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Randomized phase 3 study of datopotamab deruxtecan vs chemotherapy for patients with previously-treated inoperable or metastatic hormone receptor-positive, HER2-negative breast cancer: Results from TROPION-Breast01

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Disclosure Information

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Aditya Bardia

I have the following relevant financial relationships to disclose:

- Participation in advisory boards for Pfizer, Novartis, Genentech, Merck, Radius Health/Menarini, Immunomedics/Gilead, Sanofi, Daiichi Pharma/AstraZeneca, Phillips, Eli Lilly, Mersana, Foundation Medicine

- Research grants (to institution) from Genentech, Novartis, Pfizer, Merck, Sanofi, Radius Health/Menarini, Immunomedics/Gilead, Daiichi Pharma/AstraZeneca, Natera, Eli Lilly

Background

- **Chemotherapy** is utilised widely for management of **endocrine-resistant HR+/HER2– MBC**, but can be associated with **low response rate**, **poor prognosis**, and **significant toxicity** including myelosuppression and peripheral neuropathy, highlighting need for better therapies in this setting[1–5]
- **Dato-DXd** is a **TROP2-directed ADC**, that selectively delivers a potent Topo-I inhibitor payload directly into tumor cells,[6] and has several unique properties:
  - Optimized drug to antibody ratio ≈ 4
  - Stable linker-payload
  - Tumor-selective cleavable linker
  - Bystander antitumor effect
- **Primary results** from phase 3 **TROPION-Breast01** study presented at ESMO 2023[7] demonstrated:
  - **Statistically significant and clinically meaningful improvement in PFS by BICR with Dato-DXd compared with ICC:** HR 0.63 (95% CI 0.52–0.76); P<0.0001
  - OS data not mature, but trend favoring Dato-DXd observed: HR 0.84 (95% CI 0.62–1.14)
  - ORR (by BICR): 36.4% in the Dato-DXd arm versus 22.9% in the ICC arm
- Here we present additional **efficacy, safety** and **QoL** results from TROPION-Breast01

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; MBC, metastatic breast cancer; ICC, investigator's choice of chemotherapy; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; Topo-I, topoisomerase I; TROP2, trophoblast cell surface antigen 2.

1. Kuderer NM, et al. *Nat Rev Clin Oncol* 2022;19:681–97; 2. Gennari A, et al. *Ann Oncol* 2021;32:1475–1495; 3. Wolff AC, et al. *J Clin Oncol* 2023;41:3867–72; 4. Moy B, et al. *J Clin Oncol* 2023;41:1318–20; 5. Moy B, et al. *J Clin Oncol* 2022;40:3088–90; 6. Okajima D, et al. *Mol Cancer Ther* 2021;20:2329–40; 7. Bardia A, et al. *Ann Oncol* 2023;34(suppl_2):S1264–5.

TROPION-Breast01 Study Design[1]

Randomized, 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
- **Secondary endpoints included:** ORR, PFS (investigator assessed), TFST, safety, PROs

