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Datopotamab deruxtecan (Dato-DXd) vs chemotherapy in pretreated, inoperable/metastatic HR+/HER2– breast cancer: Additional safety analysis from TROPION-Breast01

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Declaration of Interests

Komal Jhaveri, MD, FACP

Consulting or advisory role: Novartis, Pfizer, AstraZeneca, Jounce Therapeutics, Synthon, Intellisphere, BMS, Genentech, AbbVie, Lilly, BluePrint Medicines, Seagen, Daiichi-Sankyo, Biotheranostics, Sun Pharma Advanced Research Company, Sanofi, Gilead Sciences, Scorpion Therapeutics.

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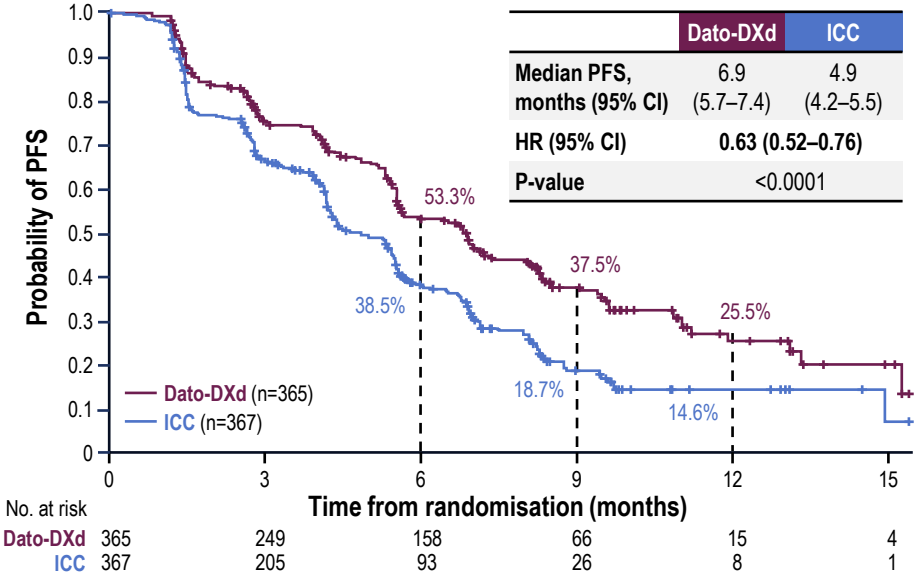
Background

- **Dato-DXd** is a **TROP2-directed ADC** that selectively delivers a potent Topo-I inhibitor payload directly into tumour cells,[1] and has several unique properties:[1,2]
  - Optimised drug to antibody ratio ≈ 4
  - Stable linker-payload
  - Tumour-selective cleavable linker
  - Bystander antitumour effect

- In the phase 3 TROPION-Breast01 study, Dato-DXd demonstrated **statistically significant and clinically meaningful improvement in PFS** by BICR compared with ICC in patients with previously treated, inoperable or metastatic HR+/HER2– breast cancer[2,3]
  - Dato-DXd was also **well tolerated compared with ICC**, with no new safety signals[2,3]

PFS by BICR: primary endpoint[3]



	Dato-DXd	ICC
Median PFS, months (95% CI)	6.9 (5.7–7.4)	4.9 (4.2–5.5)
HR (95% CI)	0.63 (0.52–0.76)	
P-value	<0.0001	

ADC, antibody-drug conjugate; BICR, blinded independent central review; CI, confidence interval; Dato-DXd, datopotamab deruxtecan; HER2–, human epidermal growth factor receptor 2-negative; HR, hazard ratio; HR+, hormone receptor-positive; ICC, investigator's choice of chemotherapy; PFS, progression-free survival; Topo-I, topoisomerase I; TROP2, trophoblast cell surface antigen 2.

1. Okajima D, et al. *Mol Cancer Ther* 2021;20:2329–40;
2. Bardia A, et al. *Ann Oncol* 2023;34(suppl_2):S1264–5;
3. Bardia A, et al. Oral presentation at ESMO 2023: abstract LBA11.

