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Datopotamab deruxtecan (Dato-DXd) in combination with durvalumab as first-line treatment for unresectable locally advanced/metastatic triple-negative breast cancer: Results from arms 7 and 8 of the phase 1b/2 BEGONIA study

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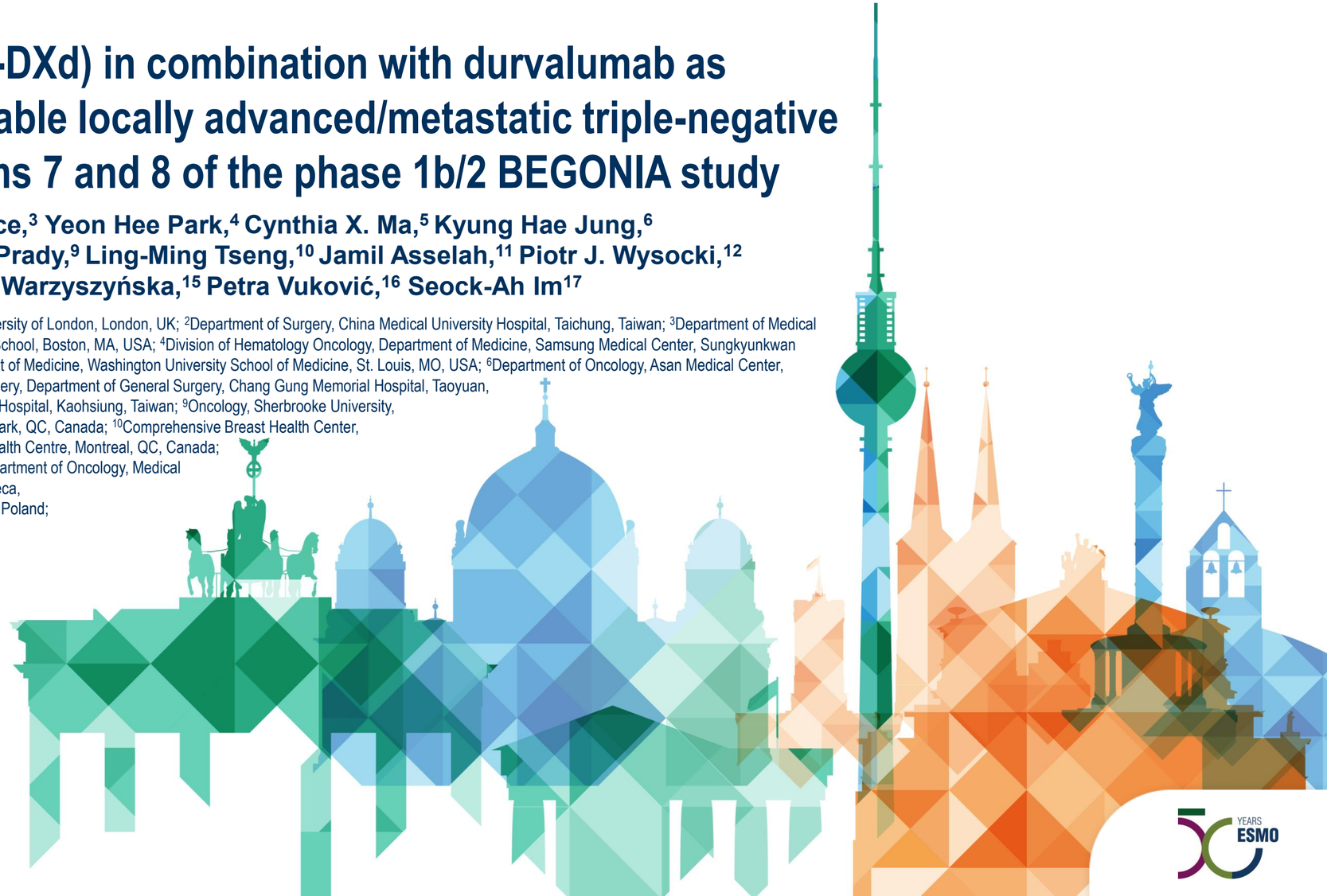

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Declaration of Interests

Peter Schmid has the following disclosures:

- **Honoraria from** AstraZeneca, Bayer, Boehringer Ingelheim, Celgene, Eisai, Merck, Novartis, Pfizer, Puma Biotechnology and Roche
- **Consultant or advisor for** AstraZeneca, Bayer, Boehringer Ingelheim, Celgene, Eisai, Merck, Novartis, Pfizer, Puma Biotechnology and Roche
- **Research funding from** Astellas Pharma, AstraZeneca, Genentech, Medivation, Merck, Novartis, OncoGenex and Roche