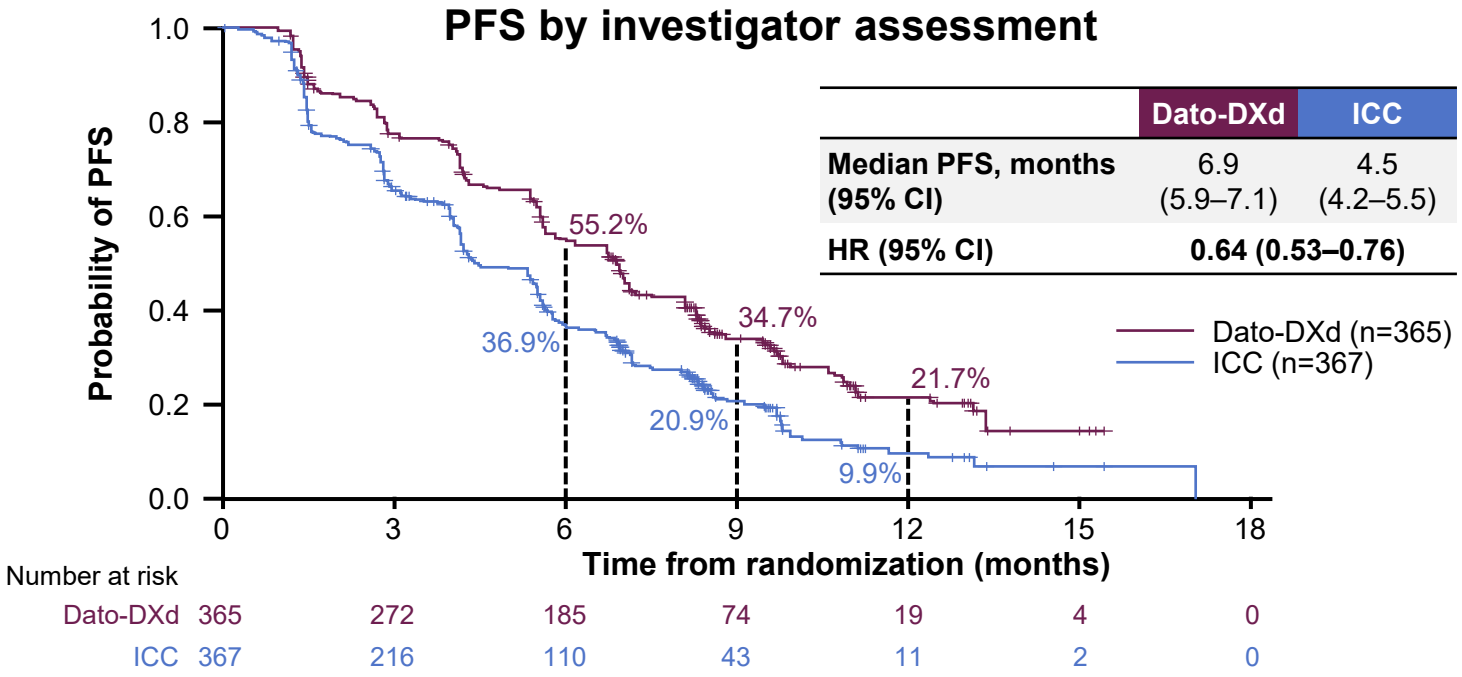
Randomization stratified by:
- **Lines of chemotherapy** in unresectable/metastatic setting (1 vs 2)
- **Geographic location** (US/Canada/Europe vs ROW)
- **Previous CDK4/6 inhibitor** (yes vs no)

- 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; or gemcitabine, 1000 mg/m^2 IV on Days 1 and 8, Q3W; 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; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; IHC, immunohistochemistry; ISH, in-situ hybridization; IV, intravenous; PD, progressive disease; PROs, patient-reported outcomes; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; ROW, rest of world; TFST, time to first subsequent therapy.

1. Bardia A, et al. *Future Oncol* 2023; doi: 10.2217/fon-2023-0188.

Progression-Free Survival



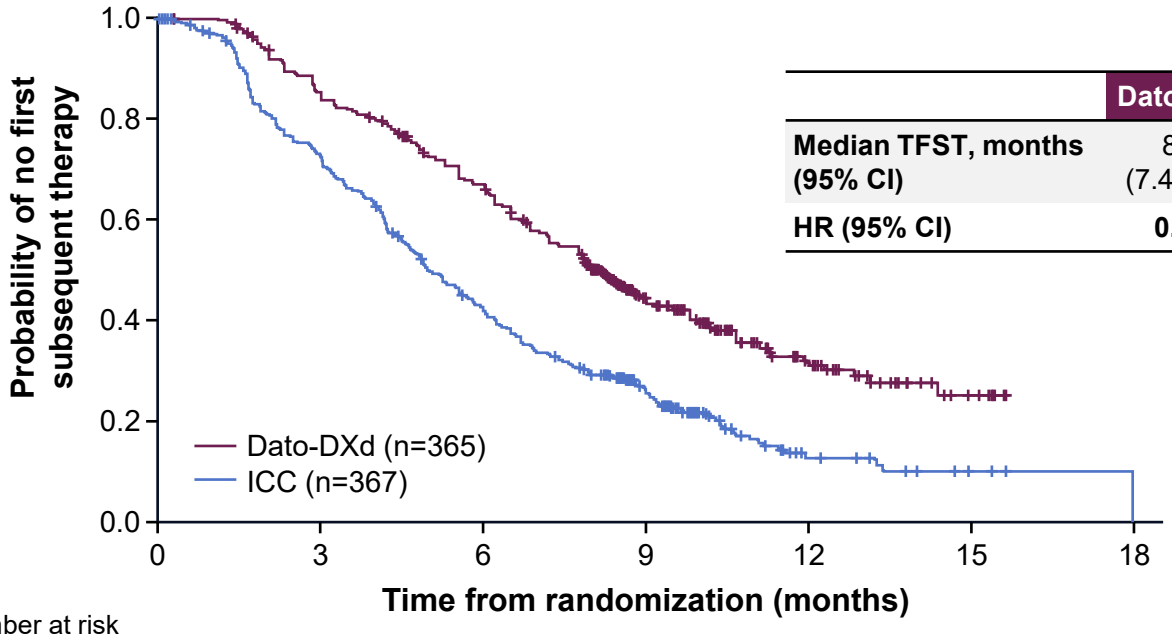
	Dato-DXd	ICC
Median PFS, months (95% CI)	6.9 (5.9–7.1)	4.5 (4.2–5.5)
HR (95% CI)	**0.64 (0.53–0.76)**	

