Poster 19

# TROPION-Breast05: A Phase 3 study of datopotamab deruxtecan (Dato-DXd) with or without durvalumab versus chemotherapy plus pembrolizumab in patients with PD-L1 positive locally recurrent inoperable or metastatic triple-negative breast cancer


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## Plain language summary

### Why are we performing this research?

- Triple-negative breast cancer (TNBC) is a type of cancer where cells do not have the HER2, estrogen, or progesterone receptors that are commonly found in breast cancer, making it difficult to treat.
- Currently, the standard-of-care treatment for patients with TNBC that has spread (metastasized) and has a protein called PD-1 (which is found on immune cells, and helps keep the body's immune responses in check) is pembrolizumab (a drug that blocks the activity of PD-1) plus chemotherapy. However, additional treatment options are needed with the aim of improving efficacy and minimizing side effects.
- Datopotamab-deruxtecan (Dato-DXd) is an antibody-drug conjugate, where a chemotherapy drug (deruxtecan [DXd], a topoisomerase I inhibitor) is linked to an antibody (datopotamab [Dato]). The Dato part of the drug connects to a protein found on cancer cells called TROP2; it is then taken inside the cell and releases DXd, which kills these cells. By connecting to the cancer cell before releasing the chemotherapy, treatment is directed to the cancer cells so there are fewer side effects in the rest of the body.
- The ongoing Phase 1 TROPION-PanTumor01 trial showed that almost half (44%) of patients with TNBC who received Dato-DXd had a reduction in the size of their tumors, as long as they had not previously received a drug with a similar mode of action.[1]
- Durvalumab is a drug that blocks the activity of PD-L1, a small protein that binds with PD-1, making cancer cells more susceptible to being killed by immune cells. The PD-L1 protein can be present at different levels in different people.
- BEGONIA is an ongoing Phase 1b/2 trial testing durvalumab in combination with novel anticancer therapies with or without chemotherapy. Arms 7 and 8 of BEGONIA are testing Dato-DXd in combination with durvalumab. Data have been released from Arm 7 for patients with metastatic TNBC, who received Dato-DXd and durvalumab as the first treatment for their metastatic cancer: over three quarters (79%) of patients had a decrease in tumor size.[2] The most common side effects of treatment were feeling sick (nausea) and sores or inflammation in the mouth (stomatitis) – these side effects could be managed.
- The TROPION-Breast05 study, was designed to compare Dato-DXd, alone or in combination with durvalumab, versus standard-of-care therapy in patients with TNBC whose cancer cannot be removed by surgery and has spread to a different part of the body. It will assess how well Dato-DXd works, alone or in combination with durvalumab, and describe its side effects, compared with current standard-of-care treatment.

### How are we performing this research?

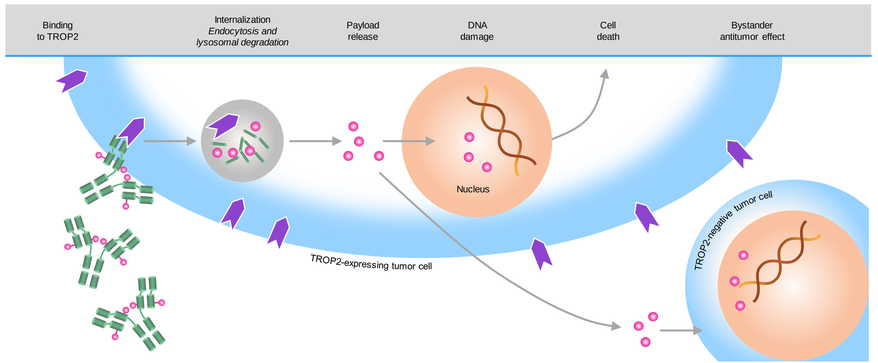
- We are planning to recruit approximately 625 adults who have:
  - TNBC that is not treatable by surgery and has spread to parts of the body distant from the initial tumor(s)
  - Cancer cells that express the protein called PD-L1.
- Eligible patients will be randomly assigned to the following treatment groups:
  - Dato-DXd + durvalumab
  - Standard-of-care therapy (chemotherapy [one of three options, chosen by the treating doctor] plus pembrolizumab)
  - Dato-DXd alone (in selected countries only).
- Patients will continue to receive treatment until the disease progresses, side effects become unacceptable, or they choose to stop. After treatment discontinuation, patients will have safety follow-up visits at regular intervals.