BEGONIA Study

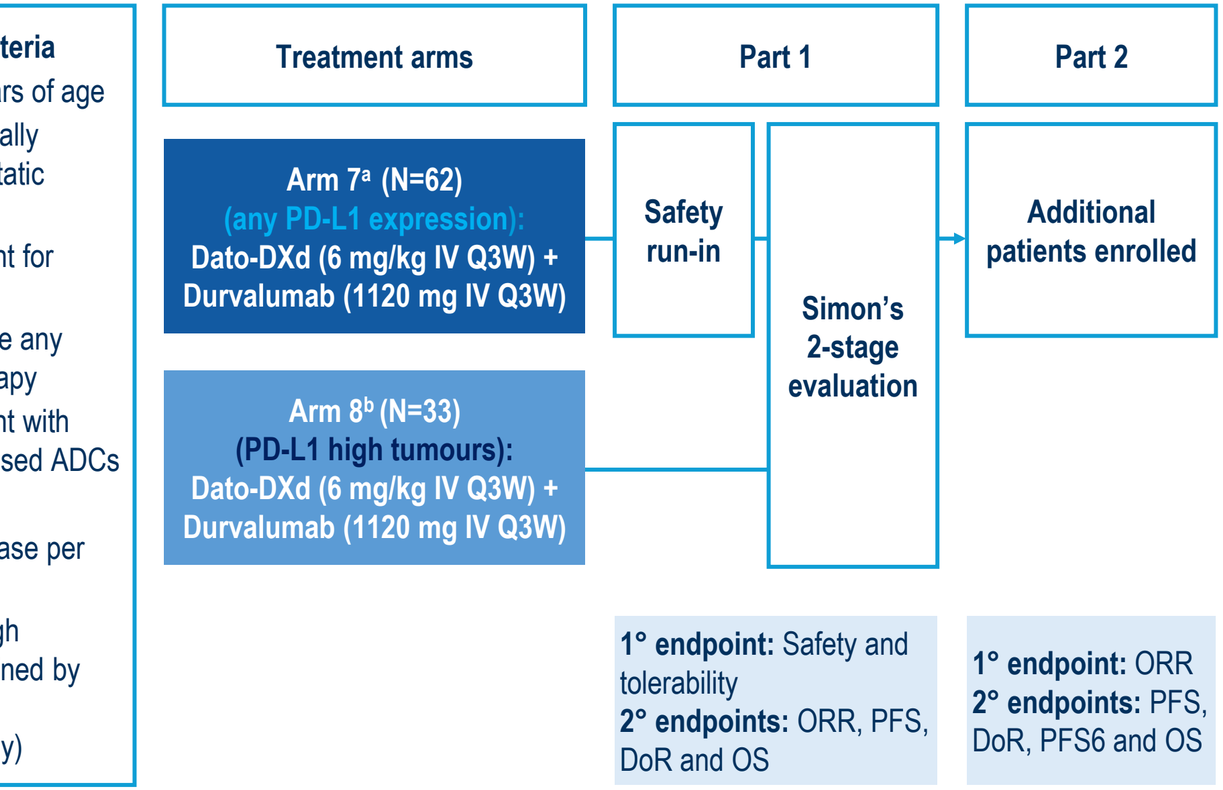
Rationale

- PD-(L)1 inhibition + chemotherapy is SoC for patients with PD-L1 high advanced/metastatic TNBC[1,2]
  - Outcomes remain poor; most patients progress within one year (PFS ~10 months)[3]
  - Treatment options are limited, particularly for patients with PD-L1 low tumours[1,4]
- Dato-DXd, a TROP2-directed ADC,[5] is approved for the treatment of adults with unresectable or metastatic HR+/HER2− breast cancer who have received prior ET and chemotherapy for unresectable or metastatic disease, based on the results of the phase 3 TROPION-Breast01 study[6,7]
- BEGONIA (NCT03742102) is a phase 1b/2, multicentre, multi-arm, 2-stage, 2-part, open-label platform study evaluating the safety and efficacy of durvalumab + other novel therapies as 1L treatment for advanced/metastatic TNBC[8]

Here we report updated data in patients regardless of PD-L1 status (Arm 7) and with PD-L1 high tumours per local testing (Arm 8)

Eligibility criteria

- Female, ≥18 years of age
- Unresectable locally advanced/metastatic TNBC
- No prior treatment for stage IV TNBC
- ≥12 months since any prior taxane therapy
- No prior treatment with ICIs or Topo I-based ADCs
- ECOG PS 0 or 1
- Measurable disease per RECIST v1.1
- Arm 8: PD-L1 high tumours, determined by local testing (IHC-based assay)