PFS by BICR (primary endpoint)[1]: Median 6.9 vs 4.9 months; HR 0.63 (95% CI 0.52–0.76); P<0.0001

Data cut-off: 17 July 2023.

1. Bardia A, et al. Oral Presentation at ESMO 2023; Abstract LBA11.

Time to First Subsequent Therapy



	Dato-DXd	ICC
Median TFST, months (95% CI)	8.2 (7.4–8.9)	5.0 (4.6–5.7)
HR (95% CI)	**0.53 (0.45–0.64)**	

Number at risk

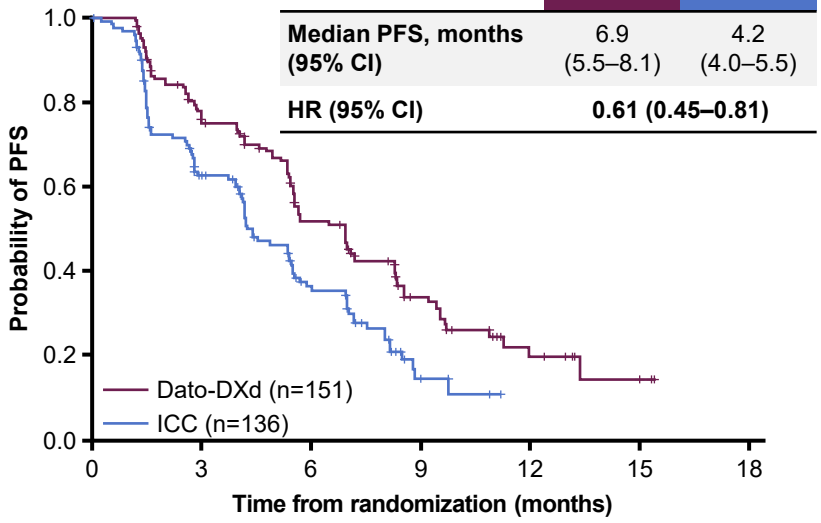
Dato-DXd	365	304	231	110	36	7	0
ICC	367	256	147	65	13	4	0

PFS by BICR in Subgroups

Prior CDK4/6 Inhibitor

Prior duration of CDK4/6 inhibitor: ≤12 months

	Dato-DXd	ICC
Median PFS, months (95% CI)	6.9 (5.5–8.1)	4.2 (4.0–5.5)
HR (95% CI)	**0.61 (0.45–0.81)**	

