TROPION-Breast04: A phase 3 study of neoadjuvant datopotamab deruxtecan (Dato-DXd) + durvalumab followed by adjuvant durvalumab vs standard of care in treatment-naive early-stage triple negative and HR-low/HER2– breast cancer

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Plain language summary

Why are we performing this research?

- Triple-negative breast cancer (TNBC) is a type of breast cancer where cells do not have the HER2, estrogen, or progesterone receptors. Therapies that target these receptors do not work in TNBC, making it difficult to treat. Currently, the standard of care for TNBC is initial treatment with pembrolizumab (a drug that blocks the activity of a protein called PD-1) plus chemotherapy, followed by surgical removal of the tumor, then additional pembrolizumab. However, there remains a need for new therapies that improve response to treatment and long-term survival, and reduce side effects associated with chemotherapy.
- Datopotamab deruxtecan (Dato-DXd) is a drug that consists of two parts: datopotamab (an antibody) and DXd (an anticancer drug), which are connected via a linker. Datopotamab binds to a protein called trophoblast cell surface antigen 2 (TROP2), which is found on TNBC tumors. Once bound, Dato-DXd is taken inside the tumor cell where the linker breaks, releasing deruxtecan to kill the tumor.
- Durvalumab is a drug that blocks the activity of a protein called PD-L1, making tumors more susceptible to being killed by immune cells.
- Promising antitumor activity has been seen in patients with TNBC treated with Dato-DXd alone (in the phase 1 TROPION-PanTumor01 study[1]) or in combination with durvalumab (in the phase 1b/2 BEGONIA study[2]).
- This study, called TROPION-Breast04, was designed to compare Dato-DXd plus durvalumab followed by surgery and durvalumab alone, with the standard-of-care pembrolizumab plus chemotherapy in patients with previously untreated TNBC or HR-low/HER2– breast cancer (where cells do not have HER2 receptors, but can have low levels of estrogen or progesterone receptors). The study will assess how well Dato-DXd plus durvalumab works and describe the side effects.

How are we performing this research?

- We aim to recruit approximately 1728 patients who have:
  - TNBC or HR-low/HER2– breast cancer that has not spread from the original site
  - Not received any prior treatment.
- Eligible patients will randomly be assigned to a treatment group in equal numbers:
  - Dato-DXd plus durvalumab, followed by surgery, then further durvalumab-based therapy
  - Pembrolizumab plus chemotherapy, followed by surgery, then further pembrolizumab-based therapy.
- Patients will continue to receive treatment until they complete the planned course of therapy, unless side effects become unacceptable, or they choose to leave the study.

1. Bardia A, et al. Poster P6-10-03. Presented at SABCS 2022; 2. Schmid P, et al. Mini Oral 379MO. Presented at ESMO 2023.

Background

- The current SoC for patients with treatment-naive Stage II–III TNBC is neoadjuvant pembrolizumab plus anthracycline/taxane/platinum-based chemotherapy followed by surgery and adjuvant pembrolizumab monotherapy.[1–3]
  - However, among patients who received pembrolizumab plus chemotherapy in the KEYNOTE-522 trial (NCT03036488), 28% discontinued therapy due to treatment-related adverse events, and 37% had residual disease at the time of surgery, which was associated with poor outcomes.[3] Consequently, there remains an unmet need to develop a treatment approach that improves pCR rates and long-term survival while reducing chemotherapy-associated toxicity in patients with early-stage TNBC.
- There is considerable evidence to show that HR-low/HER2– breast cancer is biologically similar to TNBC, supporting the inclusion of these patients into clinical trials of TNBC.[4]
- Dato-DXd is an ADC consisting of a humanized anti-TROP2 IgG1 mAb covalently linked to a potent Topo-I inhibitor payload via a plasma stable, tumor-selective, tetrapeptide-based cleavable linker (**Figure 1**).
  - In the phase 1 TROPION-PanTumor01 study (NCT03401385), Dato-DXd monotherapy demonstrated a manageable safety profile and encouraging preliminary efficacy in patients with metastatic TNBC, with a confirmed ORR of 32% in all patients and 44% in Topo-I inhibitor-naive patients with measurable disease at baseline.[5]
  - In the phase 3 TROPION-Breast01 study (NCT05104866), Dato-DXd monotherapy demonstrated statistically significant and clinically meaningful improvement in PFS with Dato-DXd compared with chemotherapy (hazard ratio 0.63 [95% CI 0.52–0.76]; p<0.0001) in patients with previously-treated inoperable or metastatic HR-positive/HER2– breast cancer.[6]
- Durvalumab is a selective, high-affinity human IgG1 mAb that inhibits interaction of PD-L1 with PD-1 and CD80 by binding to PD-L1.[7]
  - In the phase 1b/2 BEGONIA study (NCT03742102), Dato-DXd plus durvalumab demonstrated durable responses in unresectable locally advanced/metastatic TNBC (ORR 79%; median DoR 15.5 months; median PFS 13.8 months).[8]
  - The ongoing phase 3 TROPION-Breast03 trial (NCT05629585) is evaluating Dato-DXd with or without durvalumab versus SoC as adjuvant treatment in patients with Stage I–III TNBC with residual invasive disease at the time of surgery after neoadjuvant treatment.
- The TROPION-Breast04 trial aims to determine if improved efficacy and safety can be achieved with neoadjuvant Dato-DXd plus durvalumab followed by adjuvant durvalumab, compared with the pembrolizumab plus chemotherapy SoC regimen in patients with previously untreated TNBC or HR-low/HER2– breast cancer.

