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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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DECLARATION OF INTERESTS

Peter Schmid

Honoraria from AstraZeneca, Novartis, Pfizer, Roche, and Puma Biotechnology.

Consulting or advisory role from AstraZeneca, Bayer, Boehringer Ingelheim, Celgene, Eisai, Roche, Merck, Novartis, Pfizer, and Puma Biotechnology.

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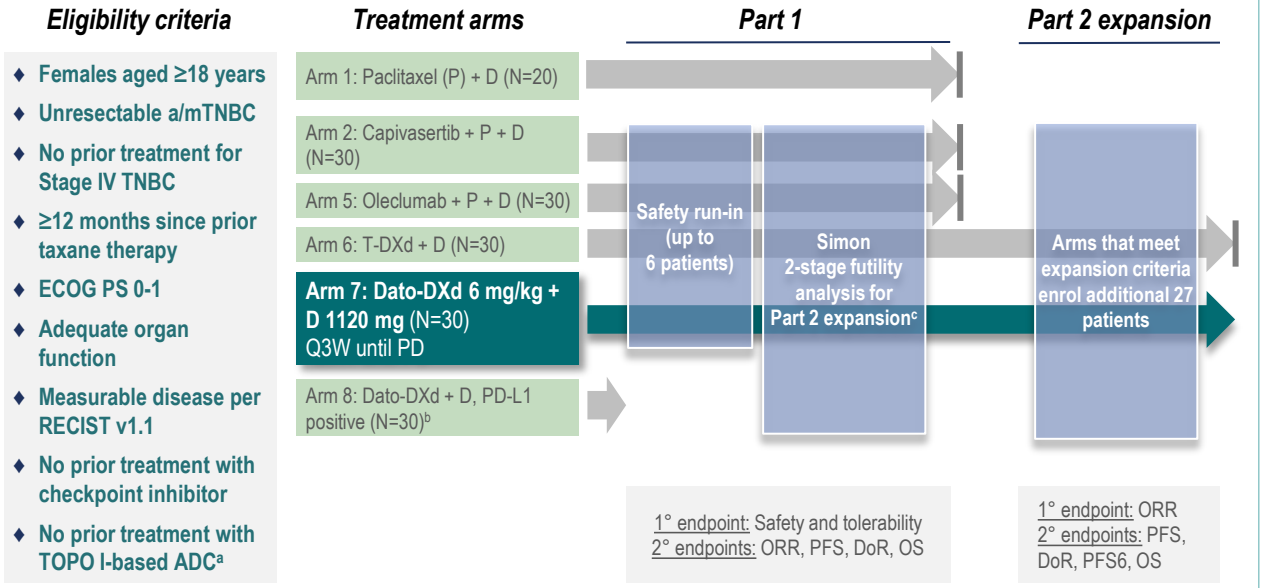
The BEGONIA Study (NCT03742102)

Rationale

- Immune checkpoint inhibitors + chemotherapy is the standard of care for patients with PD-L1 positive a/mTNBC; still, most progress within a year (median PFS ~9–10 months)[1,2]
- BEGONIA is evaluating combinations of durvalumab (D), an anti–PD-L1 antibody, with other novel therapies in first-line a/mTNBC
- Dato-DXd is a TROP2-directed ADC with a TOPO I inhibitor payload and a tumour-selective cleavable linker[3]
- At median 7.2 months follow-up, ORR was 74% for patients treated with Dato-DXd + D in BEGONIA[4]

Study Design



We report updated results with longer follow-up for patients from Parts 1 and 2 treated with Dato-DXd + D in BEGONIA Arm 7

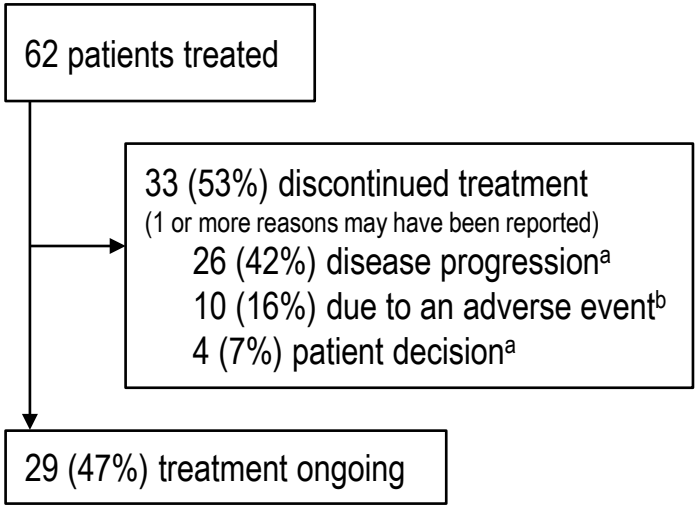
[a]ADC-cohort-specific criteria. [b]Currently enrolling; a safety run-in will not occur for this arm as Dato-DXd + D was already evaluated and found to be tolerable with no dose-limiting toxicities reported. [c]Novel treatment combinations may enter Part 2 expansion if confirmed ORR is at least 57%.