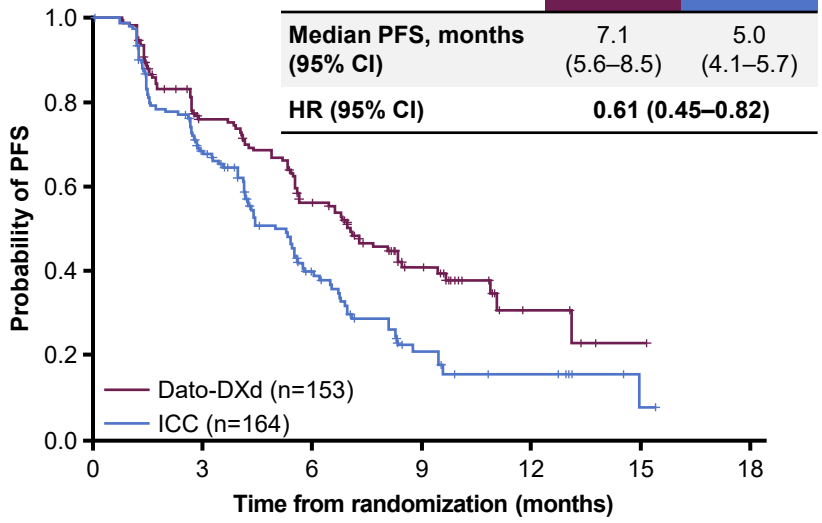


No. at risk

Dato-DXd	151	106	63	26	8	2	0
ICC	136	74	35	7	0	0	0

Prior duration of CDK4/6 inhibitor: >12 months

	Dato-DXd	ICC
Median PFS, months (95% CI)	7.1 (5.6–8.5)	5.0 (4.1–5.7)
HR (95% CI)	**0.61 (0.45–0.82)**	



No. at risk

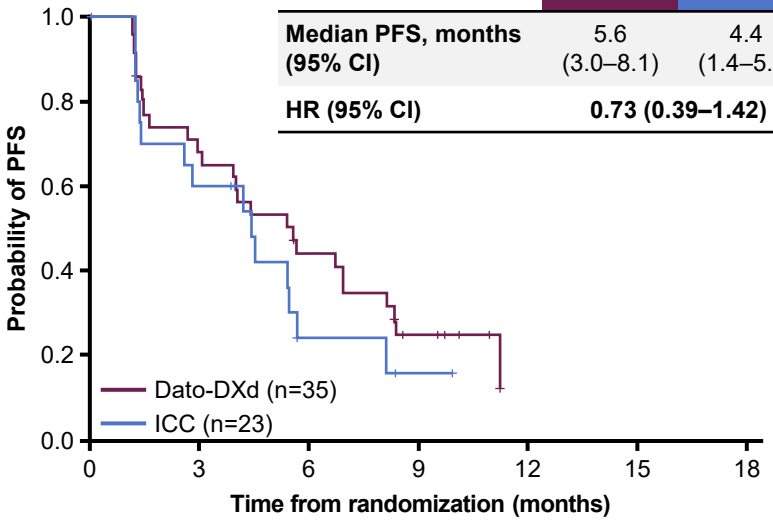
Dato-DXd	153	102	70	28	6	1	0
ICC	164	90	40	13	7	1	0

PFS by BICR in Subgroups

Brain metastases

Brain metastases at study entry: Yes*

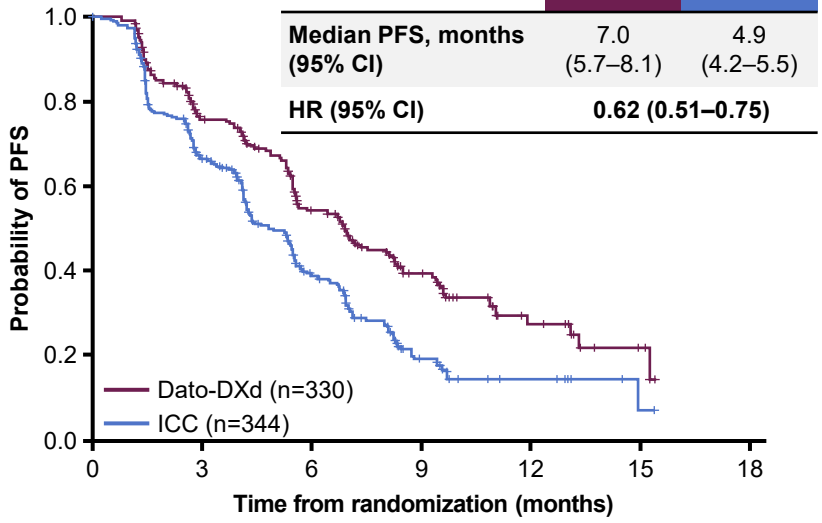
	Dato-DXd	ICC
Median PFS, months (95% CI)	5.6 (3.0–8.1)	4.4 (1.4–5.7)
HR (95% CI)	**0.73 (0.39–1.42)**	



