San Antonio Breast Cancer Symposium® - December 6-10, 2022
Poster PD11-09

Datopotamab Deruxtecan (Dato-DXd) + Durvalumab (D) as First-line (1L) Treatment for Unresectable Locally Advanced/Metastatic Triple-negative Breast Cancer (a/mTNBC): Updated Results from BEGONIA, a Phase 1b/2 Study

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Introduction

- Patients with a/mTNBC have limited treatment options and a poor prognosis (objective response rate [ORR] of 37%, median duration of response of 6.5 months, and median overall survival [OS] of 15.5 months with 1L chemotherapy).[1]
- Combining immune checkpoint inhibitors with 1L chemotherapy modestly improves outcomes but only in programmed cell death ligand-1 (PD-L1)–high a/mTNBC, emphasizing a critical unmet need for patients with PD-L1–low disease and for further improving outcomes in PD-L1–high disease.[2,3]
- 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 1L a/mTNBC, including Dato-DXd.[4]
- 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 stable, tumor-selective, tetrapeptide-based cleavable linker.[5,6]
- Early data from BEGONIA Arm 7 of durvalumab in combination with Dato-DXd were presented at ESMO Breast 2022 (n=29) and showed promising responses.[7]

Objective

- To report an update on safety, tolerability, and efficacy results as well as data from additional patients of the Dato-DXd + durvalumab combination in BEGONIA.

Methods

- The first 6 patients treated with Dato-DXd + durvalumab were evaluated for dose-limiting toxicities (DLTs), no DLTs were observed, and additional patients were enrolled in Part 1 (previously reported[7]); Part 1 ORR evaluation confirmed proceeding to the Part 2 expansion.
- Tumors were assessed per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 every 6 weeks for the first 48 weeks, then every 12 weeks thereafter.
- PD-L1 was assessed using the VENTANA PD-L1 (SP263) Assay, and expression was defined as the percentage of the tumor area populated by tumor or immune cells with membranous staining (tumor area positivity [TAP]).
- A sample was considered PD-L1 high if it demonstrated ≥10% TAP PD-L1 expression.
- Confirmed response was assessed for patients who had the opportunity for ≥2 on-treatment disease assessments, progressed, or died; unconfirmed response was assessed for patients who had the opportunity for ≥1 on-treatment disease assessment.

Poster

Plain Language Summary

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BEGONIA Study Design

Eligibility criteria

- Unresectable, locally advanced, or metastatic Stage IV TNBC
- No prior treatment for Stage IV disease.
- ≥12 months since taxane therapy for early-stage disease
- Measurable disease per RECIST v1.1
- Eastern Cooperative Oncology Group performance status of 0–1
- No autoimmune, inflammatory illnesses
- Adequate organ and marrow function

Additional criteria for Dato-DXd + durvalumab arm

- No prior treatment with immune checkpoint inhibitors or TOPO I-based antibody-drug conjugates

Treatment arms[a]

- Arm 1: D + Paclitaxel (P)
- Arm 2: D + P + Capivasertib
- Arm 5: D + P + Oleclumab
- Arm 6: D + Trastuzumab deruxtecan

Poster PD11-08

Arm 7: Dato-DXd + durvalumab (D)

Dato-DXd: 6 mg/kg IV Q3W
Durvalumab: 1120 mg IV Q3W

Treatment arm discussed in this presentation

Part 1

Arms 2–7 only: Safety run-in (up to 6 patients) → Simon 2-stage evaluation of ORR to precede initiation of Part 2 for each novel treatment arm. If expansion criteria are met, then novel treatment arm may proceed to Part 2

Primary endpoints	Safety and tolerability
Secondary endpoints	ORR, DoR, PFS, OS
Exploratory endpoint	Association of PD-L1 expression with treatment response

Part 2 Expansion

Enrollment of additional 27 patients in the novel treatment arm

Primary endpoint	ORR
Secondary endpoints	PFS, DoR, PFS6, OS

[a]Arms 3 and 4, D + P + selumetinib and D + P + danvatirsen, were removed from the protocol prior to enrolling patients.

Results and Interpretation

- As of the data cutoff of July 22, 2022, 61 patients received Dato-DXd + durvalumab in Parts 1 and 2, with 45 receiving ongoing treatment (**Table 1**).
  - Four discontinued Dato-DXd + durvalumab because of an adverse event (AE), 13 discontinued due to progression, and 1 patient decided to stop treatment (more than1 reason may have been reported).
- Median (range) follow-up time was 7.2 (1–14) months.

Table 1. Patient and disease characteristics

Characteristic	N=61
Age, median (range), years	53 (31–74)
Race, n (%)	
White	38 (62.3)
Asian	15 (24.6)
Black/African American	4 (6.6)
Other	4 (6.6)
No prior treatment, n (%)	25 (41.0)
Prior treatments for early-stage disease, n (%)	
Radiotherapy	30 (49.2)
Cytotoxic chemotherapy	32 (52.5)
Taxane	25 (41.0)
Anthracycline	28 (45.9)
Platinum compound	9 (14.8)
Hormonal therapy	9 (14.8)
Targeted therapy	3 (4.9)
Visceral metastases[a], n (%)	35 (57.4)
Lymph node metastases, n (%)	41 (67.2)
PD-L1 expression, n (%)	
High (TAP ≥10%)	7 (11.5)
Low (TAP <10%)	53 (86.9)
Missing	1 (1.6)

[a]Defined as liver/hepatic and/or respiratory metastases.

