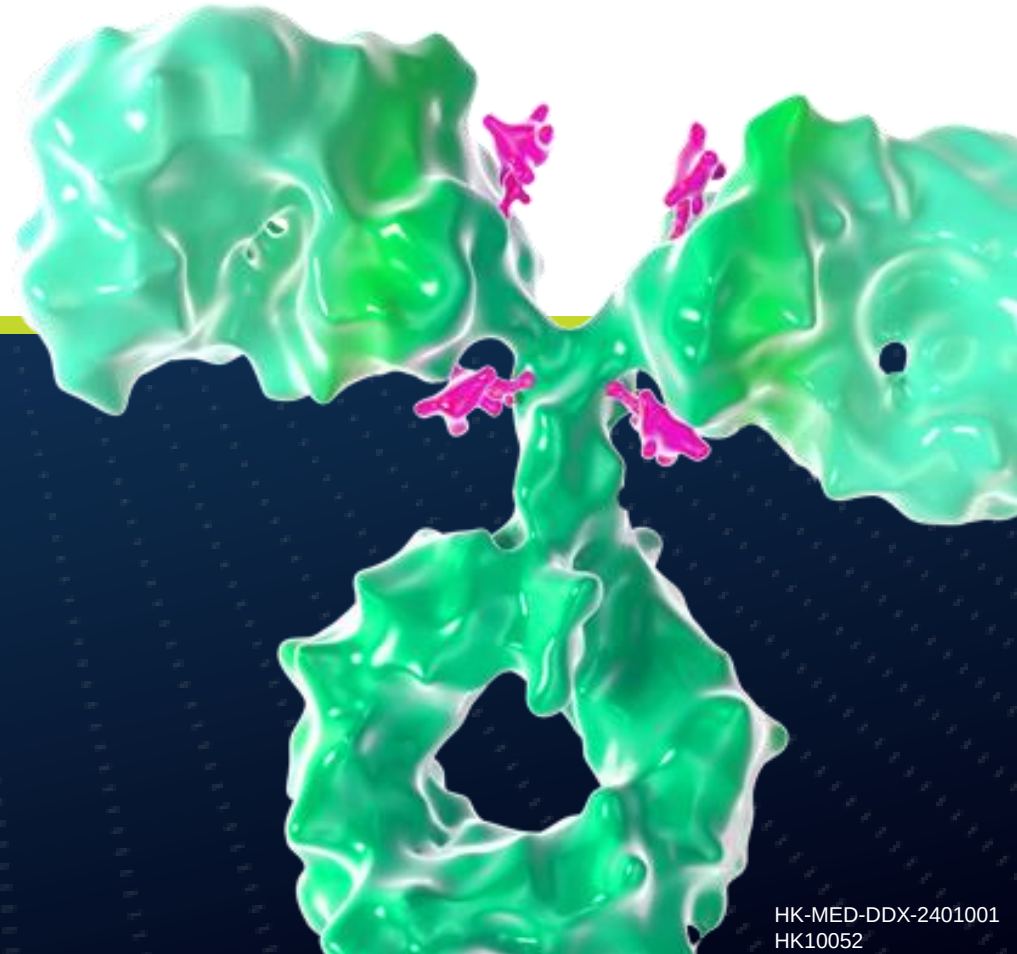
TROPION-Breast01 Study Deck

A Phase III, open-label, randomized, parallel, multicenter, global study of datopotamab deruxtecan (Dato-DXd) versus investigator's choice of chemotherapy in patients with inoperable or metastatic HR positive/HER2 negative breast cancer treated with 1 or 2 prior lines of systemic chemotherapy

December 7, 2023



HK-MED-DDX-2401001
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TROPION-Breast01: Executive Summary

Background and Study Rationale: HR positive/HER2 negative is the most common subtype of BC, accounting for ~70% of diagnoses. HR positive/HER2 negative advanced/metastatic BC has a 5-year survival rate of approximately 30%.[1] There remains a significant unmet need to displace traditional chemotherapy as the SOC in patients who have progressed on and are not suitable for ET, owing to its limited efficacy and toxicity.[2-12]

TROP2: TROP2 is a transmembrane glycoprotein that is broadly expressed in solid tumors, including BC.[13-16] Preclinical evidence suggests that TROP2 promotes cell proliferation, cell survival, invasion, and metastases.[17-23] Clinical evidence have demonstrated that high TROP2 expression is an unfavorable prognostic factor for OS in all types of BC.[20]

Datopotamab Deruxtecan: Dato-DXd is a TROP2 directed ADC designed with a stable, tumor-selective, tetrapeptide-based cleavable linker to selectively deliver a highly potent cytotoxic payload to tumor cells with minimal systemic exposure to payload.[24-27]

TROPION-Breast01 (NCT05104866): This global, randomized, multicenter, open-label, Phase III study is evaluating the efficacy and safety of Dato-DXd compared with investigator's choice of standard of care single-agent chemotherapy (eribulin mesylate, capecitabine, vinorelbine, or gemcitabine) in patients with inoperable or metastatic HR positive/HER2 negative BC who have received 1 or 2 prior lines of chemotherapy and who have progressed on and are not suitable for endocrine therapy.[28,29,30]

Results: In the TROPION-Breast01 trial, Dato-DXd demonstrated statistically significant and clinically meaningful improvement in its dual primary endpoint PFS by BICR compared with ICC: (mPFS, 6.9 vs 4.9 months; hazard ratio, 0.63; 95% CI, 0.52–0.76; p<0.0001) at 10.8 months follow up (DCO July 17, 2023). Investigator-assessed PFS was consistent with PFS by BICR and a consistent PFS benefit was observed across subgroups. OS data is not mature, but trend favoring Dato-DXd was observed (hazard ratio, 0.84; 95% CI, 0.62–1.14). The overall safety profile of Dato-DXd was manageable, with no new safety signals. Treatment-related stomatitis was reported in 50% of patients in the Dato-DXd arm, however, the majority of events were low grade and rarely led to discontinuation. Adjudicated treatment-related ILD rate was low and mainly low grade.[28,29,30]

1. National Institutes of Health. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: Female Breast Cancer Subtypes. **2.** Jerusalem G et al. *JAMA Oncol*. 2018; 4(10):1367-1374. **3.** Cortes J et al. *Lancet.* 2011; 377(9769): 914-923. **4.** Twelves C et al. Breast Cancer (Auckl). 2016;10:77-84. **5.** Gennari A et al. *Ann Oncol*. 2021;32:1475-1495. **6.** Miller KD et al. *J Clin Oncol*. 2005;23(4): 792-799. **7.** Sparano JA et al. *J Clin Oncol.* 2010; 28(20): 3256-3263. **8.** Barrios CH et al. *Breast Cancer Res Treat*. 2010;121:121-131. **9.** Thomas ES et al. *J Clin Oncol*. 2007 Nov 20;25(33):5210-5217. **10.** Martín M et al. *Lancet Oncol*. 2007;8:219-225. **11.** Yuan P et al. *Eur J Cancer*. 2019;112: 57-65. **12.** Davie A et al. *BMC Cancer.* 2020;20:855. **13.** McDougall ARA et al. *Dev Dyn*. 2015;244:99-109. **14.** Shvartsur A et al. *Genes Cancer*. 2015;6(3-4):84-105. **15.** Inamura K et al. *Oncotarget.* 2017;8(17):28725-28735. **16.** Goldenberg DM et al. *Oncotarget*. 2018;9:28989-29006. **17.** Trerotola M et al. *Oncogene*. 2013;32(2):222-233. **18.** Cubas R et al. *Mol Cancer*. 2010;9:253. **19.** Li Z et al. *Biochem Biophys Res Commun.* 2016;470(1):197-204. **20.** Ambrogi F et al. *PLoS One*. 2014;9(5):e96993. **21.** Vidula N et al. *J Clin Oncol*. 2017; 35(Suppl. 15):1075. **22**. Zaman S et al. *Onco Targets Ther*. 2019;12:1781-1790. **23.** Cardoso F et al. *Ann Oncol*. 2020;31(12):1623-1649. **24.** Okajima D et al. *Mol Cancer Ther.* 2021;20:2329-2340. **25.** Nakada T et al. *Chem Pharm Bull*. 2019;67:173-185. **26.** Ogitani Y et al. *Clin Cancer Res*. 2016;22(20):5097-5108. **27.** Ogitani Y et al. *Cancer Sci*. 2016;107(7):1039-1046. **28.** Study NCT05104866. ClinicalTrials.gov. website. **29.** Bardia A et al. Presented at: ESMO; October 20-24, 2023; Madrid, Spain. Abstract LBA11. **30.** Bardia A et al. Presented at: SABCS; December 5-9, 2023; San Antonio, TX. Abstract GS02-01.