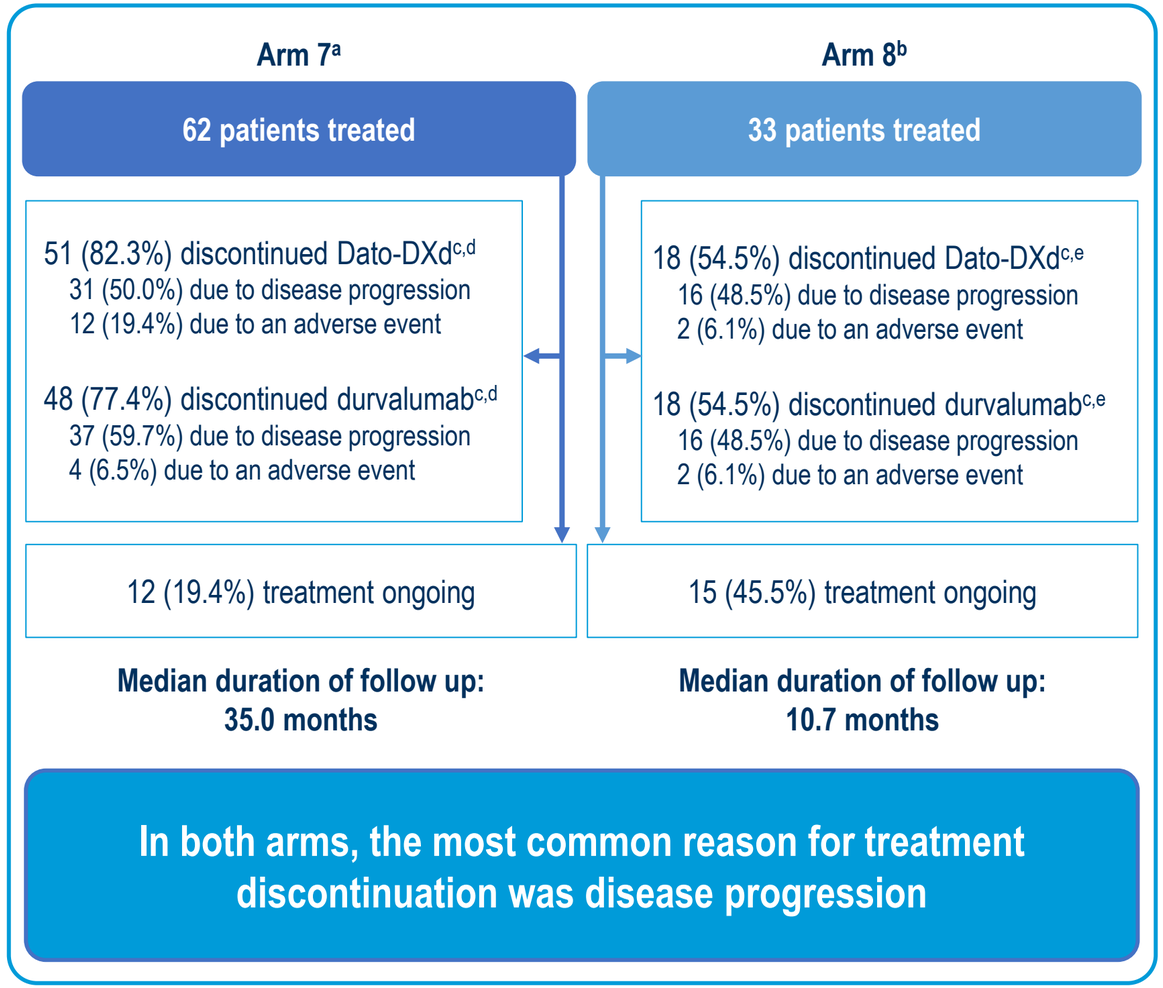
NCT03742102, DCO: 29 November 2024

[a]Patients were enrolled into Arm 7 regardless of PD-L1 expression, which was retrospectively assessed using the VENTANA® PD-L1 (IHC antibody for PD-L1, SP263 [Roche Diagnostics]) Assay (off-label use); PD-L1 high: TAP ≥10%; PD-L1 low: TAP <10%.
[b]Patients were enrolled with PD-L1 high tumours determined via local testing methods.

1L; first-line; ADC, antibody-drug conjugate; Dato-DXd, datopotamab deruxtecan; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HER2–, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; IV, intravenous; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed cell death (ligand)-1; PFS, progression-free survival; PFS6, progression-free survival 6 months following date of first dose; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SoC, standard of care; TAP, tumour area positivity; Topo-I, topoisomerase I; TNBC, triple-negative breast cancer.

1. Gennari A, et al. Ann Oncol 2021;32:1475–95; 2. European Medicines Agency, KEYTRUDA® Summary of Product Characteristics 2025; 3. Cortes J, et al. Lancet. 2020;396:1817–28; 4. European Medicines Agency, TRODELVY® Summary of Product Characteristics 2025; 5. Okajima D, et al. Cancer Res 2023;83(7_Suppl):A2932; 6. Bardia, A et al. J Clin Oncol 2025;43:285–96; 7. European Medicines Agency, DATROWAY® Summary of Product Characteristics 2025; 8. Schmid P, et al. Ann Oncol 2023;34:S337.