Figure 1. Structure of Dato-DXd[9]

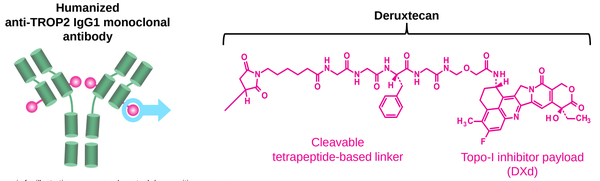


Image is for illustrative purposes only; actual drug positions may vary.

- Optimized drug to antibody ratio ≈4
- Stable linker-payload
- Tumor-selective cleavable linker
- Bystander antitumor effect

TROPION-Breast04 (NCT06112379): phase 3, randomized, open-label, multicenter, global study

Patients with histologically confirmed Stage II or III unilateral or bilateral primary invasive TNBC or HR-low/HER2– breast cancer*

No evidence of distant disease

No prior surgery, radiation, or systemic anticancer therapy

ECOG PS 0 or 1

N≈1728 randomised 1:1

Stratified by:
- Lymph node status (pos. vs neg.)
- Tumor stage (cT1–cT2 vs cT3–cT4)
- HR status (HR-negative [ER and PR <1%] vs HR-low [ER and/or PR 1% to <10%; neither may be ≥10%])
- Geographic region (US/Canada/Europe/Australia vs Rest of the World)

Neoadjuvant	Surgery	Adjuvant†
Dato-DXd[a] + durvalumab[b] for 8 cycles		**Durvalumab[b] for 9 cycles ± olaparib‡[c] chemotherapy§**
Pembrolizumab[d] + carboplatin[e] + paclitaxel[f] for 4 cycles then pembrolizumab[d] + cyclophosphamide[g] + doxorubicin[h]/epirubicin[i] for 4 cycles		**Pembrolizumab[d] for 9 cycles ± olaparib‡[c] capecitabine[j] for 8 cycles¶**

Primary endpoints:
- pCR (central assessment)
- EFS (investigator assessment)

Key secondary endpoint:
- Overall survival

*TNBC defined as: ER and PR <1% on IHC; negative for HER2 with 0 or 1+ intensity on IHC, or 2+ intensity on IHC and no evidence of amplification on ISH. HR-low/HER2– breast cancer defined as: ER 1% to <10% and/or PR 1% to <10% (neither hormone receptor may be ≥10%); negative for HER2 with 0 or 1+ intensity on IHC, or 2+ intensity on IHC and no evidence of amplification on ISH.
†Adjuvant therapy regimen will be based on pCR rates with neoadjuvant treatment.
‡Olaparib may be given for a total period of one year in patients with *gBRCA*-positive tumors and residual disease; treatment may overlap with the 9 adjuvant cycles of durvalumab/pembrolizumab but may not be given concurrently with chemotherapy.
§Chemotherapy may be given in combination with durvalumab only if patients have residual disease. Chemotherapy may be one of four regimens: 1) Either doxorubicin[h] or epirubicin[i] + cyclophosphamide[g] for 4 cycles followed by paclitaxel[f] and carboplatin[e] for 4 cycles; 2) Either doxorubicin[h] or epirubicin[i] + cyclophosphamide[g] for 4 cycles followed by paclitaxel[f] for 4 cycles; 3) Carboplatin[e] + paclitaxel[f] for 4 cycles; 4) Capecitabine[j] for 8 cycles.
¶Capecitabine may be given in combination with pembrolizumab only if patients have residual disease.
[a]6 mg/kg IV Q3W; [b]1120 mg IV Q3W; [c]300 mg PO BID for 1 year; [d]200 mg IV Q3W; [e]AUC 5 mg/mL/min IV Q3W; OR AUC 1.5 mg/mL/min IV QW (based on investigator preference); [f]80 mg/m² IV QW; [g]600 mg/m² IV Q3W; [h]60 mg/m² IV Q3W; [i]90 mg/m² IV Q3W; [j]1000 or 1250 mg/m² (based on standard institutional practice) PO BID on Days 1 to 14, Q3W.