- No DLTs were reported.
- Common AEs were mostly gastrointestinal (**Table 2**).
- 11 patients (18.0%) underwent Dato-DXd dose reduction due to an AE, 7 (11.5%) of those were associated with stomatitis.
- Of the neutropenic (2 [3.3%]) events reported, none were Grade 3 or 4; diarrhea was reported for 8 (13.1%) patients, with 1 Grade 3 event and no Grade 4 events.
- The adjudication committee confirmed 2 (3.3%) patients had Grade 1 interstitial lung disease/pneumonitis.
- Durvalumab AEs of special interest (AESIs) occurring in ≥10% of patients were rash, diarrhea, and hypothyroidism; most were Grade 1/2 events.
- Dato-DXd AESIs occurring in ≥10% of patients were predominantly Grade 1/2 events and included stomatitis, rash, pruritus, and dry eye.

Table 2. Safety summary

	N=61
Any Grade AE, n (%)	60 (98.4)
Common AEs (≥20% patients, any grade)	
Nausea	35 (57.4)
Stomatitis	34 (55.7)
Alopecia	28 (45.9)
Fatigue, constipation	24 (39.3) each
Rash	17 (27.9)
Vomiting	13 (21.3)
Any Grade 3/4 AE	25 (41.0)
Any serious AE	10 (16.4)
Any treatment-related AE[a]	57 (93.4)
Grade 3/4	21 (34.4)
Any durvalumab AESI	46 (75.4)
Any Dato-DXd AESI	49 (80.3)
AE leading to Dato-DXd + D discontinuation	4 (6.6)
AE leading to dose interruption	27 (44.3)
AE leading to death[b]	1 (1.6)
Durvalumab dose delay	25 (41.0)
Dato-DXd dose delay	23 (37.7)
Dato-DXd dose reduction	12 (19.7)

[a]Per investigator assessment.
[b]Patient died due to dehydration, unrelated to treatment.

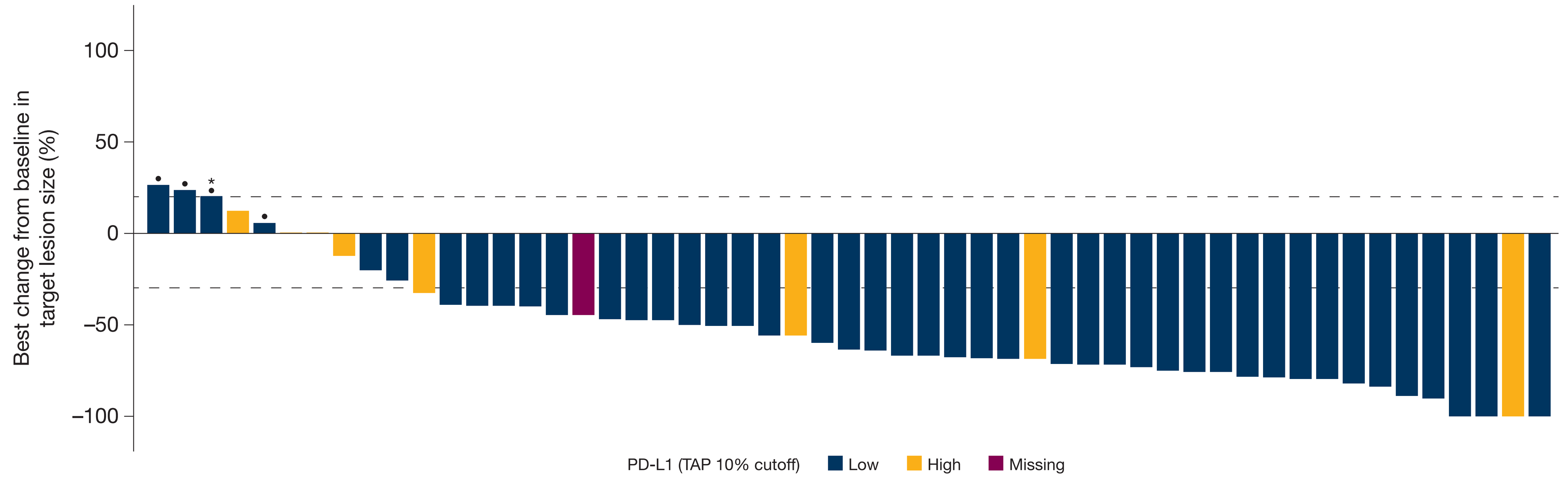
Table 3. Response and survival outcomes

	N=61
Follow up, median (range), months	7.2 (1–14)
Confirmed ORR	
Evaluable patients, n	53
ORR, n (%)	39 (73.6)
95% CI	59.7–84.7
CR, n	4
PR	35
Unconfirmed ORR	
Evaluable patients, n	60
ORR, n (%)	48 (80.0)
95% CI	67.7–89.2

CR, complete response; PR, partial response.