TROPION-Breast01 Study Design[1]

Randomised, phase 3, open-label, global study (NCT05104866)

Key inclusion criteria:

- Patients with HR+/HER2– breast cancer* (HER2– defined as IHC 0/1+/2+; ISH negative)
- Previously treated with 1–2 lines of chemotherapy (inoperable/metastatic setting)
- Experienced progression on ET and for whom ET was unsuitable
- ECOG PS 0 or 1

1:1

Dato-DXd
6 mg/kg IV Day 1 Q3W
(n=365)

Investigator's choice of chemotherapy (ICC)
as per protocol directions†
(eribulin mesylate D1,8 Q3W; vinorelbine D1,8 Q3W; gemcitabine D1,8 Q3W; capecitabine D1–14 Q3W)
(n=367)

Endpoints:

- **Dual primary:** PFS by BICR per RECIST v1.1, and OS
- **Key secondary:** ORR, PFS (investigator assessed) and **safety**

Randomisation stratified by:

- **Lines of chemotherapy** in unresectable/metastatic setting (1 vs 2)
- **Geographic location** (USA/Canada/Europe vs other geographic regions)
- **Previous CDK4/6 inhibitor** (yes vs no)

- Treatment continued until PD, unacceptable tolerability, or other discontinuation criteria

Detailed description of the statistical methods published previously.[1] *Per American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines. †ICC was administered as follows: eribulin mesylate, 1.4 mg/m^2 IV on Days 1 and 8, Q3W; vinorelbine, 25 mg/m^2 IV on Days 1 and 8, Q3W; gemcitabine, 1000 mg/m^2 IV on Days 1 and 8, Q3W; or capecitabine, 1000 or 1250 mg/m^2 orally twice daily on Days 1 to 14, Q3W (dose per standard institutional practice). CDK4/6, cyclin-dependent kinase 4/6; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; IHC, immunohistochemistry; ISH, in situ hybridisation; IV, intravenous; ORR, objective response rate; OS, overall survival; PD, progressive disease; Q3W, once every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

1. Bardia A, et al. *Future Oncol* 2024;20:423–36.

TRAEs Occurring in ≥15% of Patients[1]

System Organ Class Preferred term, n (%)	Dato-DXd (n=360)		ICC (n=351)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Blood and lymphatic system				
Anemia	40 (11)	4 (1)	69 (20)	7 (2)
Neutropenia*	39 (11)	4 (1)	149 (42)	108 (31)
Eye				
Dry eye	78 (22)	2 (1)	27 (8)	0
Gastrointestinal				
Nausea	184 (51)	5 (1)	83 (24)	2 (1)
Stomatitis	180 (50)	23 (6)	46 (13)	9 (3)
Vomiting	71 (20)	4 (1)	27 (8)	2 (1)
Constipation	65 (18)	0	32 (9)	0
General				
Fatigue	85 (24)	6 (2)	64 (18)	7 (2)
Skin and subcutaneous				
Alopecia	131 (36)	0	72 (21)	0

*Neutropenia included the PTs neutropenia and neutrophil count decreased.

1. Bardia A, et al. Oral presentation at ESMO 2023: abstract LBA11.

Overall Safety Summary[1]

TRAEs, n (%)	Dato-DXd (n=360)	ICC (n=351)
All grades	337 (93.6)	303 (86.3)
Grade ≥3	75 (20.8)	157 (44.7)
Associated with dose reduction	75 (20.8)	106 (30.2)
Associated with dose interruption	43 (11.9)	86 (24.5)
Associated with discontinuation	9 (2.5)	9 (2.6)
Associated with death	0	1 (0.3)
Serious TRAEs	21 (5.8)	32 (9.1)
Grade ≥3	17 (4.7)	31 (8.8)

- In the phase 3 **TROPION-Breast01** study:
  - Median treatment duration was **6.7** months with Dato-DXd and **4.1** months with ICC
  - **Rate of grade ≥3 TRAEs with Dato-DXd was less than half that with ICC**
  - Fewer TRAEs leading to dose reductions or interruptions with Dato-DXd compared with ICC

AESIs with Dato-DXd* included:

- Oral mucositis / stomatitis
- Ocular surface events
- Adjudicated drug-related ILD

Data cut-off: 17 July 2023. *For the Dato-DXd clinical programme, AESIs were identified based on the available pre-clinical data, review of the cumulative literature, reported toxicities for drugs with a similar monoclonal antibody and payload to Dato-DXd, and biological plausibility. AESI, adverse event of special interest; ILD, interstitial lung disease; TRAEs, treatment-related adverse events.