No. at risk					
Dato-DXd	35	23	14	6	0
ICC	23	12	3	1	0

Brain metastases at study entry: No

	Dato-DXd	ICC
Median PFS, months (95% CI)	7.0 (5.7–8.1)	4.9 (4.2–5.5)
HR (95% CI)	**0.62 (0.51–0.75)**	



No. at risk							
Dato-DXd	330	226	144	60	15	4	0
ICC	344	193	90	25	8	1	0

*Study inclusion criteria permitted enrollment of patients with clinically inactive brain metastases, who required no treatment with corticosteroids or anticonvulsants.

Overall Safety Summary

TRAEs, n (%)[1]	Dato-DXd (n=360)	ICC (n=351)
All grades	337 (94)	303 (86)
Grade ≥3	75 (21)	157 (45)
Associated with dose reduction	75 (21)	106 (30)
Associated with dose interruption	43 (12)	86 (25)
Associated with discontinuation	9 (3)	9 (3)
Associated with death	0	1 (0.3)
Serious TRAEs	21 (6)	32 (9)
Grade ≥3	17 (5)	31 (8)

- Most common TRAEs leading to dose interruption:
  - Dato-DXd: fatigue*, infusion-related reaction, ILD, stomatitis (each 1%)
  - ICC: neutropenia† (17%), leukopenia‡ (3%)
- No TRAEs led to discontinuation in ≥1% of patients in either arm
- One treatment-related death in the ICC arm due to febrile neutropenia

*Fatigue includes the preferred terms of fatigue, asthenia, and malaise. †Neutropenia includes the preferred terms neutropenia and neutrophil count decreased.
‡Leukopenia includes the preferred terms of white blood cell count decreased and leukopenia.
ILD, interstitial lung disease; TRAEs, treatment-related adverse events.

1. Bardia A, et al. Oral Presentation at ESMO 2023; Abstract LBA11.

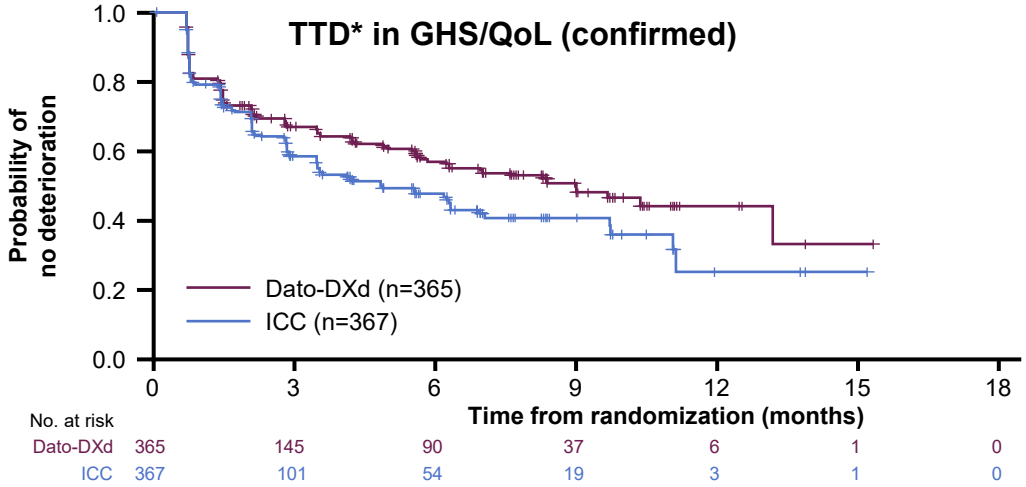
Adverse Events of Clinical Interest

Neutropenia*	Dato-DXd (n=360)	ICC (n=351)
Treatment-related neutropenia*, n (%)		
Any grade	39 (11)	149 (42)
Grade ≥3	4 (1)	108 (31)
Leading to dose interruption	0	60 (17)
Leading to dose reduction	1 (0.3)	45 (13)
Leading to dose discontinuation	0	1 (0.3)
G-CSF usage, n (%)		
On treatment	10 (3)	81 (22)
Post-treatment†	1 (0.3)	30 (8)