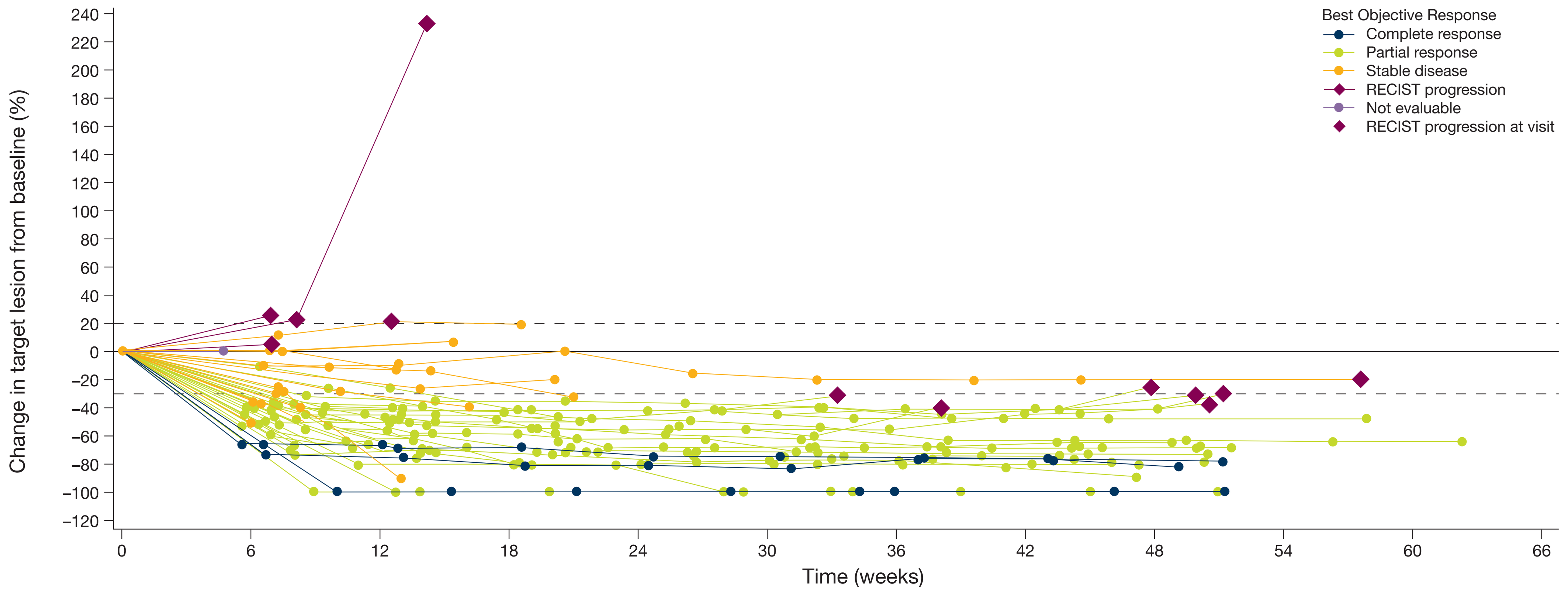
- With Dato-DXd + durvalumab treatment, 73.6% of patients had a confirmed tumor response (**Table 3, Figure 1**).
- Responses were durable, with 82% of patients remaining in response at the data cutoff (**Figure 2**).
- Responses were observed in PD-L1–low and PD-L1–high tumors (**Figure 1**).

Figure 1. Best change from baseline of target lesion size



n = 53.
Dotted reference lines at −30% and 20% indicate thresholds for partial response and progressive disease, respectively.
*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%. "•" Patients with progressive disease as best overall response.

Figure 2. Change from baseline in sum of target lesions over time



Dotted reference lines at −30% and 20% indicate thresholds for partial response and progressive disease, respectively.

Conclusions

- In this updated analysis with a median of 7 months follow-up, the combination of Dato-DXd + durvalumab in 1L a/mTNBC demonstrated a tolerable and manageable safety profile.
- A compelling high response rate, with 4 patients having complete response, was observed with Dato-DXd + durvalumab.
- Although subgroups were small, responses were observed in PD-L1–high and PD-L1–low tumors.
- While maturity is low, response durability is promising; longer follow-up will further inform efficacy results, including PFS.
- Further investigation of Dato-DXd + durvalumab is warranted in this patient population.

Acknowledgments

This study was funded by AstraZeneca and Daiichi Sankyo. In July 2020, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for datopotamab deruxtecan (Dato-DXd). The authors would like to thank the patients, their families and caregivers, and all investigators involved in this study. Medical writing support, which was in accordance with Good Publication Practice (GPP3) guidelines, was provided by Nicole Seneca, PhD, of Parexel and was funded by AstraZeneca.

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