1. Bardia A, et al. Poster P6-10-03; presented at SABCS 2022. 2. Schmid P, et al. Ann Oncol 2023, 34:S337.

## Background

- The current standard-of-care therapy for patients with metastatic TNBC whose tumors express PD-L1 (CPS ≥10) is pembrolizumab plus chemotherapy.[3–5]
  - However, despite recent advances, prognosis remains poor and new treatment options are needed to improve outcomes in this patient population.[6]
- TROP2 is a transmembrane glycoprotein that is highly expressed in breast cancer, including TNBC, and is a promising antigen for TROP2-directed therapies.[7,8]
- Dato-DXd is a TROP2-directed ADC composed of a humanized anti-TROP2 IgG1 monoclonal antibody conjugated to a highly potent topoisomerase I inhibitor payload via a plasma stable tetrapeptide-based tumor-selective cleavable linker (**Figure 1**).[9]
  - In the Phase 1 first-in-human TROPION-PanTumor01 study, Dato-DXd monotherapy demonstrated a manageable safety profile and encouraging efficacy in patients with heavily pretreated metastatic TNBC (confirmed ORR of 32% in all patients and 44% in topoisomerase I inhibitor-naïve patients with measurable disease at baseline).[1]
- Durvalumab is a selective, high-affinity human IgG1 monoclonal antibody that inhibits the interaction of PD-L1 with PD-1 and CD80 by binding to PD-L1.[10]
  - There is preclinical evidence that topoisomerase I inhibition may stimulate an antitumor immune response,[11–13] which supports the hypothesis that the combination of Dato-DXd with durvalumab may lead to improved activity compared with Dato-DXd alone.
- In the Phase 1b/2 BEGONIA study, Dato-DXd plus durvalumab showed durable responses in patients with unresectable locally advanced or metastatic TNBC (ORR of 79%; median DoR of 15.5 months; median PFS of 13.8 months).[2] The safety profile of the combination was manageable, with no new safety signals reported; the most common adverse events were nausea and stomatitis (each in 65% of patients).

## Figure 1: Proposed mechanism of action of Dato-DXd[14]




## TROPION-Breast05 (NCT06103864): A Phase 3, randomized, open-label, 3-arm, multicenter, international study

**Patients with previously untreated locally recurrent inoperable or metastatic PD-L1+ (CPS ≥10) TNBC**

**Key eligibility:**
- **Measurable disease per RECIST 1.1**
- **No active brain metastases**
- **DFI ≥6 months since treatment in the curative setting**
- **ECOG PS 0 or 1**

**N=625 Randomized**

Stratified by:
- DFI history (de novo vs prior DFI >12 months)
- Geographic location (US/Canada/Europe vs Dato-DXd monotherapy enrolling countries vs rest of the world)
- Prior PD-1/PD-L1 treatment for early-stage TNBC (Yes vs No)

**Arm 1**
**Dato-DXd**
6 mg/kg IV Q3W
+
**Durvalumab**
1120 mg IV Q3W
(n=275)

**Arm 2**
**Investigator's Choice of Chemotherapy[‡]**
+
**Pembrolizumab**
200 mg IV Q3W
(n=275)

**Arm 3**
**Dato-DXd**
6 mg/kg IV Q3W
(n=75)[‡]

*DFI 6–12 months capped at 20%.
†Chemotherapy options include paclitaxel (90 mg/m$^2$ IV on Days 1, 8, and 15, Q4W), nab-paclitaxel (100 mg/m$^2$ IV on Days 1, 8, and 15, Q4W) or gemcitabine 1000 mg/m$^2$ IV + carboplatin AUC 2 IV on Days 1 and 8 Q3W.
‡In selected countries only.
All patients received study treatment until investigator-assessed disease progression per RECIST 1.1, unacceptable toxicity or withdrawal of consent. Patients may continue to receive treatment beyond RECIST 1.1-defined PD if they continue to show clinical benefit as per the investigator.

## Key inclusion criteria

- Age ≥18 years.
- Histologically confirmed locally recurrent inoperable or metastatic TNBC (ER and PR <1% on IHC; negative for HER2 with 0 or 1+ intensity on IHC and no evidence of amplification on ISH).
- PD-L1+ TNBC with CPS ≥10 (per 22C3 PD-L1 assay at a central laboratory).
- Measurable disease by CT or MRI as per RECIST 1.1.
- Eligible for one of the chemotherapy options listed as investigator's choice of chemotherapy (paclitaxel, nab-paclitaxel, or gemcitabine + carboplatin).
- No prior chemotherapy or targeted systemic anticancer therapy for metastatic or locally recurrent inoperable breast cancer.
- ECOG PS 0 or 1.
- Adequate bone marrow reserve and organ function.
- DFI of ≥6 months between completion of treatment with curative intent and first documented local or distant disease recurrence.
  - Use of prior checkpoint inhibitors in the curative setting is permitted.