Study endpoints

1°
- pCR rate by central assessment
- EFS by investigator assessment

2°
- Overall survival
- Distant disease-free survival
- Pharmacokinetics and immunogenicity
- Safety and tolerability
- PROs in terms of:
  - Breast and arm symptoms, physical function, fatigue, GHS/QoL

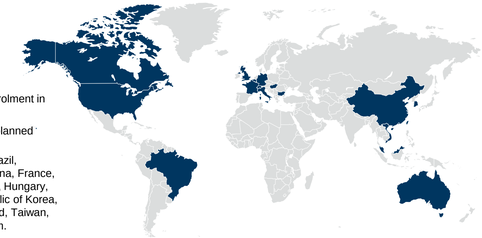
Key inclusion criteria

- Adults (aged ≥18 years) with histologically confirmed Stage II or III unilateral or bilateral primary invasive TNBC or HR-low/HER2– breast cancer per AJCC 8th edition,[10] as assessed by the investigator.
  - TNBC defined as: ER and PR <1% on IHC; negative for HER2 with 0 or 1+ intensity on IHC, or 2+ intensity on IHC and no evidence of amplification on ISH.
  - HR-low/HER2– breast cancer defined as: ER 1% to <10% and/or PR 1% to <10% (neither hormone receptor may be ≥10%); negative for HER2 with 0 or 1+ intensity on IHC, or 2+ intensity on IHC and no evidence of amplification on ISH.
- ECOG PS of 0 or 1.
- Provision of an acceptable tumor sample prior to randomization.
- Adequate bone marrow reserve and organ function within 7 days before randomization.

Key exclusion criteria

- Evidence of severe/uncontrolled systemic diseases including active infection requiring intravenous treatment, serious chronic gastrointestinal conditions associated with diarrhea, active bleeding diseases, significant cardiac or psychological illness, chronic or previously complicated diverticulitis, or history of allogenic organ transplant.
- History of another primary malignancy except for malignancy treated with curative intent with no known active disease within 3 years before randomization and of low potential risk for recurrence. Exceptions include adequately resected non-melanoma skin cancer and curatively treated in situ disease.
- Active or prior documented autoimmune or inflammatory disease (with certain exceptions).
- Evidence of distant disease.
- Clinically significant corneal disease.
- Active or uncontrolled hepatitis B or C infection, uncontrolled HIV infection, or active tuberculosis.
- Suspected, current, or previous non-infectious ILD/pneumonitis that require(d) steroids.
- Any prior or concurrent surgery, radiotherapy or systemic anticancer therapy for TNBC or HR-low/HER2– breast cancer including chemotherapy, radiation therapy, endocrine therapy, immune-mediated therapy (e.g., anti-CTLA-4 and anti-PD-(L)1 antibodies, excluding therapeutic anticancer vaccines), retinoid therapy, or targeted therapy.
- Prior exposure to the following treatment:
  - Chloroquine/hydroxychloroquine with ≤14 days washout before randomization
  - Immunosuppressive medication <14 days before first dose of study intervention
  - Live, attenuated vaccine <30 days before first dose of study intervention.

Study status



- The study opened for enrolment in November 2023.
- 143 study locations are planned across 19 countries.
  - Australia, Belgium, Brazil, Bulgaria, Canada, China, France, Germany, Hong Kong, Hungary, Italy, Malaysia, Republic of Korea, Singapore, Switzerland, Taiwan, UK, USA, and Vietnam.

Poster

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Abbreviations

ADC, antibody-drug conjugate; AJCC, American Joint Committee on Cancer; AUC, area under the curve; BID, twice daily; CI, confidence interval; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; Dato-DXd, datopotamab deruxtecan; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; ER, estrogen receptor; GHS, global health status; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IgG, immunoglobulin G; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, in situ hybridization; IV, intravenous; mAb, monoclonal antibody; ORR, objective response rate; pCR, pathologic complete response; PD-(L)1, programmed cell death (ligand)-1; PFS, progression-free survival; PO, orally; PR, progesterone receptor; PRO, patient-reported outcome; QoL, quality of life; QxW, every *x* weeks; SoC, standard of care; TNBC, triple-negative breast cancer; Topo-I, topoisomerase I; TROP2, trophoblast cell surface protein 2.

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Disclosures

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