Baseline Demographics and Characteristics



	Dato-DXd + durvalumab	
	Arm 7 (N=62)	Arm 8 (N=33)
Median age (range), years	53.0 (31–74)	47.0 (29–74)
Race, n (%)		
Asian	15 (24.2)	20 (60.6)
Black or African American	4 (6.5)	1 (3.0)
White	39 (62.9)	11 (33.3)
Other	4 (6.5)	1 (3.0)
No prior treatment, n (%)	26 (41.9)	13 (39.4)
Prior treatments for early-stage disease, n (%)		
Radiotherapy	30 (48.4)	14 (42.4)
Chemotherapy	33 (53.2)	18 (54.5)
Anthracyclines	29 (46.8)	16 (48.5)
Taxanes	26 (41.9)	16 (48.5)
Platinum compounds	9 (14.5)	7 (21.2)
Hormonal therapy	10 (16.1)	5 (15.2)
Targeted therapy	2 (3.2)	0
Visceral metastases,[f] n (%)	40 (64.5)	21 (63.6)
CNS metastases, n (%)	2 (3.2)	3 (9.1)

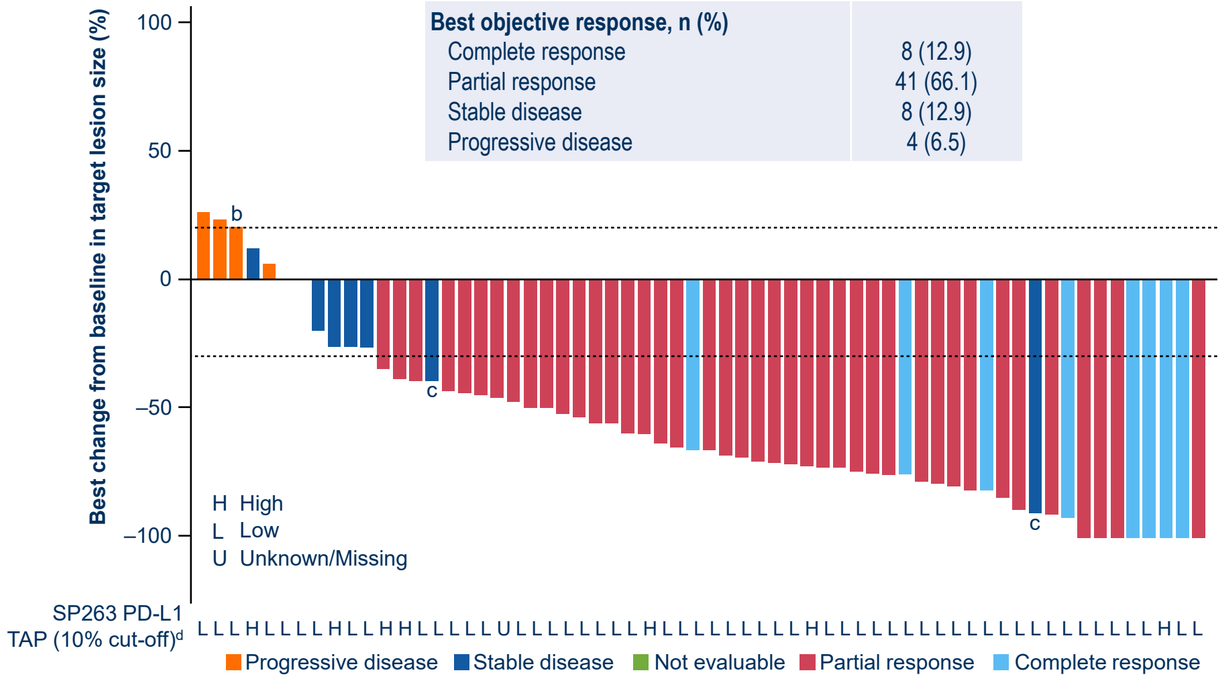
[a]In Arm 7, central testing using the VENTANA® PD-L1 SP263 Assay showed 7 (11.3%) patients had PD-L1 high tumours (TAP ≥10%) and 54 (87.1%) had PD-L1 low tumours (TAP <10%). [b]All patients in Arm 8 had PD-L1-high tumours by local testing. [c]More than one reason may have been reported. [d]In Arm 7, additional reasons for discontinuation of Dato-DXd/durvalumab included patient decision (6 [9.7%]/5 [8.1%]), severe non-compliance to protocol (1 [1.6%]/1 [1.6%]) and other (1 [1.6%]/1 [1.6%]). [e]There were no additional reasons for discontinuation of Dato-DXd or durvalumab in Arm 8. [f]Visceral metastases are defined as liver and/or hepatic and/or respiratory metastases.

CNS, central nervous system; Dato-DXd, datopotamab deruxtecan; PD-L1, programmed cell death ligand-1; TAP, tumour area positivity.

