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Durvalumab + Datopotamab Deruxtecan in Patients With PD-L1–Positive Advanced/Metastatic Triple-Negative Breast Cancer: Arm 8 of the Phase 1b/2, Open-Label, Platform BEGONIA Study

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Plain Language Summary

Why are we performing this research?

- Triple-negative breast cancer (TNBC) is a type of breast cancer in which cells do not have the HER2, estrogen, or progesterone receptors, which makes TNBC challenging to treat.
- Durvalumab is a drug that blocks the activity of a protein called PD-L1, making cancer cells more susceptible to being killed by immune cells. The PD-L1 protein can be present at different levels in different people; referred to as high or low PD-L1 expression.
- Datopotamab deruxtecan (Dato-DXd) is an antibody-drug conjugate, which is a chemotherapy (deruxtecan [DXd], a topoisomerase I inhibitor) that 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.
- BEGONIA is an ongoing Phase 1b/2 study testing durvalumab in combination with novel anticancer therapies with or without chemotherapy. Arms 7 and 8 of BEGONIA are testing Dato-DXd with durvalumab. In the data released so far for Arm 7, patients with TNBC that had spread from its original site received Dato-DXd and durvalumab as the first treatment for their metastatic cancer, and over three quarters (79%) had a decrease in tumor size.[1]
- However, most patients (87%) who were treated with Dato-DXd and durvalumab in Arm 7 were found to have tumors with low expression of the PD-L1 protein when tested after study entry. Therefore, this study arm (Arm 8) was designed to include patients who had confirmed PD-L1-positive tumors at study entry and assess how well Dato-DXd and durvalumab works in these patients.

Who will participate in this study?

- We are planning to recruit approximately 30 adults in Part 1 of Arm 8 who have:
  - TNBC that has already spread to other parts of the body, but that has not been treated yet.
  - Been tested and found to have tumors positive for the PD-L1 protein.
- Eligible patients will be given Dato-DXd + durvalumab until their disease gets worse or they have unacceptable side effects.
- If the first 30 patients show that the treatment is working, then another 27 patients may be recruited.

Where can I access more information?

- To learn more about the BEGONIA study, you can visit ClinicalTrials.gov, entry NCT03742102, or the European Union Drug Regulating Authorities Clinical Trials Database, entry 2018-000764-29.
- The combination of Dato-DXd + durvalumab for people with TNBC is also being investigated in the Phase 3 study TROPION-Breast03 (ClinicalTrials.gov, entry NCT05629585; European Union Drug Regulating Authorities Clinical Trials Database, entry 2022-002680-30).

1. Schmid P, et al. Presented at ESMO 2023. 379MO.

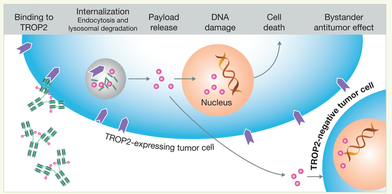
Background

- Patients with advanced/metastatic (a/m) TNBC have limited treatment options and a poor prognosis.[1,2]
- PD-1/PD-L1 immune checkpoint pathways block T-cell function and activation, reducing T-cell–mediated antitumor activity and proliferation.[3]
- The combination of immune checkpoint inhibitor therapy with chemotherapy is the standard of care for patients with PD-L1–positive a/mTNBC; still, most patients progress within a year (median progression-free survival [PFS] ~9–10 months).[4,5]
- BEGONIA (NCT03742102) is an ongoing 2-part, open-label platform study, evaluating safety and efficacy of durvalumab, an anti–PD-L1 antibody, combined with other novel therapies in first-line (1L) a/mTNBC, including Dato-DXd.[6]
- **Durvalumab** blocks PD-L1 from binding to PD-1 and CD80 on antigen-presenting cells and tumor cells, thereby enhancing the antitumor immune response by allowing T cells to recognize and kill tumor cells.[7]
- **Dato-DXd** is an antibody-drug conjugate consisting of a humanized anti-TROP2 antibody covalently linked to a highly potent topoisomerase I inhibitor payload via a plasma-stable, tumor-selective, tetrapeptide-based cleavable linker[8,9] (**Figure 1**).
- For patients treated with Dato-DXd + durvalumab in Arm 7 of BEGONIA, at a median follow-up of 11.7 months, objective response rate (ORR) was 79% with a manageable safety profile (**Figure 2**); median PFS was 13.8 months.[6]
- Of the biomarker-unselected population included in Arm 7, most patients (87%) with a/mTNBC treated with Dato-DXd + durvalumab were found to have tumors with low PD-L1 expression (**Figure 2**); Arm 8 will investigate Dato-DXd + durvalumab safety and efficacy in patients who have PD-L1-positive tumors at study entry.

Focus on TROP2 and Dato-DXd

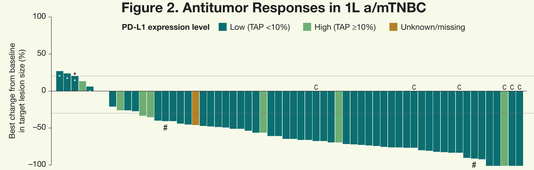
- TROP2 is highly expressed on breast and other epithelial tumors,[10] which makes it a possible target for anticancer therapies.
- Dato-DXd displayed encouraging results in an ongoing Phase 1 study, TROPION-PanTumor01, with an ORR of 44% and a manageable safety profile in heavily pretreated patients with TNBC who were not previously exposed to a topoisomerase I inhibitor.[11]
- An ongoing Phase 3 study (TROPION-Breast01) investigating Dato-DXd efficacy in patients with metastatic HR+/HER2 breast cancer met the primary endpoint of PFS; patients receiving Dato-DXd had significantly improved PFS versus chemotherapy (HR, 0.63 [95% CI, 0.52-0.76]; p<0.0001).[12]
- Dato-DXd can produce DNA damage and apoptosis in TROP2-expressing tumor cells[8] and may eliminate surrounding cells through a bystander antitumor effect[9] (**Figure 1**).
- Preclinical evidence demonstrates that the adminstration of an anti–PD-L1 antibody + Dato-DXd leads to a synergistic effect and enhances the antitumor activity of Dato-DXd,[13] supporting the hypothesis that the combination of Dato-DXd with immune cell–activating agents, such as durvalumab, may provide an enhanced antitumor effect over the individual therapies.[14]

