159TiP

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

Sibylle Loibl,[1] Sara M. Tolaney,[2] Peter Schmid,[3] Barbara Pistilli,[4] Rebecca A. Dent,[5] Jamil Asselah,[6] Qiang Liu,[7] Jane Lowe Meisel,[8] Naoki Niikura,[9] Yeon Hee Park,[10] Gustavo Werustky,[11] Giampaolo Bianchini,[12] Jay C. Andersen,[13] Robert Kozarski,[14] Nana Rokutanda,[15] Heather L. McArthur[16]

[1]Department of Medicine and Research, German Breast Group, Neu-Isenburg, Germany; [2]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [3]Barts Cancer Institute, Queen Mary University of London, London, UK; [4]Department of Medical Oncology, Gustave Roussy Cancer Center, Villejuif, France; [5]Department of Medical Oncology, National Cancer Center Singapore, Singapore; [6]Gerald Bronfman Department of Oncology, McGill University Health Centre, Cedars Cancer Centre, Montreal, QC, Canada; [7]Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China; [8]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [9]Department of Breast Oncology, Tokai University School of Medicine, Kanagawa, Japan; [10]Samsung Medical Center, Sungkyunkwan University School of Medicine / Samsung Advanced Institute for Health Sciences & Technology, Sungkyunkwan University, Seoul, Republic of Korea; [11]Breast Cancer Program, Hospital Moinhos de Vento, Porto Alegre, Brazil; [12]Department of Medical Oncology, IRCCS Ospedale San Raffaele, Milan, Italy; [13]Medical Oncology, Compass Oncology/Sarah Cannon Research Institute, Portland, OR, USA; [14]Biostatistics, AstraZeneca, Cambridge, UK; [15]Oncology R&D, AstraZeneca, Gaithersburg, MD, USA; [16]Department of Medicine, Breast Cancer Program, Harold C. Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX, USA

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, oestrogen, or progesterone receptors. Therapies that target these receptors do not work in TNBC, making it difficult to treat. Currently, the standard of care for nearly TNBC is neoadjuvant chemotherapy plus pembrolizumab (a drug that blocks the activity of a protein called PD-1), followed by surgical removal of the tumour, 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 tumours. Once bound, Dato-DXd is taken inside the tumour cell where the linker breaks, releasing DXd to kill the tumour.
- Durvalumab is a drug that blocks the activity of a protein called PD-L1, making tumours more susceptible to being killed by immune cells.
- Promising antitumour 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 chemotherapy plus pembrolizumab in patients with previously untreated early-stage TNBC or HR-low/HER2–breast cancer (where cells do not have HER2 receptors, but can have low levels of oestrogen 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
  - Chemotherapy plus pembrolizumab, 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-naïve stage II–III TNBC is neoadjuvant anthracycline/taxane/platinum-based chemotherapy plus pembrolizumab followed by surgery and adjuvant pembrolizumab monotherapy.[1–3]
  - However, among patients who received chemotherapy plus pembrolizumab 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 humanised anti-TROP2 IgG1 mAb covalently linked to a potent Topo-I inhibitor payload via a plasma stable, tumour-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-naïve 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 chemotherapy plus pembrolizumab SoC regimen in patients with previously untreated early-stage TNBC or HR-low/HER2–breast cancer.

Figure 1. Structure of Dato-DXd[9]

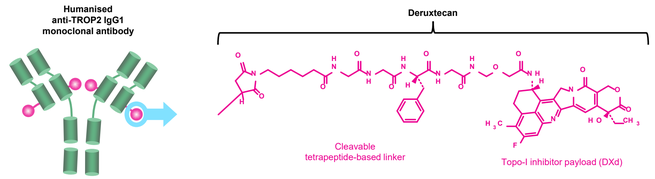
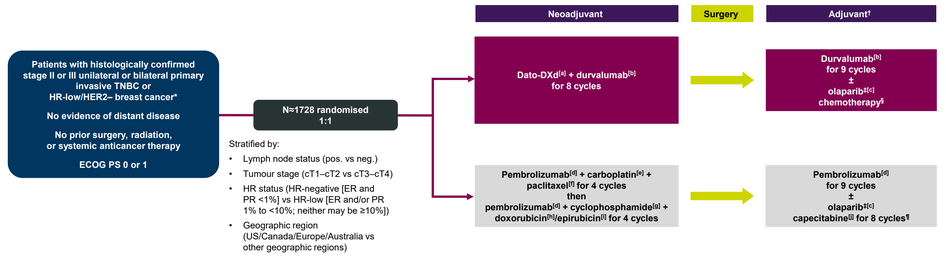


Image is for illustrative purposes only; actual drug positions may vary.