## Key exclusion criteria

- Severe or uncontrolled systemic diseases, including active or uncontrolled infections, uncontrolled or significant cardiac disease, or active or prior autoimmune or inflammatory disorders.
- Neoplastic spinal cord compression or active brain metastases.
- History of leptomeningeal carcinomatosis.
- Clinically significant corneal disease.
- Persistent toxicities caused by previous anticancer therapy not yet improved to Grade ≤1 or baseline (some chronic, stable Grade 2 toxicities permitted at the discretion of the investigator).
- History of non-infectious ILD/pneumonitis treated with steroids, current or suspected ILD/pneumonitis.
- Concurrent anticancer treatment.
- Prior anticancer treatment with another topoisomerase I ADC or any TROP2-directed therapy.
- Concomitant systemic corticosteroids or other immunosuppressive medications.

## Study endpoints

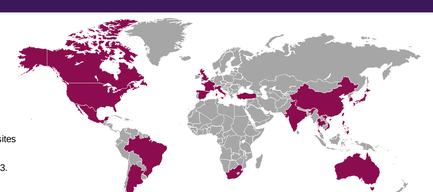
***Primary***

1° PFS by BICR per RECIST 1.1.

***Secondary***

2°
- OS.
- ORR, DoR and CBR at 24 weeks by BICR and investigator assessment per RECIST 1.1.
- PFS by investigator assessment per RECIST 1.1.
- Time to first subsequent therapy.
- Time to second subsequent therapy.
- PFS2.
- Patient-reported outcomes.
- Pharmacokinetics and immunogenicity.
- Safety and tolerability.

## Study status



- The study will recruit patients from ~250 sites across 20 countries/regions.
- Enrollment commenced in November 2023.

Planned/active recruitment

Poster

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## Abbreviations

ADC, antibody-drug conjugate; AUC, area under the concentration-time curve; BICR, blinded independent central review; CBR, clinical benefit rate; CPS, combined positive score; CT, computed tomography; Dato-DXd, datopotamab deruxtecan; DFI, disease-free interval; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IgG1, immunoglobulin G1; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, in-situ hybridization; IV, intravenous; MRI, magnetic resonance imaging; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed cell death (ligand) 1; PFS, progression-free survival; PFS2, time to second progression or death; PR, progesterone receptor; Q3(4)W, every three (four) weeks; RECIST, Response Evaluation Criteria In Solid Tumors; TNBC, triple-negative breast cancer; TROP2, trophoblast cell surface antigen 2.

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## Disclosures

Stephanie L. Graff reports participation in advisory boards for Menarini Stemline, Daiichi-Sankyo, AstraZeneca, Gilead Sciences, Lilly, Genentech, Pfizer, SeaGen, Novartis; has personal stock ownership of HCA Healthcare; and has received research funding from Novartis, Daiichi-Sankyo, AstraZeneca. For co-author disclosures, please refer to the abstract.

## References


1. Bardia A, et al. Poster P6-10-03; presented at SABCS 2022.
2. Schmid P, et al. Ann Oncol 2023, 34:S337.
3. Cortes J, et al. N Engl J Med 2022, 387:217–26.
4. Sukhun S, et al. JCO Glob Oncol 2024, 10:e2300285.
5. Gennari A, et al. Ann Oncol 2021, 32:1475–95.
6. Yin L, et al. Breast Cancer Res 2020, 22:61.
7. Tarantino P, et al. CA Cancer J Clin 2022, 72:165–82.
8. Shastry M, et al. Breast 2022, 66:169–77.
9. Okajima D, et al. Mol Cancer Ther 2021, 20:2329–40.
10. Syed YY. Drugs 2017, 77:1369–76.
11. Yum S, et al. Cell Res 2020, 30:639–48.
12. McKenzie JA, et al. J Natl Cancer Inst 2018, 110:777–86.
13. Huang KC, et al. Cancers (Basel) 2021, 13:1218.
14. Dent R, et al. Future Oncol 2023, 19:2349–59.



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