1. Cortes J, et al. *Lancet.* 2020;396(10265):1817-1828. 2. Emens LA, et al. *J Natl Cancer Inst.* 2021;113(8):1005-1016. 3. Bardia A, et al. Presented at SABCS 2022. P6-10-03. 4. Schmid P, et al. Presented at SABCS 2022. PD11-09.

ADC, antibody-drug conjugate; a/mTNBC, advanced/metastatic triple-negative breast cancer; Dato-DXd, datopotamab deruxtecan; DoR, duration of response; D, durvalumab; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-L1, programmed death ligand-1; PFS, progression-free survival; PFS6, progression-free survival at 6 months; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria In Solid Tumors; T-DXd, trastuzumab deruxtecan; TOPO I, topoisomerase I; TROP2, trophoblast cell-surface antigen 2.

BEGONIA Arm 7: Dato-DXd + Durvalumab

Disposition and Baseline Characteristics



Median follow-up: 11.7 (range, 2–20) months

Characteristic	Dato-DXd + D N=62
Age, median (range), years	53 (31–74)
No prior treatment, n (%)	26 (42)
Prior treatments for early-stage disease, n (%)	
Radiotherapy	30 (48)
Cytotoxic chemotherapy	33 (53)
Taxane	26 (42)
Anthracycline	29 (47)
Platinum compound	9 (15)
Hormonal therapy	10 (16)
Targeted therapy	1 (2)
Visceral metastases,[c] n (%)	37 (60)
Lymph node metastases, n (%)	42 (68)
PD-L1 expression,[d] n (%)	
High (TAP ≥10%)	7 (11)
Low (TAP <10%)	54 (87)
Unknown/Missing	1 (2)

[a]Discontinued all study drugs. [b]Discontinued any study drug. [c]Defined as liver/hepatic and/or respiratory metastases. [d]PD-L1 expression was assessed by immunohistochemistry using the VENTANA PD-L1 (SP263) Assay, and expression was defined as the percentage of the tumour area populated by tumour or immune cells with membranous staining (TAP). A sample was considered PD-L1 high if it had ≥10% TAP PD-L1 expression.

Dato-DXd, datopotamab deruxtecan; D, durvalumab; PD-L1, programmed cell death ligand-1; TAP, tumour area positivity.