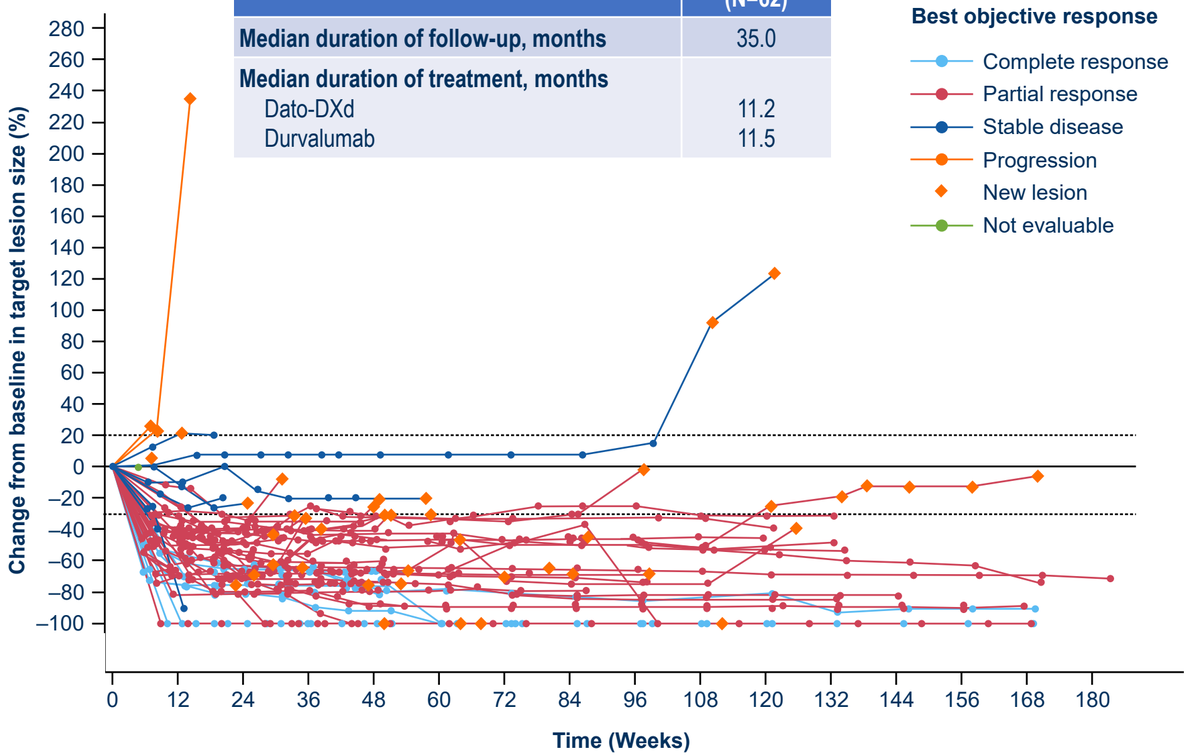
Overall Response and Duration of Response (Arm 7)

Overall, 11.3% patients had PD-L1 high tumours and 87.1% had PD-L1 low tumours

	Arm 7 (N=62)
Confirmed ORR,[a] % (95% CI)	49 (79.0) (66.8–88.3)
Best objective response, n (%)	
Complete response	8 (12.9)
Partial response	41 (66.1)
Stable disease	8 (12.9)
Progressive disease	4 (6.5)



	Arm 7 (N=62)
Median duration of follow-up, months	35.0
Median duration of treatment, months	
Dato-DXd	11.2
Durvalumab	11.5



Responses were observed in patients with PD-L1 high and PD-L1 low tumours

Median **DoR** was 17.6 months (95% CI 10.5–27.3)
Median **PFS** was 14.0 months (95% CI 11.0–21.1)

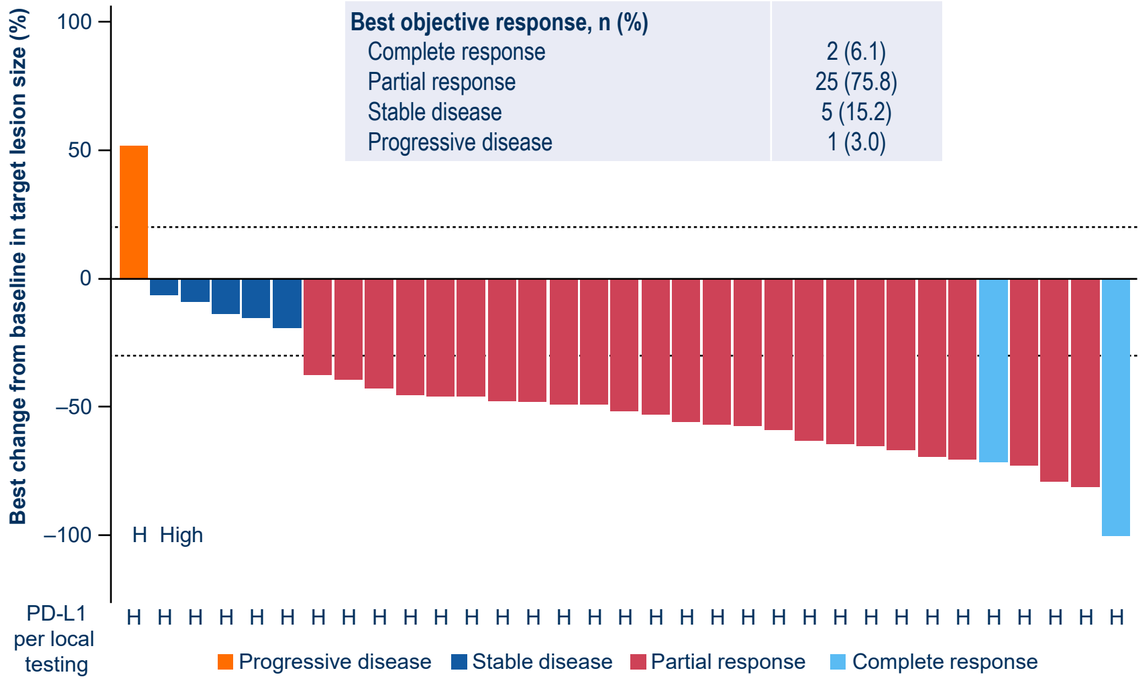
[a]Investigator-assessed, per RECIST v1.1. [b]Patient with imputed values. [c]Unconfirmed response. [d]PD-L1 status determined by central testing using the SP263 TAP 10% cut-off.