Stomatitis‡	Dato-DXd (n=360)	ICC (n=351)
Treatment-related stomatitis‡, n (%)		
Any grade	180 (50)	46 (13)
Grade 3	23 (6)	9 (3)
Leading to dose interruption	5 (1)	3 (1)
Leading to dose reduction	44 (12)	5 (1)
Leading to dose discontinuation	1 (0.3)	0

*Neutropenia includes the preferred terms neutropenia and neutrophil count decreased. Treatment-related febrile neutropenia occurred in 0 patients in the Dato-DXd arm and 8 patients (2.3%; all grade ≥3) in the ICC arm.
†Administered after discontinuation of study treatment.
‡As part of the Oral Care Protocol specified in the study protocol, daily use of prophylaxis with a steroid-containing mouthwash (e.g., dexamethasone oral solution or a similar mouthwash regimen using an alternative steroid advocated by institutional/local guidelines) was highly recommended.
G-CSF, granulocyte colony stimulating factor.

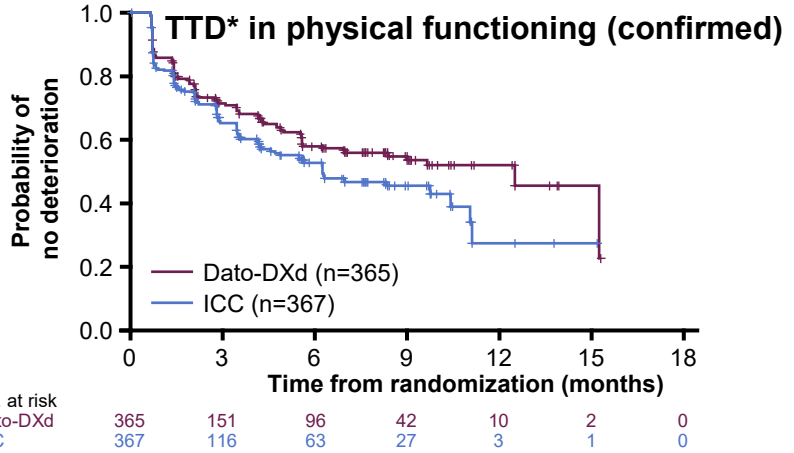
TTD in Global Health Status/Quality of Life

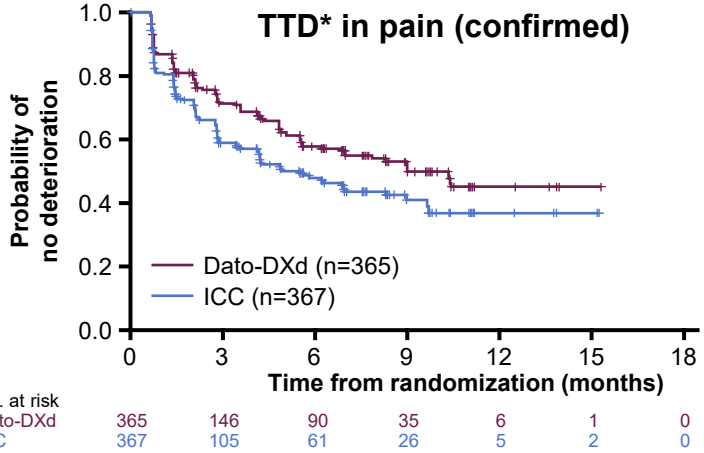


TTD*	Median TTD, months (first instance)		HR (95% CI)	Median TTD, months (confirmed)		HR (95% CI)
	Dato-DXd	ICC		Dato-DXd	ICC	
GHS/QoL	3.4	2.1	0.85 (0.68–1.06)	9.0	4.8	0.76 (0.58–0.98)

*TTD in pain, physical functioning and GHS/QoL are secondary endpoints. The primary analysis was based on time to first deterioration, defined as the time from date of randomization to date of first deterioration. Sensitivity analysis was based on time to confirmed deterioration, which required deterioration to be confirmed at a subsequent timepoint. Deterioration was defined as change from baseline that reached a clinically meaningful deterioration threshold (16.6 for GHS/QoL and pain, 13.3 for physical functioning). GHS/QoL, global health status/quality of life; TTD, time to deterioration.