Abbreviations available in slide notes.

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TROPION-Breast01: Study Design and Results

TROPION-Breast01: Study Design[1-4]

A Phase III, Open-Label, Randomized, Parallel, Multicenter, Global Study of Dato-DXd Versus ICC in Patients With Inoperable or Metastatic HR Positive/HER2 Negative BC Treated With 1 or 2 Prior Lines of Systemic Chemotherapy

Study Design

Patients with HR positive/HER2 negative BC[a] (HER2 negative 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

Randomization (1:1)

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

Investigator's Choice of Chemotherapy
as per protocol directions[b]
(eribulin mesylate, vinorelbine, capecitabine, or gemcitabine)
(n=367)

Dual Primary Endpoints

- PFS by BICR per RECIST v1.1
- OS

Key Secondary Endpoints

- ORR
- PFS (investigator assessed)
- TFST
- Safety
- PROs

Locations: North America, South America, Europe, Africa, Asia
ClinicalTrials.gov Identifier: NCT05104866
EudraCT Identifier: 2020-005620-12
Japan Clinical Trial Identifier: jRCT2031210440

Randomization stratified by:

- **Lines of chemotherapy** in unresectable/metastatic setting (1 vs 2)
- **Geographic location** (US/Canada/Europe vs rest of world)
- **Previous CDK4/6 inhibitor** (yes vs no)

- Treatment continued until progressive disease, unacceptable tolerability, or other discontinuation criteria

[a]Per American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines; [b]ICC was administered as follows: eribulin mesylate, 1.4 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); 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; [c]Per RECIST v1.1; [d]The date of second progression will be recorded by the Investigator in the eCRF and defined according to local standard clinical practice.

1. Study NCT05104866. ClinicalTrials.gov website. **2.** Bardia A et al. Online ahead of print. *Future Oncol*. 2023. **3.** Bardia A et al. Presented at: ESMO; October 20-24, 2023; Madrid, Spain. Abstract LBA11. **4.** Bardia A et al. Presented at: SABCS; December 5-9, 2023; San Antonio, TX. Abstract GS02-01.

TROPION-Breast01: Statistical Methods[1,2]

Primary efficacy analysis performed in intention-to-treat population and analysed by treatment group

Primary analysis of PFS ~ 419 PFS events

- Interim OS analysis at the time of the primary PFS analysis

The final analysis of OS will be conducted at ~ 444 OS events

PFS analysed using log-rank test utilising stratification factors

Study considered positive if PFS and/or OS analysis statistically significant

1. Bardia A et al. Online ahead of print. Future Oncol. 2023. **2.** Bardia A et al. Presented at: ESMO; October 20-24, 2023; Madrid, Spain. Abstract LBA11.
Abbreviations available in slide notes.

TROPION-Breast01: Key Eligibility Criteria[1-4]

Key Inclusion Criteria

- Male or female patients age ≥18 years at the time of screening
- Inoperable or metastatic HR positive/HER2 negative BC per ASCO/CAP guidelines
- Progressed on and not suitable for ET per investigator assessment and treated with 1 to 2 lines of prior standard of care chemotherapy in the inoperable/metastatic setting
  - Must have documented progression on the most recent line of chemotherapy
- Eligible for one of the chemotherapy options listed as ICC (eribulin mesylate, capecitabine, vinorelbine, gemcitabine) per investigator assessment
- ECOG PS 0 or 1
- ≥1 measurable lesion per RECIST v1.1 not previously irradiated
- Patients with clinically inactive brain metastases may be included
- Adequate organ and bone marrow function within 7 days before day of first dosing
- LVEF ≥50% by echocardiogram or MUGA
- Availability of a FFPE tumor sample (block preferred, or a minimum of 20 freshly cut slides), at the time of screening[a]

Key Exclusion Criteria

- History of another primary malignancy except for malignancy treated with curative intent with no known active disease within 3 years
- Persistent toxicities caused by previous anticancer therapy (excluding alopecia)
- Uncontrolled infection requiring IV antibiotics, antivirals, or antifungals; suspected infections
- Known HIV infection, active or uncontrolled hepatitis B or C infection
- Uncontrolled or significant cardiac disease
- History of (non-infectious) ILD/pneumonitis that required steroids, current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening
- Severe pulmonary compromise, significant corneal disease, leptomeningeal carcinomatosis or known active tuberculosis infection
- Prior anticancer therapy with another agent targeting topoisomerase I (including an ADC), TROP2 directed therapy, same ICC chemotherapy
- Concurrent anticancer treatment or hormonal therapy for non-cancer related conditions
- Prior participation in the present trial or any T-DXd study (regardless of whether T-DXd was received).

[a]Sample collection in China will comply with local regulatory approval.

1. Study NCT05104866. ClinicalTrials.gov website. **2.** Bardia A et al. Online ahead of print. *Future Oncol*. 2023. **3.** Bardia A et al. Presented at: ESMO; October 20-24, 2023; Madrid, Spain. Abstract LBA11. **4.** Bardia A et al. Presented at: SABCS; December 5-9, 2023; San Antonio, TX. Abstract GS02-01.

Abbreviations available in slide notes.

TROPION-Breast01: Patient Disposition

Disposition	Screened (n=1003)	
	Randomized (n=732)	
	Dato-DXd (n=365)[a]	ICC (n=367)[a]
Ongoing study treatment	93	39
Discontinued study treatment	267	312
Progressive disease	229	240
Adverse Event	11	10
Patient decision	13	32
Death	2	7
Other	12	23

- ICC:
  - Eribulin mesylate: n=220
  - Vinorelbine: n=38
  - Capecitabine: n=76
  - Gemcitabine: n=33
- Median study follow-up was 10.8 months

Data cut-off: July 17, 2023
[a]360 and 351 patients received treatment with Dato-DXd and ICC, respectively.
Bardia A et al. Presented at: ESMO; October 20-24, 2023; Madrid, Spain. Abstract LBA11.
Abbreviations available in slide notes.