CI, confidence interval; Dato-DXd, datopotamab deruxtecan; DoR, duration of response; ORR, objective response rate; PD-L1, programmed death ligand-1; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; TAP, tumour area positivity.

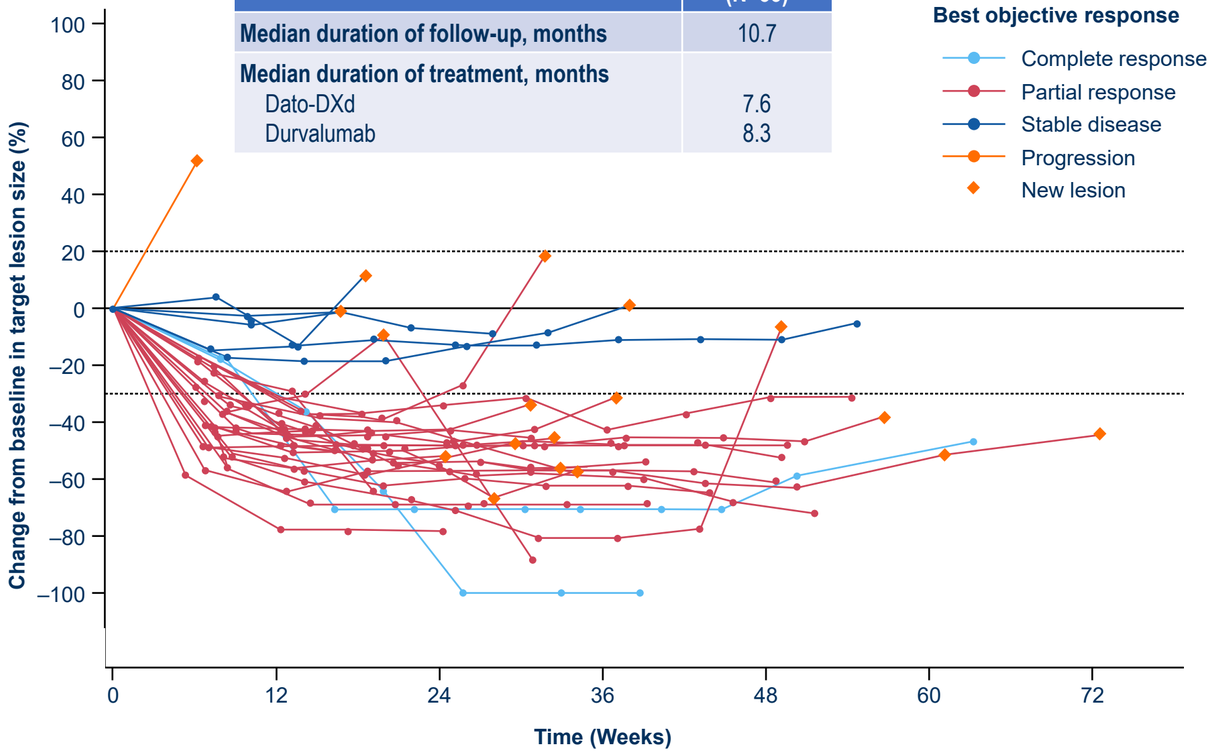
Overall Response and Duration of Response (Arm 8)

PD-L1 high tumours

	Arm 8 (N=33)
Confirmed ORR,[a] % (95% CI)	27 (81.8) (64.5–93.0)
Best objective response, n (%)	
Complete response	2 (6.1)
Partial response	25 (75.8)
Stable disease	5 (15.2)
Progressive disease	1 (3.0)



	Arm 8 (N=33)
Median duration of follow-up, months	10.7
Median duration of treatment, months	
Dato-DXd	7.6
Durvalumab	8.3



Confirmed ORR was 81.8% (95% CI 64.5–93.0)

Median **DoR** and median **PFS** were immature given the short duration of median follow-up of 8.3 months in censored patients

[a]Investigator-assessed, per RECIST v1.1.

CI, confidence interval; Dato-DXd, datopotamab deruxtecan; DoR, duration of response; ORR, objective response rate; PD-L1, programmed death ligand-1; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1.