1. Bardia A, et al. Oral presentation at ESMO 2023: abstract LBA11.

AESIs for Dato-DXd – Oral Mucositis / Stomatitis

Treatment-related oral mucositis / stomatitis,* n (%)	Dato-DXd (n=360)
All grades†	200 (55.6)
Grade 1	91 (25.3)
Grade 2	84 (23.3)
Grade 3	25 (6.9)
Leading to dose reduction	48 (13.3)
Leading to dose interruption	5 (1.4)
Leading to dose discontinuation	1 (0.3)

- Low rate of grade 3 events, and low rates dose discontinuation (0.3%)

Median time to onset: **22 days**

Median time to resolution‡: **36.5 days**

Toxicity management guidelines

- **Daily use of prophylaxis with a steroid-containing mouthwash highly recommended** (e.g., dexamethasone oral solution 4 times daily or a similar mouthwash regimen using an alternative steroid advocated by institutional/local guidelines)
  - In the absence of steroid-containing mouthwash, daily use of inert, bland mouth rinses (e.g., non-alcoholic/bicarbonate-containing mouthwash, 4–6 times daily) recommended
- **Prophylactic cryotherapy** (ice chips or ice water held in the mouth throughout the infusion) also suggested

*Comprising the preferred terms of: aphthous ulcer, dysphagia, glossitis, mouth ulceration, odynophagia, oral mucosal blistering, oral pain, oropharyngeal pain, pharyngeal inflammation, and stomatitis.
†No grade 4/5 events. ‡For events recovered/resolved at data cutoff.

AESIs for Dato-DXd – Ocular Surface Events

Treatment-related ocular surface events*, n (%)	Dato-DXd (n=360)
All grades†	144 (40.0)
Grade 1	115 (31.9)
Grade 2	26 (7.2)
Grade 3	3 (0.8)
Leading to dose reduction and/or interruption	12 (3.3)
Leading to dose discontinuation	1 (0.3)

Toxicity management guidelines

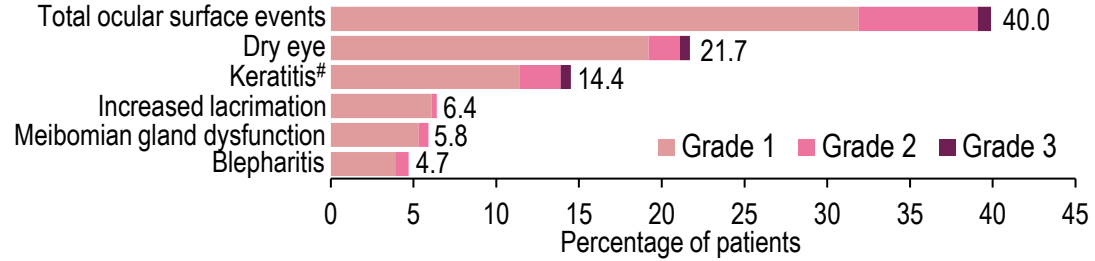
Daily use of **artificial tears** and **avoidance of contact lenses** recommended

- Most events were grade 1, with low rates of grade 2/3, low rates of dose reduction/ interruption (3.3%), and discontinuation (0.3%); over half of events were dry eye

Median time to onset: **65 days**

Median time to resolution‡: **67 days**

Most common preferred terms§



Ophthalmologic assessments were mandated during study (per regulatory request) every three 21-day cycles

Frequent assessments likely contributed to high rate of low-grade events in both arms; incidence of ocular surface events with ICC (11.7%) was higher than historic benchmarks.[1]

*Comprising the preferred terms of: blepharitis, conjunctivitis, corneal disorder, corneal erosion, corneal lesion, dry eye, foreign body sensation in eyes, keratitis, keratopathy, lacrimation increased, limbal stem cell deficiency, meibomian gland dysfunction, ocular toxicity, photophobia, punctate keratitis, superior limbic keratoconjunctivitis, ulcerative keratitis, vision blurred, visual impairment, and xerophthalmia. †No grade 4/5 events. ‡For events recovered/resolved at data cutoff. §Reported in ≥15 patients. #Grouped term comprising keratitis, punctate keratitis, and ulcerative keratitis.

