTCAE grade and (B) by corneal toxicity severity grade

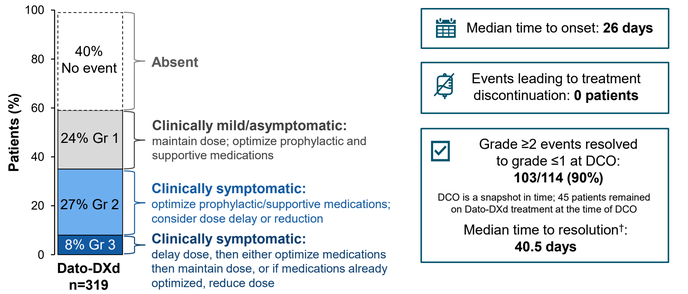




*Comprising the preferred terms of acquired corneal dystrophy, blepharitis, conjunctivitis, corneal disorder, corneal epithelium defect, corneal erosion, corneal exfoliation, corneal lesion, corneal toxicity, dellen, dry eye, keratitis, keratopathy, lacrimation increased, limbal stem cell deficiency, meibomian gland dysfunction, photophobia, punctate keratitis, ulcerative keratitis, vision blurred, visual acuity reduced, visual impairment, and xerophthalmia.
†Resolution of events may only have been captured at a scheduled visit, which took place every 3 weeks for patients in the Dato-DXd arm.

‡‡149 patients had treatment-related ocular surface events. Among 76 patients with CTCAE gr 1 events, 37 had CTS gr 1 events, 3 had CTS gr 2 events, and 36 had no event per CTS; among 50 patients with CTCAE gr 2 events, 17 had CTS gr 1 events, 15 had CTS gr 2 events, and 18 had no event per CTS; among 20 patients with CTCAE gr 3 events, 2 had CTS gr 1 events, 8 had CTS gr 2 events, 9 had CTS gr 3 events, and 1 had no event per CTS; among 3 patients with CTCAE gr 4 events, all 3 had CTS gr 3 events. For patients with treatment-related ocular surface events with a CTCAE grade but no CTS grade, management was based on CTCAE grade.

Figure 4. Treatment-related oral mucositis/stomatitis* by CTCAE grade



*Comprising the preferred terms of aphthous ulcer, mouth ulceration, oral pain, oropharyngeal pain, pharyngeal inflammation, and stomatitis.
†Resolution of events may only have been captured at a scheduled visit, which took place every 3 weeks for patients in the Dato-DXd arm.

Abbreviations

AEs, adverse events; AESIs, adverse events of special interest; BICR, blinded independent central review; CI, confidence interval; CPS, combined positive score; CTCAE, Common Terminology Criteria for Adverse Events; CTS, corneal toxicity severity; D, days; Dato-DXd, datopotamab deruxtecan; DCO, data cutoff; DFI, disease-free interval; DoR, duration of response; EAIR, exposure-adjusted incidence rate; ECOG PS, Eastern Cooperative Oncology Group performance status; gr, grade; HR, hazard ratio; ICC, investigator's choice of chemotherapy; ILD, interstitial lung disease; IV, intravenously; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; QXW, every X weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TNBC, triple-negative breast cancer; TRAEs, treatment-related adverse events.

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Disclosures

Dr Traina has acted as a consultant or advisor for AstraZeneca, bioTheranos, Daiichi Sankyo, Exact Sciences, GE Healthcare, Genentech/Roche, Gilead Sciences, GlaxoSmithKline, G1 Therapeutics, Hengrui Pharmaceutical, Merck, Novartis, Stemline Therapeutics, and TerSera Therapeutics, and has received research funding (to institution) from Astellas, AstraZeneca, Ayala Pharmaceuticals, Daiichi Sankyo, Genentech/Roche, and Pfizer.

Reference

1. Dent RA, et al. Oral presentation at ESMO 2025 Congress; Abstract LBA21.
2. Heist RS, et al. Cancer Treat Rev 2024:125:102720.