TROPION-Breast04 (NCT06112379): phase 3, randomised, open-label, multicentre, global study



*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 tumours 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

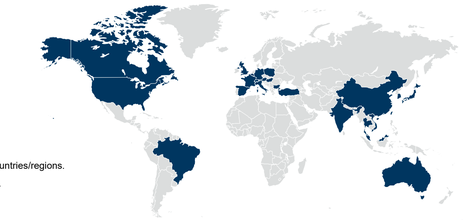
Key inclusion criteria

- 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 tumour sample prior to randomisation.
- Adequate bone marrow reserve and organ function within 7 days before randomisation.

Key exclusion criteria

- Evidence of severe/uncontrolled systemic diseases including active infection requiring intravenous treatment, serious chronic gastrointestinal conditions associated with diarrhoea, 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 randomisation 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 randomisation
  - 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 will recruit patients across 26 countries/regions.
- Enrolment commenced in November 2023.

Planned/active recruitment

Poster

Mobile-friendly Poster

Please scan this quick response (QR) code with your smartphone camera or app to obtain a copy of these materials. Alternatively, please use the link below.

https://bit.ly/49mHJnr

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, oestrogen 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 hybridisation; 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.

Acknowledgements

This study (NCT06112379) is sponsored by AstraZeneca. In July 2020, Daiichi-Sankyo entered into a global development and commercialisation collaboration with AstraZeneca for datopotamab deruxtecan (Dato-DXd). Medical writing support for the development of this poster, under the direction of the authors, was provided by Werner Gerber, PhD, of Ashfield MedComms (Fourways, South Africa), an Inizio company, and was funded by AstraZeneca.

Disclosures

Sibylle Loibl has participated in advisory boards/advisory role for AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, Celgene, DSI, Exgenix, Gilead, GSK, Lilly, Merck, Novartis, Olema, Pfizer, Pierre Fabre, Relay Therapeutics, Roche, Sanofi, SeaGen; has been an invited speaker for AstraZeneca, DSI, Gilead, MedScape, Novartis, Pfizer, Roche, SeaGen, Stemline-Menarini, VMScope; employment as CEO for GBG Forschungs; has received research grants/funding from AbbVie, AstraZeneca, Celgene, Daiichi-Sankyo, Greenwich, Immunomedics, Molecular Therapeutics, Novartis, Pfizer, Roche; has served as Principal Investigator for PI, Aphinity; is a member of AGO, DKG, ASCO and ESMO; and has other financial relationships with AstraZeneca, Daiichi-Sankyo, Immunomedics, Novartis, Pfizer, Roche, SeaGen; and involvement with patents.
For co-author disclosures, please refer to abstract.

References

1. Denduluri N, et al. J Clin Oncol 2020;39:685–93.
2. Korde LA, et al. J Clin Oncol 2021;39:1485–505.
3. Schmid P, et al. N Engl J Med 2022;386:556–67.
4. Dieci MV, et al. NPJ Breast Cancer 2021;7:101.
5. Bardia A, et al. Cancer Res 2023;83(5_suppl):P6-10-03.
6. Bardia A, et al. Ann Oncol 2023;34(suppl_2):S1264–5.
7. Syed YY. Drugs 2017;77:1369–76.
8. Schmid P, et al. Ann Oncol 2023;34(suppl_2):S337.
9. Dent RA, et al. Future Oncol 2023;19:2349–59.
10. Amin MB, et al, eds, AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017.

Poster presented at the ESMO Breast Cancer Congress 2024; Berlin, Germany; 15–17 May 2024. Corresponding author email address: sibylle.loibl@gbg.de.