TROPION-Breast01: Demographics and Baseline Characteristics

Characteristic	Dato-DXd (n=365)	ICC (n=367)
Age, median (range), years	56 (29-86)	54 (28–86)
Female, n (%)	360 (99)	363 (99)
Race, n (%)		
Black or African American	4 (1)	7 (2)
Asian	146 (40)	152 (41)
White	180 (49)	170 (46)
Other[a]	35 (10)	38 (10)
Ethnicity[b], n (%)		
Hispanic or Latino	40 (11)	43 (12)
Not Hispanic or Latino	322 (88)	318 (87)

Characteristic	Dato-DXd (n=365)	ICC (n=367)
Prior lines of chemotherapy[c], n (%)		
1	229 (63)	225 (61)
2	135 (37)	141 (38)
Prior CDK4/6 inhibitor, n (%)		
Yes	299 (82)	286 (78)
No	66 (18)	81 (22)
Prior taxane and/or anthracycline, n (%)		
Taxane and/or anthracycline	330 (90)	339 (92)
Neither	35 (10)	28 (8)

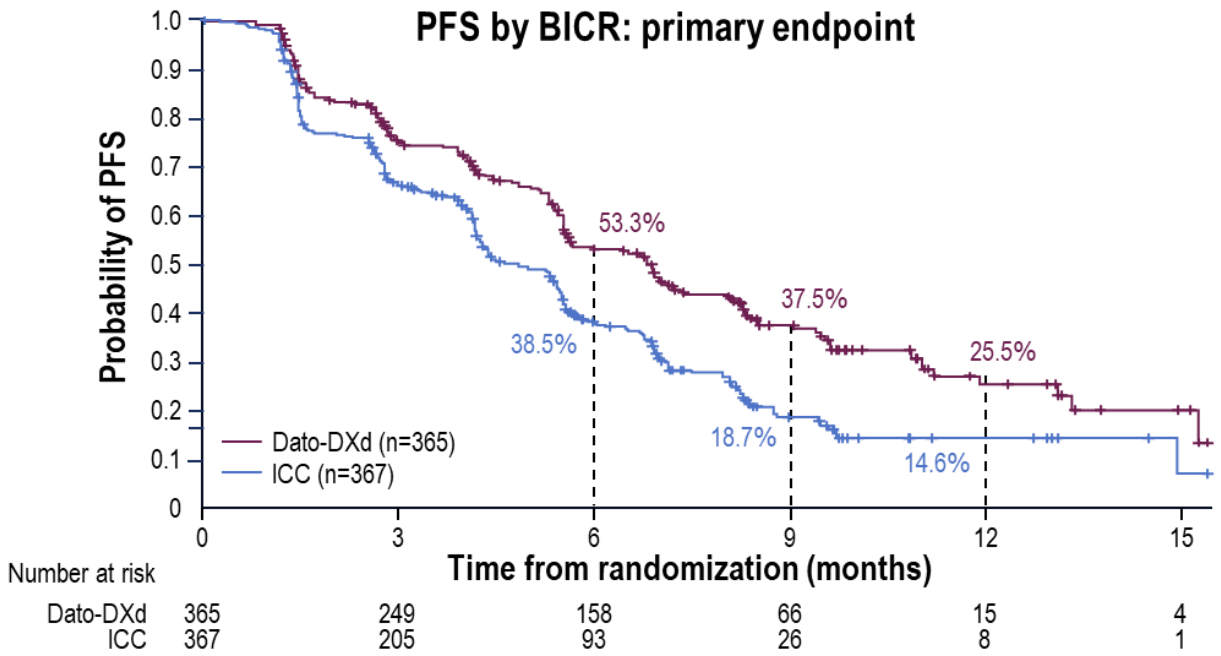
Data cut-off: July 17, 2023

[a]Including not reported; [b]Ethnicity missing: 3 patients in Dato-DXd group and 6 patients in ICC group; [c]In the inoperable/metastatic setting, 1 patient in the Dato-DXd group had 3 prior lines of chemotherapy and 1 patient in the ICC group had 4 prior lines.

Bardia A et al. Presented at: ESMO; October 20-24, 2023; Madrid, Spain. Abstract LBA11.

Abbreviations available in slide notes.

TROPION-Breast01: Progression-Free Survival by BICR



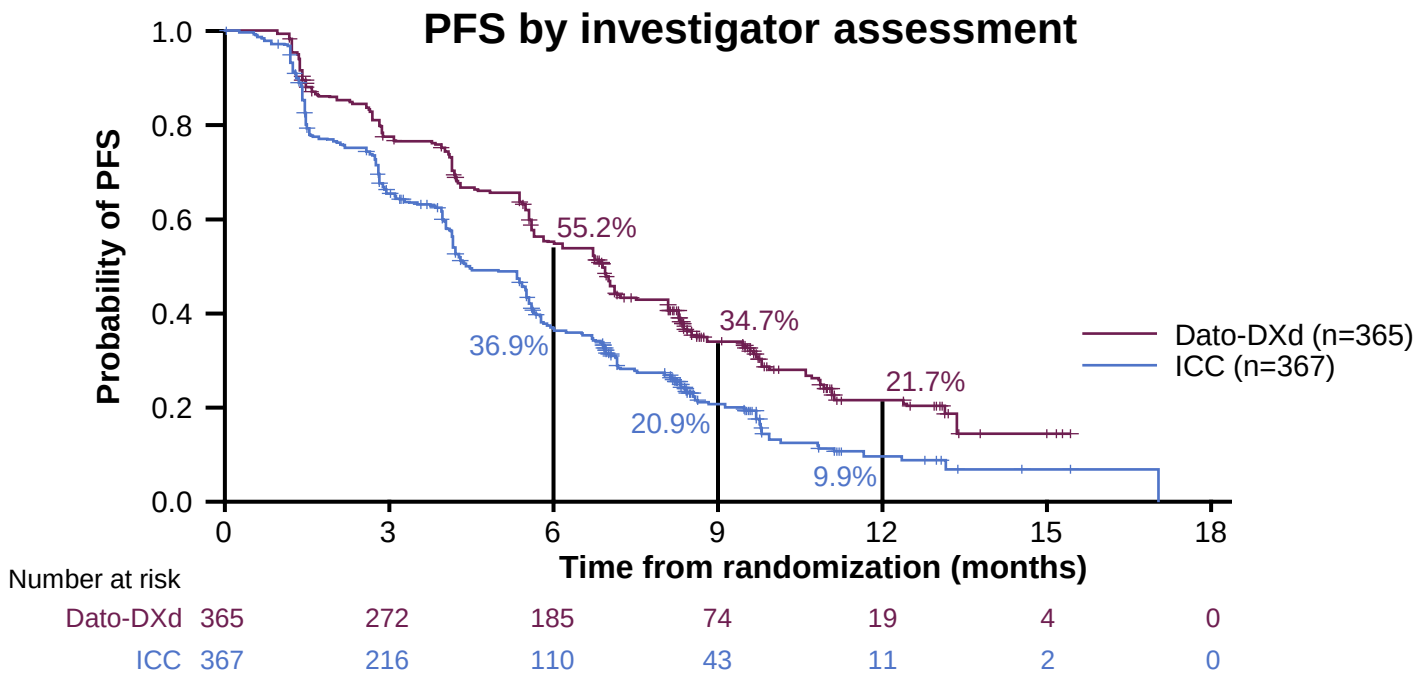
	Dato-DXd	ICC
Median PFS, months (95% CI)	6.9 (5.7–7.4)	4.9 (4.2–5.5)
Hazard Ratio (95% CI)	**0.63 (0.52–0.76)**	
p-value	<0.0001	

- Dato-DXd reduced the risk of progression or death by 37% compared to standard chemotherapy
- 9-month PFS rate was double with Dato-DXd (37.5%) vs standard chemotherapy (18.7%)

Dato-DXd demonstrated a statistically significant and clinically meaningful PFS compared with ICC (standard chemotherapy).

Data cut-off: July 17, 2023
Bardia A et al. Presented at: ESMO; October 20-24, 2023; Madrid, Spain. Abstract LBA11.
Abbreviations available in slide notes.

TROPION-Breast01: Progression-Free Survival by Investigator Assessment



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

Investigator-assessed PFS was consistent with PFS by BICR.

Data cut-off: July 17, 2023
Bardia A et al. Presented at: SABCS; December 5-9, 2023; San Antonio, TX. Abstract GS02-01.
Abbreviations available in slide notes.