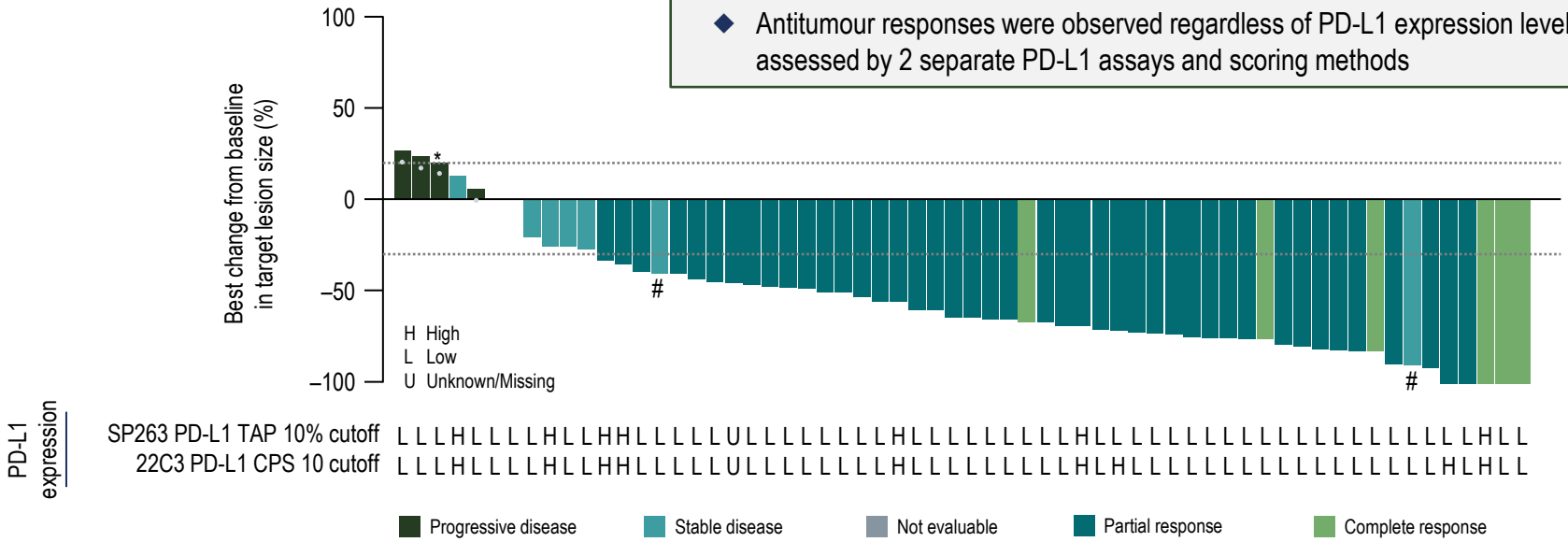
Data cutoff: 02 Feb 2023

BEGONIA Arm 7: Dato-DXd + Durvalumab

Antitumour Responses in 1L a/mTNBC

Confirmed ORR was **79%** (49/62; 95% CI, 66.8–88.3) with 6 CR and 43 PR

- Antitumour responses were observed regardless of PD-L1 expression level as assessed by 2 separate PD-L1 assays and scoring methods



Dotted lines indicate thresholds for partial response (−30%) and progressive disease (20%). PD-L1 expression was assessed by 1) immunohistochemistry using the VENTANA PD-L1 (SP263) Assay with expression defined as the percentage of the tumour area populated by tumour or immune cells with membranous staining (TAP), or 2) immunohistochemistry using the 22C3 antibody with expression defined as the number of PD-L1–staining tumour cells, lymphocytes, and macrophages, divided by the total number of viable tumour cells, multiplied by 100 (CPS). *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 PD as best overall response. #Unconfirmed response.

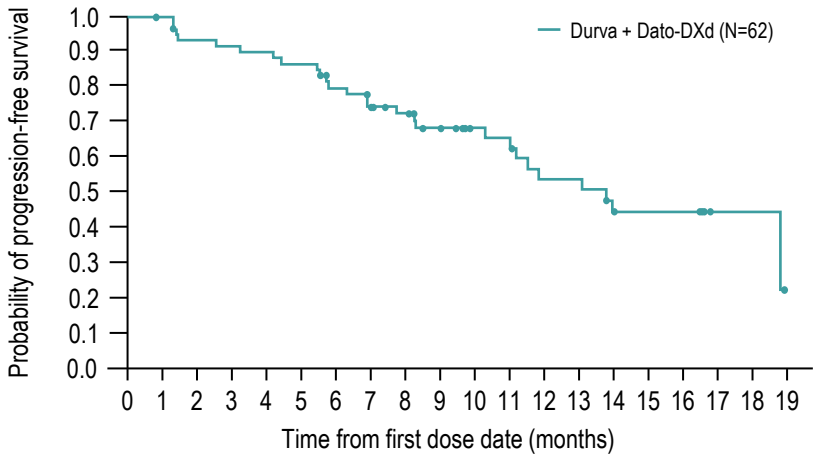
1L, first line; a/m TNBC, advanced/metastatic triple–negative breast cancer; CI, confidence interval; CPS, combined positive score; CR, complete response; Dato-DXd, datopotamab deruxtecan; ORR, objective response rate; PD-L1, programmed cell death ligand-1; PR, partial response; TAP, tumour area positivity.

Data cutoff: 02 Feb 2023

BEGONIA Arm 7: Dato-DXd + Durvalumab

Progression-Free Survival and Duration of Response

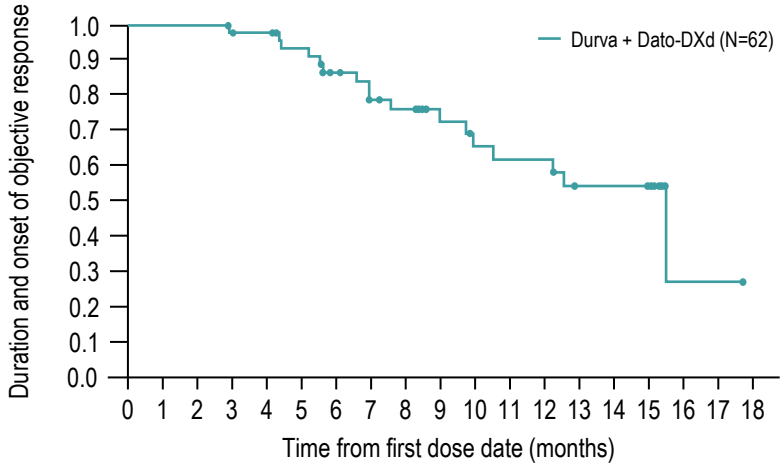
Median PFS was **13.8** months (95% CI, 11.0–NC)