Figure 1. Proposed Mechanism of Action of Dato-DXd



Previously Presented Results From BEGONIA Arm 7, Dato-DXd + Durvalumab[6]

Figure 2. Antitumor Responses in 1L a/mTNBC



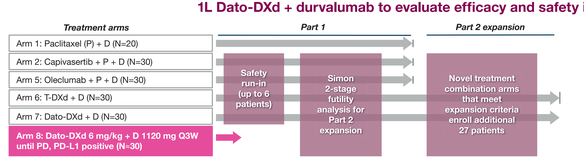
C, complete response as best overall response. "•" Patients with progressive disease as best overall response. #Unconfirmed response.

Dotted lines indicate thresholds for partial response (–30%) and progressive disease (20%). PD-L1 expression was assessed by immunohistochemistry using the VENTANA PD-L1 (SP263) Assay with expression defined as the percentage of the tumor area populated by tumor or immune cells with membranous staining (TAP). *If the best percentage change from baseline of target lesions cannot be calculated due to progression, withdrawal, or death, the value is imputed at +20%.

- **Confirmed ORR** was **79%** (49/62; 95% CI, 66.8–88.3) with 6 CR and 43 PR and a median follow-up of 11.7 (range, 2–20) months (**Figure 2**).
- **Median PFS** was **13.8 months** (N=62; 95% CI, 11.0–NC); **median duration of response (DoR)** was **15.5 months** (N=62; 95% CI, 9.9–NC).
- Antitumor responses were observed regardless of PD-L1 expression level.
- Although responses were observed in both PD-L1 high- and low-expressing tumors, most patients (87%) had PD-L1 low-expressing tumors.
- The combination of Dato-DXd + durvalumab had a tolerable and manageable safety profile, with no new safety signals.
  - The most common adverse events were stomatitis and nausea (both 65%) and generally of low grade.

BEGONIA Study Design: Addition of Arm 8, and Participating Countries

In Arm 8, patients determined to have PD-L1–positive tumors by pre-existing/local testing will be recruited and treated with 1L Dato-DXd + durvalumab to evaluate efficacy and safety in a PD-L1–high population.



- A safety run-in will not occur for Arm 8 as Dato-DXd + durvalumab was already evaluated and found to be tolerable with no dose-limiting toxicities reported in the Arm 7 safety run-in.
- Novel treatment combinations may enter Part 2 expansion if confirmed ORR is at least 57%; Arms 6 and 7 have met the expansion criteria.

Participating countries in BEGONIA Arm 8

Arm 8 enrollment commenced in June 2023.

Key Inclusion Criteria for Arm 8

- Female patients aged ≥18 years.
- Untreated unresectable, locally advanced, or mTNBC.
- ≥6 months between completion of treatment for earlier-stage breast cancer and recurrence of distant disease.
- ≥12 months since prior taxane therapy.
- ECOG PS 0/1, adequate organ function.
- ≥1 nonirradiated measurable lesion (measurable disease per RECIST v1.1).
- A PD-L1–positive tumor as determined by local immunohistochemistry testing (either pre-existing or obtained during prescreening).

Key Exclusion Criteria for Arm 8

- Untreated central nervous system metastases.
- History or suspicion of interstitial lung disease/pneumonitis.
- Underlying pulmonary disorder or other lung-specific illnesses.
- Prior exposure to immune-mediated therapy.
- Clinically significant corneal disease.
- Active autoimmune or inflammatory disorders.
- Prior treatment with an antibody-drug conjugate containing a topoisomerase I inhibitor.

Study Endpoints

1°
- **Part 1**
  - Safety and tolerability
- **Part 2**
  - ORR

2°
- **Part 1 only**
  - ORR
  - Testing for antidrug antibodies
  - Pharmacokinetics
- **Parts 1 and 2**
  - DoR
  - PFS
  - Overall survival

PD-L1 Testing in Arm 8

At enrollment:

- A PD-L1–positive tumor as determined by local immunohistochemistry testing is required (either pre-existing or obtained during prescreening).

Additional testing:

- Additional PD-L1 confirmatory testing with the VENTANA PD-L1 (SP263) Assay will be performed on pretreatment tumor samples.
- High expression is defined as ≥10% of the tumor area populated by PD-L1–expressing tumor or immune cells.

Poster

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

https://bit.ly/3srZbYa

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Abbreviations

1L, first line; a/mTNBC, advanced/metastatic triple-negative breast cancer; CI, confidence interval; CR, complete response; Dato-DXd, datopotamab deruxtecan; DoR, duration of response; D, durvalumab; ECOG PS, Eastern Cooperative Oncology Group performance status; NC, non-calculable; ORR, objective response rate; PD, progressive disease; PD-1, programmed death-1; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; PR, partial response; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria In Solid Tumors; T-DXd, trastuzumab deruxtecan; TAP, tumor area positivity; TROP2, trophoblast cell-surface antigen 2.

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