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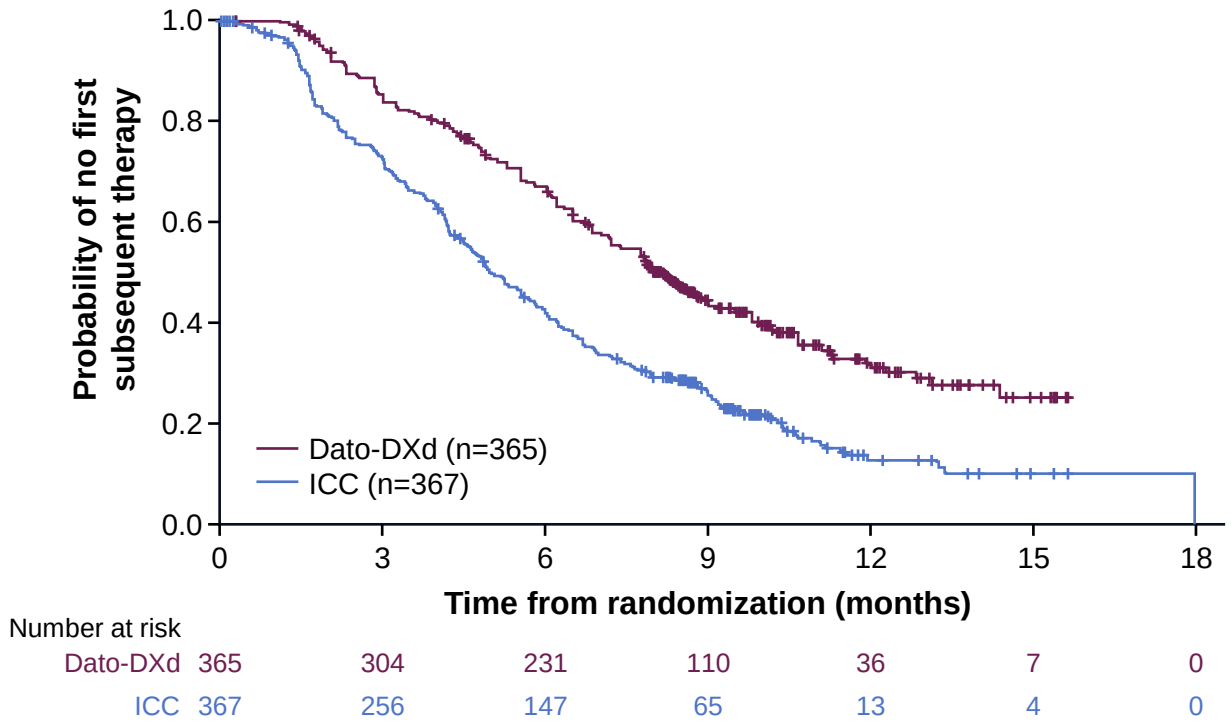
TROPION-Breast01: Time to First Subsequent Therapy



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

TFST was prolonged with Dato-DXd compared to standard chemotherapy.

Data cut-off: July 17, 2023
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Abbreviations available in slide notes.

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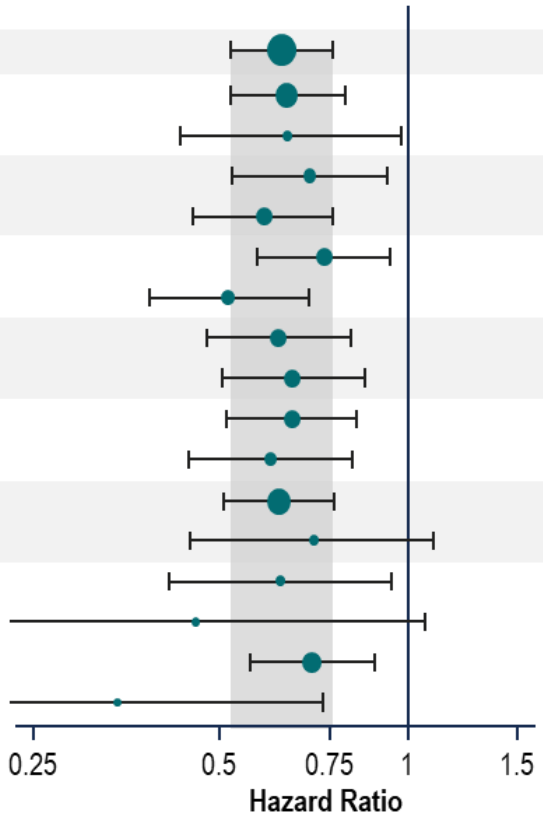
TROPION-Breast01: PFS by BICR Across Subgroups

		Events/n Dato-DXd	Events/n ICC	Hazard ratio
All patients		212/365	235/367	0.63
Age at randomisation	<65 years	163/274	190/295	0.64
	≥65 years	49/91	45/72	0.65
Race	Asian	88/146	101/152	0.70
	Non-Asian	109/187	119/183	0.59
ECOG performance status	0	119/197	136/220	0.73
	1	91/165	98/145	0.52
Geographic region	US, Canada, Europe	110/186	112/182	0.62
	Rest of World[a]	102/179	123/185	0.66
Number of previous lines of chemotherapy	1	128/229	145/225	0.65
	2	84/135	90/141	0.60
Prior use of CDK4/6 inhibitor	Yes	177/299	190/286	0.62
	No	35/66	45/81	0.70
Prior use of taxane and/or anthracycline	Taxane alone	48/80	47/71	0.62
	Anthracycline alone	9/14	16/21	0.46
	Both taxane and anthracycline	141/236	155/247	0.70
	Neither taxane nor anthracycline	14/35	17/28	0.34



Consistent PFS benefit was seen across subgroups.

Data cut-off: July 17, 2023
Size of circle is proportional to the number of events across both treatment groups.
[a]Three patients from Canada were incorrectly stratified to Rest of World.
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Abbreviations available in slide notes.

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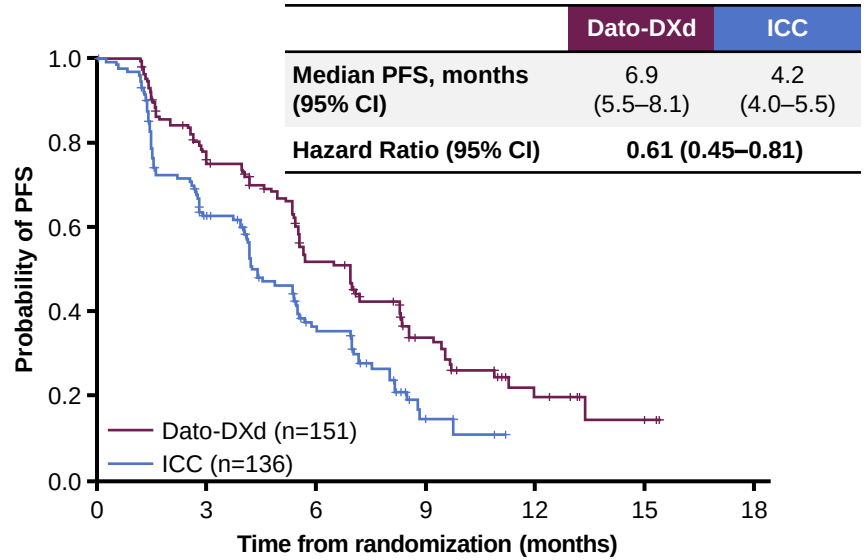
TROPION-Breast01: PFS by BICR in Subgroups