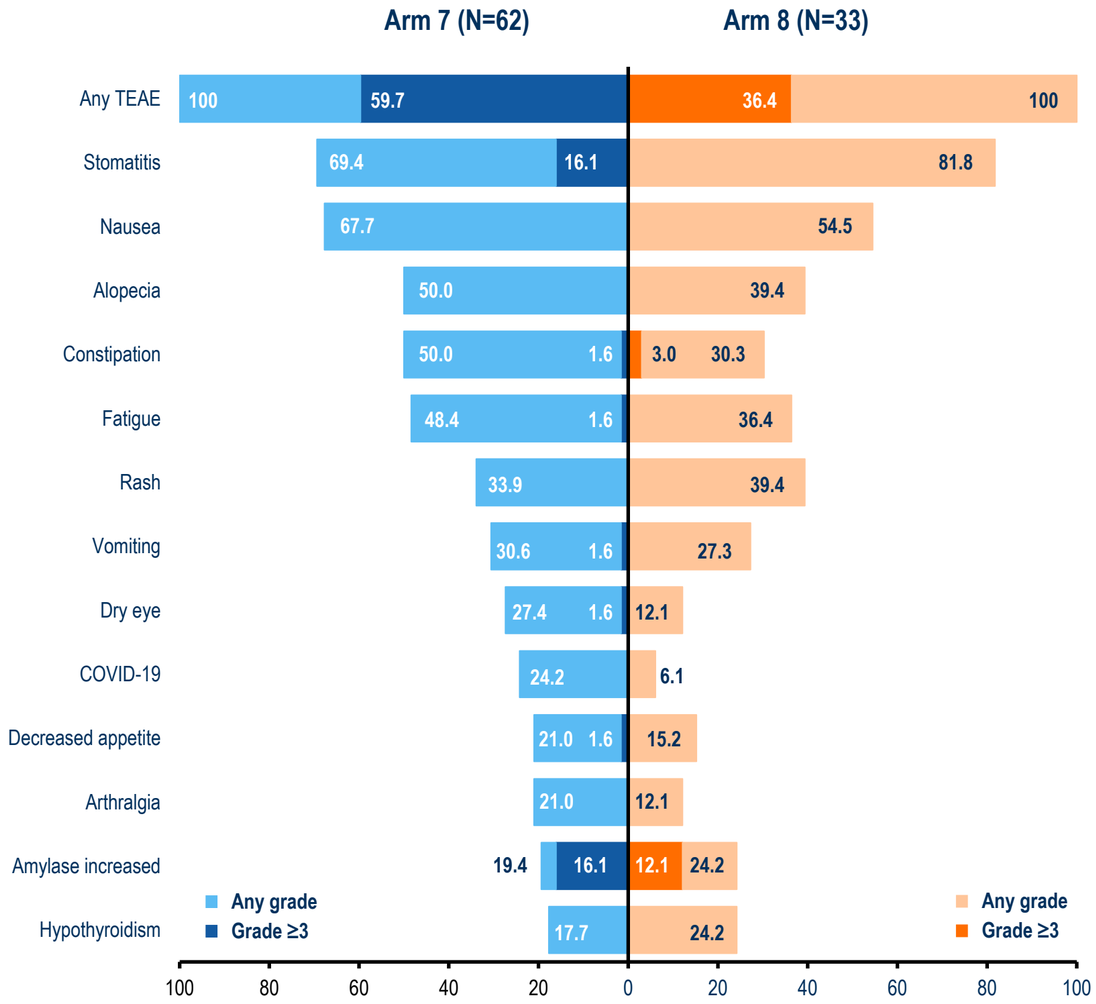
Overall Safety Summary[a]

	Arm 7 (N=62)	Arm 8 (N=33)
Median duration of treatment, months		
Dato-DXd	11.2	7.6
Durvalumab	11.5	8.3
Any TEAE, n (%)	62 (100)	33 (100)
Maximum CTCAE grade 3/4	37 (59.7)	12 (36.4)
Any treatment-related AE, n (%)	62 (100)	33 (100)
Maximum CTCAE grade 3/4	30 (48.4)	8 (24.2)
Any SAE, n (%)	18 (29.0)	5 (15.2)
Any TEAE leading to death, n (%)	1 (1.6)[b]	0
Any TEAE leading to discontinuation of either treatment, n (%)	12 (19.4)	3 (9.1)
Discontinuation of Dato-DXd	12 (19.4)	2 (6.1)
Discontinuation of durvalumab	3 (4.8)	2 (6.1)
Any TEAE leading to dose reduction of Dato-DXd[c], n (%)	24 (38.7)	7 (21.2)
Any TEAE leading to dose interruption (either treatment), n (%)	44 (71.0)	23 (69.7)
Any imAE, n (%)	20 (32.3)	11 (33.3)
Maximum CTCAE grade 3/4	1 (1.6)	0

[a]CTCAE grading was reported per CTCAE v4.03. [b]Due to dehydration, considered to be not related to study treatment. [c]Dose reductions were not permitted for durvalumab.