Number of patients at risk

Durva + Dato-DXd	62	61	56	55	54	52	45	40	37	32	24	23	18	18	14	13	13	2	2	0

Median DoR was **15.5** months (95% CI, 9.92–NC)



Number of patients at risk

Durva + Dato-DXd	49	49	49	47	46	42	35	30	28	21	18	17	17	13	13	12	1	1	0

Kaplan-Meier analysis was performed. Circles indicate censored observations.
CI, confidence interval; Dato-DXd, datopotamab deruxtecan; DoR, duration of response; NC, not calculable; PFS, progression-free survival.

Data cutoff: 02 Feb 2023

BEGONIA Arm 7: Dato-DXd + Durvalumab

Safety Summary

Patients, n (%)	Dato-DXd + D N=62
Any AEs	62 (100)
Grade 3/4	35 (57)
Any treatment-related AEs[a]	62 (100)
Grade 3/4	27 (44)
Any serious AEs	14 (23)
Treatment-related	6 (10)
AEs leading to discontinuation of any treatments	10 (16)
AEs leading to death[b]	1 (2)
Dose adjustments	
Dato-DXd dose reduction	18 (29)
Dato-DXd dose delay	28 (45)
Durvalumab dose delay	31 (50)

[a]Per investigator assessment. [b]Patient died due to dehydration, unrelated to treatment.
AE, adverse event; Dato-DXd, datopotamab deruxtecan; D, durvalumab.

Data cutoff: 02 Feb 2023

BEGONIA Arm 7: Dato-DXd + Durvalumab

Adverse Events

Most frequently reported adverse events (≥15%) (N=62)		
AE preferred term	**Any grade, n (%)**	**Grade 3/4, n (%)**
Nausea	40 (65)	0
Stomatitis	40 (65)	7 (11)
Alopecia	31 (50)	0
Constipation	29 (47)	1 (2)
Fatigue	28 (45)	1 (2)
Rash	20 (32)	0
Vomiting	16 (26)	1 (2)
Amylase increased	13 (21)	11 (18)
COVID-19	13 (21)	0
Dry eye	13 (21)	0
Decreased appetite	12 (19)	1 (2)
Pruritus	10 (16)	0
Cough	10 (16)	0

- The most common AEs were gastrointestinal and generally of low grade (**Table**)
- Stomatitis was the most common AE leading to Dato-DXd dose reduction (11 patients)
- There were 3 (5%) adjudicated treatment-related ILD/pneumonitis events (2 grade 2 events, 1 grade 1 event)
- Limited rates of diarrhea (13% any grade, 1 grade 3 event) and neutropenia (5% any grade, 1 grade 3 event) were reported
- The most frequent AESIs for Arm 7 were stomatitis (65%), rash (32%), dry eye (21%), hypothyroidism (14.5%), and keratitis (14.5%)

AE, adverse event; AESI, adverse event of special interest; ILD, interstitial lung disease.

Data cutoff: 02 Feb 2023

BEGONIA Arm 7: Dato-DXd + Durvalumab

Conclusions

Dato-DXd + durvalumab continues to demonstrate robust, durable responses in first-line a/mTNBC in a biomarker-unselected population with median 11.7 months of follow-up

- Confirmed ORR was 79% (95% CI, 66.8–88.3), responses observed regardless of PD-L1 expression
- Median DoR was 15.5 months (95% CI, 9.92–NC)
- Median PFS was 13.8 months (95% CI, 11.0–NC)

The combination of Dato-DXd + durvalumab had a tolerable and manageable safety profile, with no new safety signals

- Comprehensive toxicity management guidelines were implemented during the course of the study

BEGONIA is currently enrolling for Arm 8, Dato-DXd + durvalumab in a PD-L1–high population

a/mTNBC, advanced/metastatic triple-negative breast cancer; CI, confidence interval; Dato-DXd, datopotamab deruxtecan; DoR, duration of response; NC, not calculable; ORR, objective response rate; PD-L1, programmed death ligand-1; PFS, progression-free survival.

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