Prior CDK4/6 Inhibitor

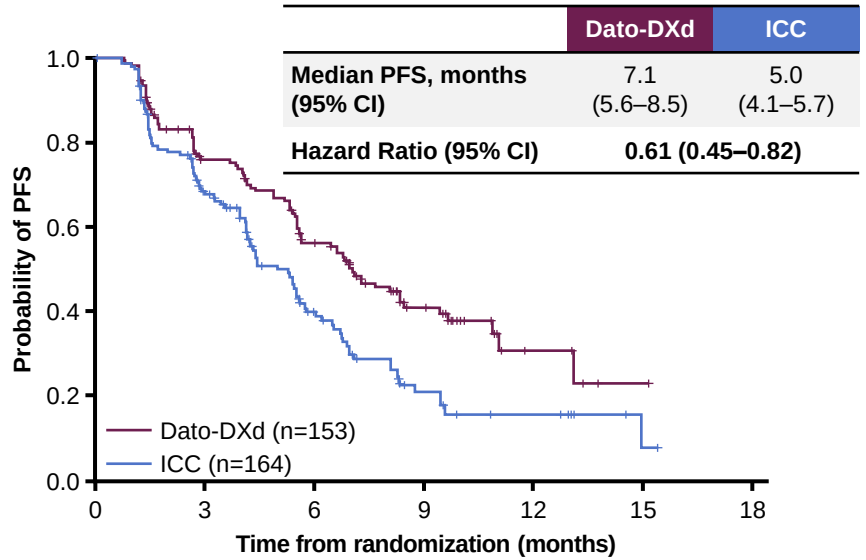
Prior duration of CDK4/6 inhibitor: ≤12 months



	Dato-DXd	ICC
Median PFS, months (95% CI)	6.9 (5.5–8.1)	4.2 (4.0–5.5)
Hazard Ratio (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)
Hazard Ratio (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

Consistent PFS benefit was seen across subgroups.

Data cut-off: July 17, 2023
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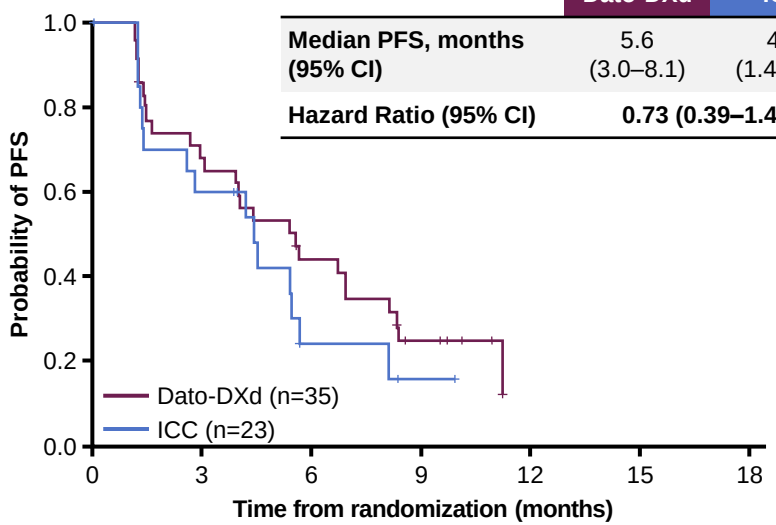
TROPION-Breast01: PFS by BICR in Subgroups

Brain Metastases

Brain metastases at study entry: Yes[a]

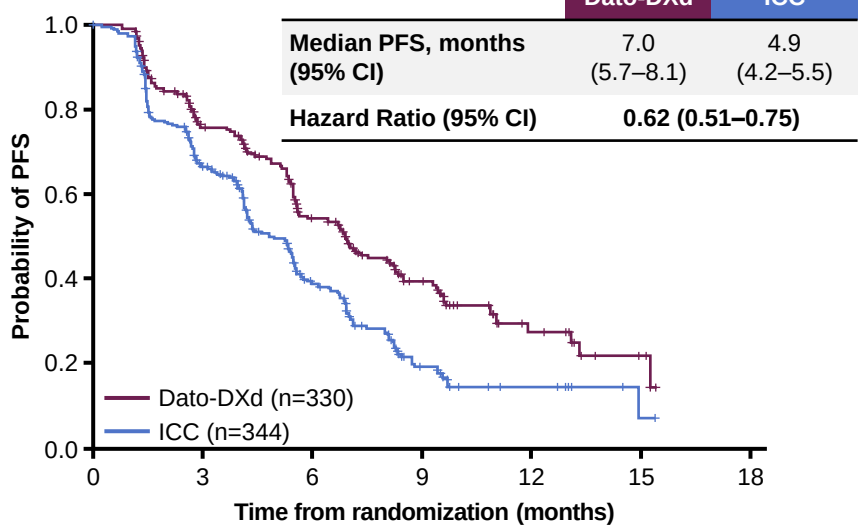
	Dato-DXd	ICC
Median PFS, months (95% CI)	5.6 (3.0–8.1)	4.4 (1.4–5.7)
Hazard Ratio (95% CI)	**0.73 (0.39–1.42)**	



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)
Hazard Ratio (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

Consistent PFS benefit was seen across subgroups.

Data cut-off: July 17, 2023

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

Bardia A et al. Presented at: SABCS; December 5-9, 2023; San Antonio, TX. Abstract GS02-01.

Abbreviations available in slide notes.

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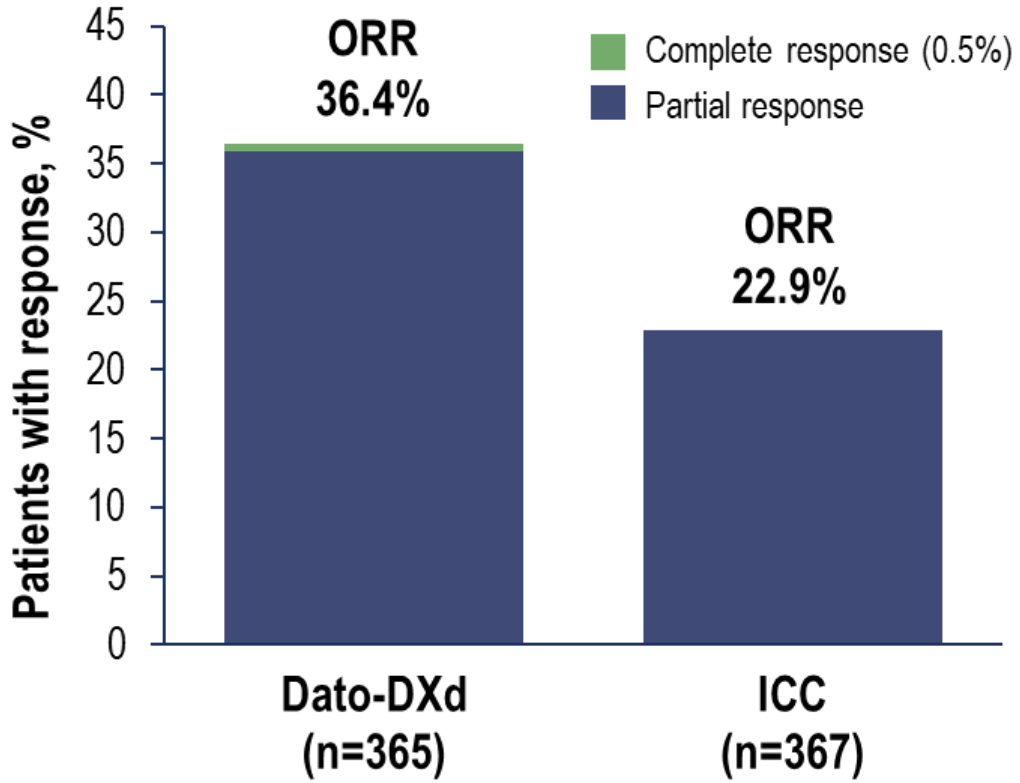
TROPION-Breast01: Response and Interim OS

Response Rate



OS: Dual Primary Endpoint

- OS data were not mature[a]
  - Median follow-up 9.7 months
- A trend favoring Dato-DXd was observed:
  - HR 0.84 (95% CI, 0.62-1.14)
- The study is continuing to the next planned analysis for OS

ORR was higher with Dato-DXd (36.4%; 2 CR) vs standard chemotherapy (22.9%; 0 CR).
OS data not mature, but a trend favoring Dato-DXd was observed.