1. Canino F, et al. *Clin Breast Cancer* 2022;22:289–99.

AESIs for Dato-DXd – Adjudicated Drug-Related ILD

Adjudicated drug-related ILD*, n (%)	Dato-DXd (n=360)
All grades	12 (3.3)
Grade 1	5 (1.4)
Grade 2	4 (1.1)
Grade ≥3†	3 (0.8)
Leading to dose reduction	1 (0.3)
Leading to dose interruption	3 (0.8)
Leading to dose discontinuation	5 (1.4)

- Rate of adjudicated drug-related ILD **consistent with rates reported previously** with Dato-DXd in breast cancer[1]
- **Low rates of symptomatic ILD**
  - One patient had an adjudicated grade 5 drug-related event; this event was characterised by the investigator as grade 3 pneumonitis, with death attributed to disease progression

Median time to onset: **84.5 days**

Median time to resolution‡: **28 days**

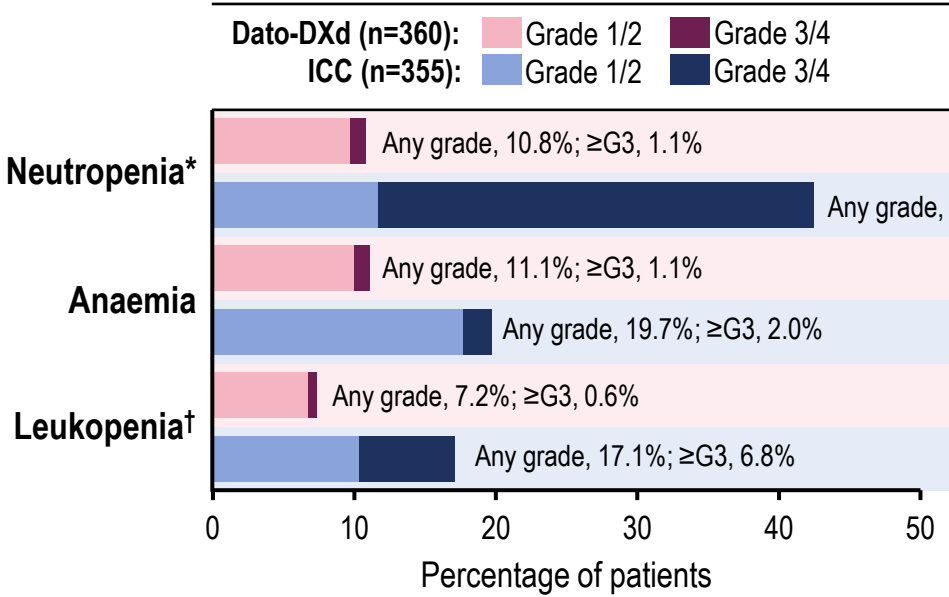
All cases of potential ILD/pneumonitis were reviewed by an independent adjudication committee to assess whether the event was ILD/pneumonitis, and if so, whether it was drug-related

*Comprising the preferred terms of: interstitial lung disease and pneumonitis. †Grade 3: n=2 (0.6%); grade 5: n=1 (0.3%).
‡For events recovered/resolved at data cutoff.

1. Bardia A, et al. *J Clin Oncol* 2024; doi: 10.1200/JCO.23.01909 (EPub).

TRAEs of Clinical Interest – Haematological Toxicity

- ICC was most notable for high-grade neutropenia leading to dose interruption / reduction