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; Dato-DXd, datopotamab deruxtecan; imAE, immune-mediated adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Most Common TEAEs (≥20% of patients in either arm)[a,b]



- Across both arms, rates of adjudicated drug-related ILD were low, with no grade ≥3 events:
  - Arm 7: two grade 2 events, one grade 1 event
  - Arm 8: one grade 2 event
- The most frequently reported AESI preferred terms (≥15%) for Dato-DXd were stomatitis (Arm 7: 69.4%; Arm 8: 81.8%), dry eye (Arm 7: 27.4%; Arm 8: 12.1%), keratitis (Arm 7: 16.1%; Arm 8: 3.0%), vision blurred (Arm 7: 8.1%; Arm 8: 15.2%) and oropharyngeal pain (Arm 7: 11.3%; Arm 8: 15.2%)
- The most frequently reported imAEs for durvalumab were thyroid events (hypothyroid events [Arm 7: 22.6%; Arm 8: 24.2%]; hyperthyroid events [Arm 7: 8.1%; Arm 8: 0%])
- Rates of diarrhoea and neutropenia were limited in both arms:

  Arm 7:
  - Diarrhoea: 16.1% any grade, one grade 3 event
  - Neutropenia: 4.8% any grade, one grade 3 event

  Arm 8:
  - Diarrhoea: 6.1% any grade, no grade 3 events
  - Neutropenia: 0% any grade

[a]CTCAE grading was reported per CTCAE v4.03; [b]TEAEs (by MedDRA preferred term) of any grade reported in ≥20% of patients.

AESI, adverse event of special interest; CTCAE, Common Terminology Criteria for Adverse Events; Dato-DXd, datopotamab deruxtecan; ILD, interstitial lung disease; imAE, immune-mediated adverse event; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

Conclusions

- **The combination of Dato-DXd + durvalumab demonstrated robust antitumour activity in patients with advanced/metastatic TNBC with any PD-L1 expression (Arm 7) and in those with high PD-L1 expression (Arm 8)**

  Arm 7

  – Median duration of follow-up was 35.0 months
  – Confirmed ORR was 79.0% (95% CI 66.8–88.3); consistent response rates were observed regardless of PD-L1 status
  – Median DoR was 17.6 months (95% CI 10.5–27.3)
  – Median PFS was 14.0 months (95% CI 11.0–21.1)

  Arm 8

  – Median duration of follow-up was 10.7 months
  – Confirmed ORR was 81.8% (95% CI 64.5–93.0)
  – Median DoR and median PFS were immature given the short duration of median follow-up of 8.3 months in censored patients

- **The safety profile of the combination of Dato-DXd + durvalumab was manageable, with no new safety signals**

CI, confidence interval; Dato-DXd, datopotamab deruxtecan; DoR, duration of response; ORR, objective response rate; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; TNBC, triple-negative breast cancer.

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Datopotamab deruxtecan (Dato-DXd) in combination with durvalumab as first-line treatment for unresectable locally advanced/metastatic triple-negative breast cancer: Results from arms 7 and 8 of the phase 1b/2 BEGONIA study

Plain Language Summary

Why did we perform this research?

- Triple-negative breast cancer (TNBC) is a type of breast cancer in which cells do not have oestrogen or progesterone receptors or too much HER2. Programmed cell death ligand-1 (PD-L1), a protein found in the tumour microenvironment (cells, molecules and blood vessels that surround and support tumour cells), can help TNBC evade the immune system. The current standard of care for patients with high PD-L1 expression is pembrolizumab and chemotherapy, while chemotherapy is the standard treatment for patients with low PD-L1 expression[1-3]
- Durvalumab is a drug that blocks the activity of PD-L1, making cancer cells more susceptible to being killed by immune cells, and has shown potential in treating TNBC[4]
- Datopotamab deruxtecan (Dato-DXd) is an antibody-drug conjugate that consists of an antibody (datopotamab) and an anticancer drug (DXd).[5] Dato-DXd has shown efficacy in patients with metastatic TNBC when given alone[6,7]
- The BEGONIA study is designed to see whether durvalumab in combination with different treatments that work against cancer are tolerable, and have beneficial effect, in patients with advanced or metastatic TNBC. Here we report the results from Arm 7, patients with any level of PD-L1 expression, and Arm 8, patients with high PD-L1 expression, in which patients received treatment with Dato-DXd + durvalumab in both arms

How did we perform this research?

- Ninety-five eligible patients who had not previously received treatment for advanced or metastatic disease were enrolled and received Dato-DXd + durvalumab every 3 weeks. Each patient continued treatment until their cancer started growing or side effects became unacceptable

What were the findings of this research?

- The safety profile of Dato-DXd + durvalumab was manageable and consistent with the safety profiles of the two drugs when given separately. The percentage of patients who had a decrease in the size or number of tumours after treatment (objective response rate) was 79% in Arm 7 and 82% in Arm 8

What are the implications of this research?

- The combination of Dato-DXd + durvalumab could provide a promising alternative treatment option for patients with TNBC with any PD-L1 expression and for those with high PD-L1 expression

Where can I access more information?

- For more information about BEGONIA, please visit https://clinicaltrials.gov/study/NCT03742102. You may also speak to your doctor about clinical studies. The combination of Dato-DXd and durvalumab is also being evaluated in these ongoing studies: TROPION-Breast03 (NCT05629585), TROPION-Breast04 (NCT06112379) and TROPION-Breast05 (NCT06103864)

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