Data cut-off: July 17, 2023
[a]Information fraction; 39%.
Bardia A et al. Presented at: ESMO; October 20-24, 2023; Madrid, Spain. Abstract LBA11.
Abbreviations available in slide notes.

TROPION-Breast01: Overall Safety Summary[1,2]

TRAEs, n (%)	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)

- Median treatment duration was **6.7** months with Dato-DXd and **4.1** months with ICC[1]
- Most common TRAEs leading to dose interruption:[2]
  - Dato-DXd: fatigue[a], infusion-related reaction, ILD, stomatitis (each 1%)
  - ICC: neutropenia[b] (17%), leukopenia[c] (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

In TROPION-Breast01, the overall safety profile of Dato-DXd was manageable, with no new safety signals.

Data cut-off: July 17, 2023

[a]Fatigue includes the preferred terms of fatigue, asthenia, and malaise; [b]Neutropenia includes the preferred terms neutropenia and neutrophil count decreased; [c]Leukopenia includes the preferred terms of white blood cell count decreased and leukopenia.

1. Bardia A et al. Presented at: ESMO; October 20-24, 2023; Madrid, Spain. Abstract LBA11. **2.** Bardia A et al. Presented at: SABCS; December 5-9, 2023; San Antonio, TX. Abstract GS02-01.

Abbreviations available in slide notes.

TROPION-Breast01: TRAEs Occurring in ≥15% of Patients and AESIs

System Organ Class Preferred term, n (%)	Dato-DXd (n=360)		ICC (n=351)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Blood and lymphatics system				
Anemia	40 (11)	4 (1)	69 (20)	7 (2)
Neutropenia[a]	39 (11)	4 (1)	149 (42)	108 (31)
Eye disorders				
Dry eye	78 (22)	2 (1)	27 (8)	0 (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 (0)	32 (9)	0 (0)
General				
Fatigue	85 (24)	6 (2)	64 (18)	7 (2)
Skin and subcutaneous				
Alopecia	131 (36)	0 (0)	72 (21)	0 (0)

- Most TRAEs were grade 1-2 and manageable

AESIs

- Oral mucositis/stomatitis:[b] led to treatment discontinuation in one patient in the Dato-DXd group
- Ocular events:[c] most were dry eye; one patient discontinued treatment in the Dato-DXd group
- Adjudicated treatment-related ILD:[d] rate was low; mainly grade 1/2

Adjudicated treatment-related ILD	Dato-DXd	ICC
All grades, n (%)	9 (3)	0
Grade ≥3, n (%)	2 (1)[e]	0

- Toxicity management guidelines have been implemented across TROPION clinical trials for the management of AESIs associated with Dato-DXd treatment in order to maximize clinical benefit

Data cut-off: July 17, 2023

[a]Neutropenia includes the PTs neutropenia and neutrophil count decreased; [b]Oral stomatitis/mucositis events included PTs of aphthous ulcer, dysphagia, glossitis, mouth ulceration, odynophagia, oral mucosal blistering, oral pain, oropharyngeal pain, pharyngeal inflammation, stomatitis, tongue ulceration; all grade: 59% with Dato-DXd, 17% with ICC; grade 3: 7% with Dato-DXd, 3% with ICC; [c]Ophthalmologic assessments were required at screening, and then every 3 cycles from C1D1 and at end of therapy; ocular events included selected PTs from Corneal Disorder SMQ and select relevant PTs from Eye Disorder SOC; all grade: 49% with Dato-DXd, 23% with ICC; grade 3: 1% with Dato-DXd (one patient with dry eye, one patient with punctate keratitis, and one patient with dry eye and ulcerative keratitis), 0% with ICC; [d]ILD includes events that were adjudicated as ILD and related to use of Dato-DXd or ICC (includes cases of potential ILD/pneumonitis, based on MedDRA v23.0 for the narrow ILD SMQ, selected terms from the broad ILD SMQ, and PTs of respiratory failure and acute respiratory failure); [e]One adjudicated treatment-related grade 5 ILD event: attributed to disease progression by investigator.

Bardia A et al. Presented at: ESMO; October 20-24, 2023; Madrid, Spain. Abstract LBA11.

Abbreviations available in slide notes.

TROPION-Breast01: AEs of Clinical Interest

Neutropenia[a]	Dato-DXd (n=360)	ICC (n=351)
Treatment-related neutropenia[a], 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[b]	1 (0.3)	30 (8)

Stomatitis[c]	Dato-DXd (n=360)	ICC (n=351)
Treatment-related stomatitis[c], 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 was lower and G-CSF use was less common with Dato-DXd compared with standard chemotherapy.**
- **Treatment-related stomatitis was reported in half of patients in the Dato-DXd arm, majority of which were low grade and rarely led to discontinuation.**

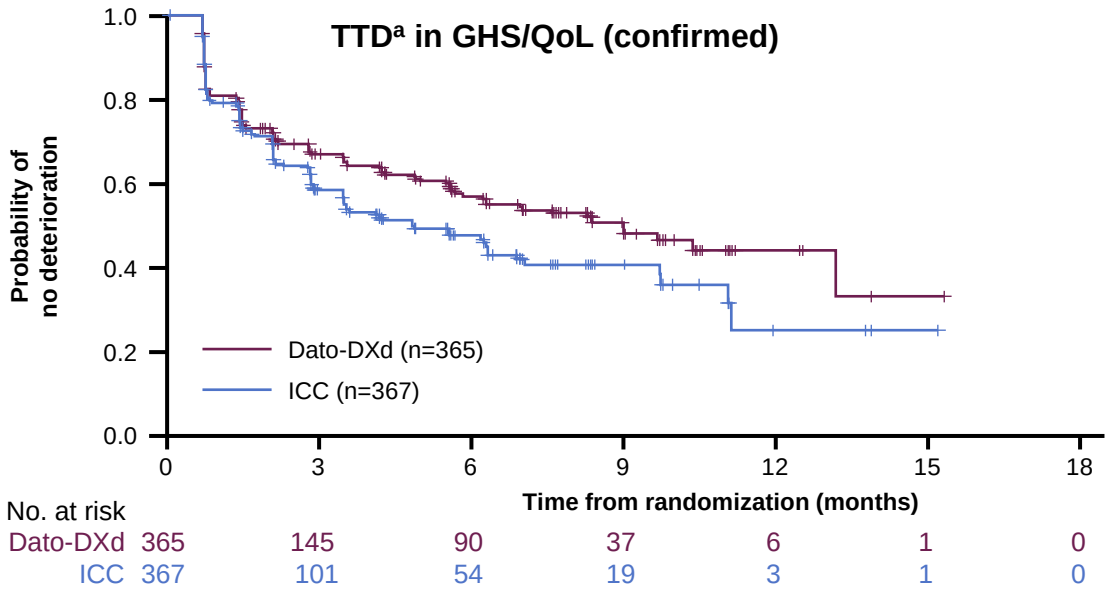
Data cut-off: July 17, 2023

[a]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; [b]Administered after discontinuation of study treatment; [c]As part of the Oral Care Protocol (OCP) 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.