TTD in Physical Functioning and Pain





TTD*	Median TTD, months (first instance)		HR (95% CI)	Median TTD, months, (confirmed)		HR (95% CI)
	Dato-DXd	ICC		Dato-DXd	ICC	
Physical Functioning	5.6	3.5	0.77 (0.61–0.99)	12.5	6.2	0.77 (0.59–1.01)
Pain	3.5	2.8	0.85 (0.68–1.07)	9.0	5.5	0.72 (0.55–0.94)

*TTD in pain, physical functioning and GHS/QoL are secondary endpoints. The primary analysis was based on time to first deterioration, defined as the time from date of randomization to date of first deterioration. Sensitivity analysis was based on time to confirmed deterioration, which required deterioration to be confirmed at a subsequent timepoint. Deterioration was defined as change from baseline that reached a clinically meaningful deterioration threshold (16.6 for GHS/QoL and pain, 13.3 for physical functioning). GHS/QoL, global health status/quality of life; TTD, time to deterioration.

Conclusions

- TROPION-Breast01 met its dual primary PFS endpoint, demonstrating statistically significant and clinically meaningful improvement in PFS (by BICR) with Dato-DXd compared with ICC
  - Investigator-assessed PFS was consistent with PFS by BICR
  - Median PFS improvement observed regardless of prior duration of CDK4/6 inhibitor or brain metastases
  - Time to first subsequent therapy was longer with Dato-DXd compared with ICC
- Overall, Dato-DXd demonstrated a favorable safety profile compared with ICC
  - Patients receiving Dato-DXd had fewer grade ≥3 TRAEs and fewer dose interruptions/reductions vs ICC
  - Treatment-related stomatitis with Dato-DXd was generally low grade and manageable
  - Neutropenia was the most common TRAE with ICC, which frequently led to dose interruption/reduction, and one death
- Time to deterioration in quality of life was delayed in the Dato-DXd arm compared with ICC

Overall, results support Dato-DXd as a potential new therapeutic option for patients with endocrine-resistant metastatic HR+/HER2– breast cancer

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- Families and caregivers
- TROPION-Breast01 investigators and site personnel

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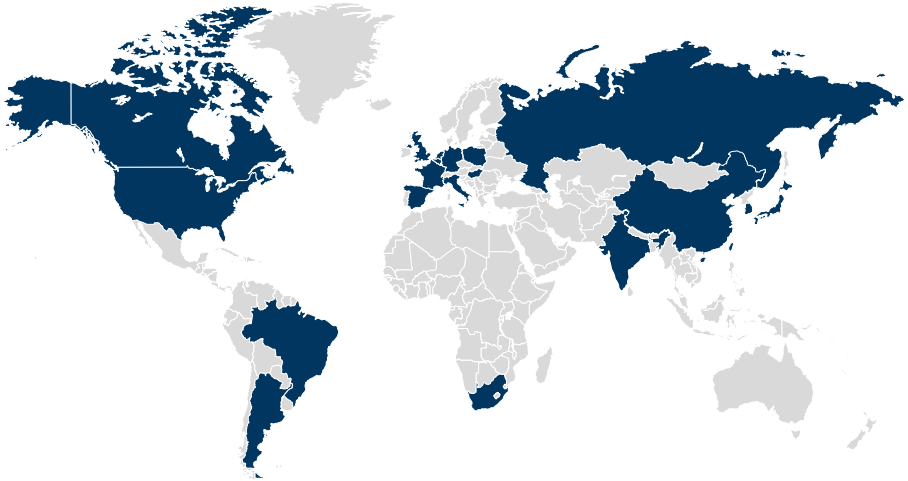

732 patients randomized from: Argentina, Belgium, Brazil, Canada, China, France, Germany, Hungary, India, Italy, Japan, Republic of Korea, Netherlands, Poland, Russia, South Africa, Spain, Taiwan, United Kingdom, United States

Acknowledgments

Patients enrolled in TROPION-Breast01 (N=732)