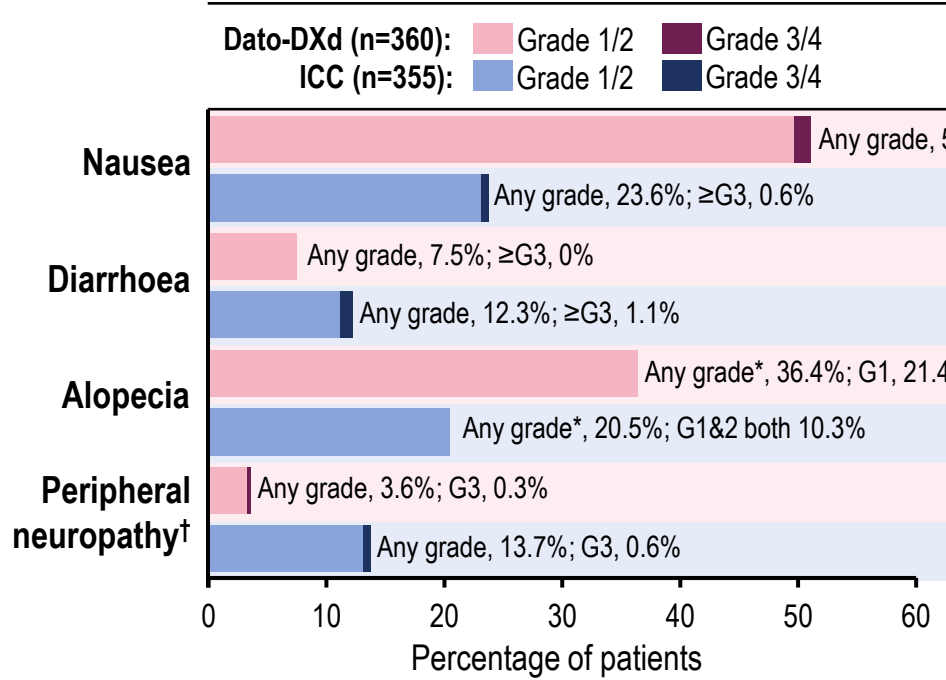


	Leading to dose reduction and/or interruption, %	Leading to dose discontinuation, %
Neutropenia*	0.3	0
	29.9	0.3
Anaemia	0.8	0
	1.7	0
Leukopenia†	0	0
	4.6	0

- G-CSF was used during treatment in 2.7% of patients in the Dato-DXd arm vs 22.1% in the ICC arm

*Grouped term comprising neutropenia and neutrophil count decreased. †Grouped term comprising leukopenia and white blood cell count decreased. G-CSF, granulocyte colony stimulating factor.

Other TRAEs of Clinical Interest



	Leading to dose reduction and/or interruption, %	Leading to dose discontinuation, %
Nausea	2.8	0
	1.1	0
Diarrhoea	0.3	0
	2.6	0
Alopecia	0	0
	0	0
Peripheral neuropathy†	0.3	0
	2.8	0.9

Toxicity management guidelines

Prophylactic anti-emetic agents highly recommended prior to infusion of Dato-DXd, and on subsequent days as needed

*Maximum CTCAE grade for alopecia is grade 2. †Comprising the preferred terms of neuropathy peripheral, peripheral motor neuropathy, polyneuropathy, paraesthesia, peripheral sensory neuropathy.

Conclusions

- In the TROPION-Breast01 study, Dato-DXd demonstrated **statistically significant and clinically meaningful improvement in PFS** by BICR compared with ICC (HR 0.63). OS data were not mature at this DCO
- The **rate of grade ≥3 TRAEs with Dato-DXd was less than half that with ICC**, and **fewer TRAEs led to dose interruption/reduction**, indicating that Dato-DXd offers better tolerability vs ICC
- Further safety data from TROPION-Breast01 showed that **AESIs with Dato-DXd** (oral mucositis / stomatitis, ocular surface events, and adjudicated drug-related ILD), were typically **low grade**, and were **manageable using toxicity management guidelines**
  - Among other TRAEs of clinical interest, **low grade nausea** was the most common event with Dato-DXd
- The **ICC** safety profile was most notable for **high-grade neutropenia** leading to dose interruption / reduction

These data further support Dato-DXd as a potential new therapeutic option for patients with previously-treated, inoperable or metastatic, HR+/HER2– breast cancer

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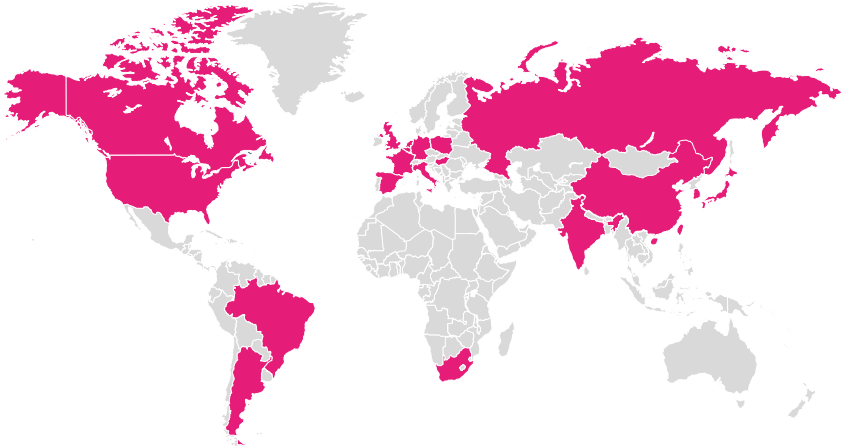

732 patients randomised from: Argentina, Belgium, Brazil, Canada, China, France, Germany, Hungary, India, Italy, Japan, Republic of Korea, Netherlands, Poland, Russia, South Africa, Spain, Taiwan, United Kingdom, United States