Bardia A et al. Presented at: SABCS; December 5-9, 2023; San Antonio, TX. Abstract GS02-01.

Abbreviations available in slide notes.

TROPION-Breast01: TTD in Global Health Status/Quality of Life



TTD[a]	Median TTD, months (first instance)		Hazard Ratio (95% CI)	Median TTD, months (confirmed)		Hazard Ratio (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)

Time to deterioration (TTD) in global health status/QoL was delayed with Dato-DXd compared with standard chemotherapy (median 9.0 vs 4.8 months).

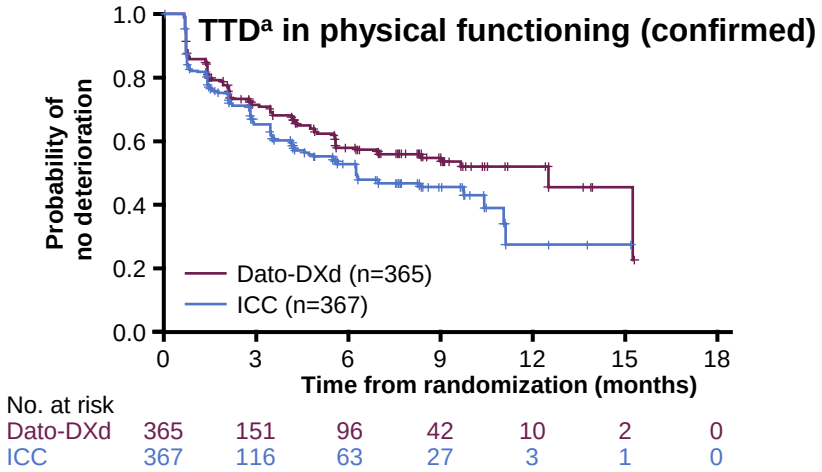
Data cut-off: July 17, 2023

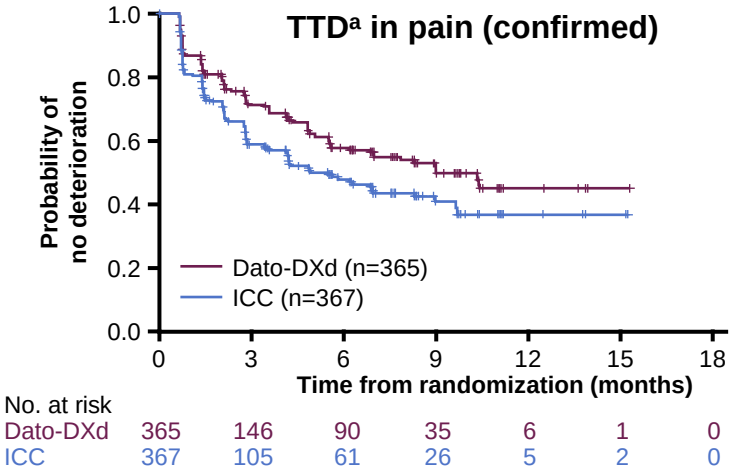
[a] TTD in pain, physical functioning and GHS/QoL are secondary endpoints. The primary analysis was based on time to first deterioration, defined as the time from date of randomization to date of first deterioration. Sensitivity analysis was based on time to confirmed deterioration, which required deterioration 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).

Bardia A et al. Presented at: SABCS; December 5-9, 2023; San Antonio, TX. Abstract GS02-01.

Abbreviations available in slide notes.

TROPION-Breast01: TTD in Physical Functioning and Pain





TTD[a]	Median TTD, months (first instance)		Hazard Ratio (95% CI)	Median TTD, months, (confirmed)		Hazard Ratio (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 physical functioning and pain were delayed in the Dato-DXd arm compared with standard chemotherapy, (median 12.5 vs 6.2 months, and 9.0 vs 5.5 months, respectively).

Data cut-off: July 17, 2023

[a]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).

Bardia A et al. Presented at: SABCS; December 5-9, 2023; San Antonio, TX. Abstract GS02-01.

Abbreviations available in slide notes.

TROPION-Breast01: Summary[1,2]

- TROPION-Breast01 met its dual primary PFS endpoint (July 17, 2023 DCO), demonstrating statistically significant and clinically meaningful improvement in PFS (by BICR) with Dato-DXd compared with ICC (standard chemotherapy)
  - Dato-DXd reduced the risk of progression or death by 37% compared to standard chemotherapy (**Hazard Ratio, 0.63**; 95% CI, 0.52-0.76; p<0.0001; **mPFS 6.9 vs 4.9 months**)
  - Investigator-assessed PFS was consistent with PFS by BICR
  - Consistent PFS benefit was observed across subgroups
  - Higher ORR with Dato-DXd and a trend at interim OS favoring Dato-DXd
- Time to first subsequent therapy (TFST) was prolonged with Dato-DXd compared with ICC
  - TFST was more than 3 months longer with Dato-DXd compared to standard chemotherapy (median 8.2 vs 5.0 months; Hazard Ratio, 0.53; 95% CI, 0.45-0.64)
- The overall safety profile of Dato-DXd was manageable compared with ICC, with no new safety signals observed
  - Patients receiving Dato-DXd had fewer grade ≥3 TRAEs and fewer TRAEs leading to dose reductions or interruption compared with standard chemotherapy
  - Neutropenia was lower (grade ≥3, 1% vs 31%) and G-CSF use was less common with Dato-DXd compared with standard chemotherapy (3% vs 22%)
  - Treatment-related stomatitis was reported in half of patients in the Dato-DXd arm, the majority of which were low grade and manageable
- Time to deterioration (TTD) was delayed in the Dato-DXd arm compared with standard chemotherapy in GHS/QoL (median 9.0 vs 4.8 months), physical functioning (median 12.5 vs 6.2 months), and pain (9.0 vs 5.5 months).

Dato-DXd is a potential new therapeutic option for patients with endocrine-treated metastatic HR+/HER2- (IHC 0, 1+, 2+/ISH-) breast cancer.

Data cut-off: July 17, 2023

1. Bardia A et al. Presented at: ESMO; October 20-24, 2023; Madrid, Spain. Abstract LBA11. **2.** Bardia A et al. Presented at: SABCS; December 5-9, 2023; San Antonio, TX. Abstract GS02-01.

Abbreviations available in slide notes.

TROPION-Breast01: Appendix

TROPION-Breast01: Summary[1-3]

Study summary	The open-label, randomized, parallel, multicenter, international phase 3 study will evaluate efficacy and safety of Dato-DXd compared with ICC (eribulin, capecitabine, vinorelbine, or gemcitabine) in patients with inoperable or metastatic HR positive / HER2 negative breast cancer who have been treated with one or two prior lines of systemic chemotherapy and who have progressed on and are not suitable for endocrine therapy[1-3]
Primary endpoints	PFS assessed by BICR per RECIST v1.1 and OS[1-3]
Actual enrollment	733 patients[1]
Sites	Enrollment began in October 2021 in site across North America, South America, Europe, Africa, Asia[1]
Estimated primary completion date	August 2025[1]

1. Study NCT05104866. ClinicalTrials.gov website. **2.** Bardia A et al. Presented at: ESMO; October 20-24, 2023; Madrid, Spain. Abstract LBA11. 3**.** Bardia A et al. Presented at: SABCS; December 5-9, 2023; San Antonio, TX. Abstract GS02-01.
Abbreviations available in slide notes.

TROPION-Breast01: Endpoints[1-3]

Dual Primary Endpoints	Secondary Endpoints	Exploratory Endpoints

• Progression-free survival assessed by BICR[a]
• Overall survival
	• ORR (CR or PR)[b]
	• DOR[b]
	• DCR at 12 weeks[b]
	• PFS assessed by investigator assessment[a]
	• TTD in pain, physical functioning, and GHS/QoL
	• TFST
	• TSST
	• PFS2
	• PK of Dato-DXd, total anti-TROP2 antibody, and MAAA-1181a (payload)
	• Immunogenicity (presence or absence of ADA)
	• Safety and tolerability
		• Patient-reported Outcomes
		  • PGIC
		  • PGIS
		  • PRO-CTCAE, EORTC, PGI-TT
		  • EORTC QLQ-C30
		  • TTD in breast and arm symptoms
		  • EQ-5D-5L
		• Association of TROP2 or other tumor-derived biomarkers with clinical response and tolerability to Dato-DXd and ICC
		• Association of exploratory biomarkers in tumor, plasma, whole blood, or serum collected before, during treatment or at disease progression with disease status and/or response and tolerability to Dato-DXd
		• Assessment of ctDNA levels and mutational status of cancer-associated genes in ctDNA
		• Impact of treatment and disease on healthcare resource utilization

[a]Assessed per RECIST v1.1. [b]Assessed by BICR and investigator per RECIST v1.1.

1. Study NCT05104866. ClinicalTrials.gov website. **2.** Bardia A et al. Online ahead of print. *Future Oncol*. 2023. **3.** Bardia A et al. Presented at: ESMO; October 20-24, 2023; Madrid, Spain. Abstract LBA11.

Abbreviations available in slide notes.

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TROPION-Breast01: Other Outcomes and Assessments[1,2]

Patient-Reported Outcomes

This study will use the following PRO assessments:

- PGIC
- PGIS
- PRO-CTCAE
- PGI-TT
- EORTC-QLQ-C30
- EORQLQ-C30, 30-item core quality of life questionnaire; TC QLQ-BR45
- EORTC IL116
- EQ-5D-5L

Immunogenicity Assessments

- Whole blood samples for plasma antidrug antibody (ADA) analyses will be collected at specified time points from patients receiving Dato-DXd

Biomarker Assessments

- Tumor tissue for biomarkers including (but not limited to) TROP2 protein and gene expression, TROP2 interacting proteins and topoisomerase I expression, and tumor mutational profile to evaluate their association with the observed clinical responses to Dato-DXd
- Whole blood sample for RNA and DNA to conduct gene expression and mutational analyses to understand immunological changes following treatment with Dato-DXd and to assess gene signatures that may predict treatment response
- ctDNA from blood samples will be analyzed throughout the study to assess changes in tumor mutations in response to treatment
- An optional tumor biopsy will be offered at the time of disease progression which will provide real-time next-generation sequencing (NGS) results from the FoundationOne® CDx. These samples will be used to explore mechanisms of resistance and guide subsequent treatment options.

1. Study NCT05104866. ClinicalTrials.gov website. **2.** In House Data, AstraZeneca Pharmaceuticals LP. CSP D9268C00001 v4.0 (Amendment 3).
Abbreviations available in slide notes.

TROPION-Breast01: Mandatory Pre-treatment Tumor Sample[1-3]

FFPE tumor sample is required at the time of screening

(block preferred, or a minimum of 20 freshly cut slides collected)[a,b]

Tumor sample can be from either the primary disease setting (surgical resection or diagnostic sample), or from a metastatic lesion (excluding bone) for tissue-based analysis (including but not restricted/limited to IHC staining of potential predictive biomarkers as well as tumor mutational analysis).

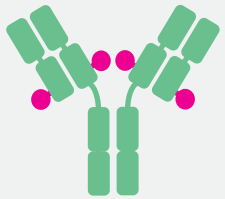
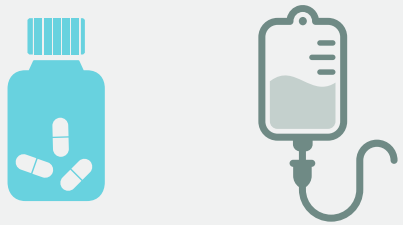
The mandatory FFPE tumor sample submitted for analysis should be obtained as close to the time of diagnosis of metastatic or inoperable disease as possible.

[a]If a block is not available, a minimum of 20 slides freshly prepared, unstained, 4 to 5-micron sections from the archival tumor block; [b]If neither an adequate FFPE block nor the minimum of 20 slides are available, a patient may still be considered eligible. In this situation, approval by the Study Team for patient's entry into the study is required.

1. Study NCT05104866. ClinicalTrials.gov website. **2.** In House Data, AstraZeneca Pharmaceuticals LP. CSP D9268C00001 v4.0 (Amendment 3). **3.** Bardia A et al. Online ahead of print. *Future Oncol*. 2023.

Abbreviations available in slide notes.

TROPION-Breast01: Administration of Dato-DXd and ICC[1-4]

Study Arm	Dose	Administration
Dato-DXd 	Dato-DXd 6 mg/kg IV infusion Day 1 Q3W[a]	• The initial dose of Dato-DXd will be infused over ~90 minutes. • If there is no IRR, subsequent doses will be infused over 30 minutes. In case of IRR at any time during treatment, infusion time should be reduced by 50%
Investigator's Choice of Chemotherapy 	Capecitabine (1000 or 1250 mg/m^2 oral BID on Days 1 to 14, Q3W)[b] Gemcitabine (1000 mg/m^2 IV Days 1 and 8, Q3W) 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)	• Investigators should consult the manufacturer's instructions for complete prescribing information and follow institutional procedures for administration

[a]Premedication is required prior to any dose of Dato-DXd and must include antihistamines and acetaminophen, with and without glucocorticoids. Participants should remain at the site for at least 1-hour post infusion of every dose of Dato-DXd for close observation for possible allergic reaction. [b]Dose wil be determined by standard institutional practice.

1. Study NCT05104866. ClinicalTrials.gov website. **2.** In House Data, AstraZeneca Pharmaceuticals LP. CSP D9268C00001 v4.0 (Amendment 3). **3.** Bardia A et al. Online ahead of print. *Future Oncol*. 2023. **4.** Bardia A et al. Presented at: ESMO; October 20-24, 2023; Madrid, Spain. Abstract LBA11.

Abbreviations available in slide notes.

TROPION-Breast01: Efficacy Assessments Throughout the Study

Imaging Tumor Assessments

- Tumor imaging must include CT (preferred) or MRI of the chest, abdomen, and pelvis[a]
- Brain MRI or CT imaging[b]
- Whole body bone scan[c]

All radiographic scans will be sent to a central imaging vendor for blinded independent central review

PFS2

- Participants will be followed up for time to second progression or death (PFS2) and subsequent anticancer therapy use after intervention discontinuation every 3 months (±14 days) from the date of randomization until death, withdrawal of consent, or the end of the study

Survival Status

- Assessments for survival will be conducted every 3 months (±14 days) following intervention discontinuation until death, withdrawal of consent, or the end of the study

[a]Tumor assessments are being performed every 6 or 9 weeks until RECIST 1.1 disease progression (as assessed by the investigator), regardless of start of subsequent anticancer therapy, with a follow-up scan after disease progression. Screening/baseline imaging should have been performed no more than 28 days before randomization;.[b]Patients randomized with stable brain metastases at baseline have mandatory follow-up brain scans per RECIST 1.1 schedule;-[c]Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI, or X ray should be recorded as NTLs and followed by the same method (CT, MRI, or X-ray).
In House Data, AstraZeneca Pharmaceuticals LP. CSP D9268C00001 v4.0 (Amendment 3).
Abbreviations available in slide notes.

TROPION-Breast01: Prohibited and Permitted Therapies During the Treatment Period

Prohibited Therapies[a]	Permitted Therapies
• **Other anticancer therapy**, including cytotoxic therapy, targeted agents, immunotherapy, antibodies, retinoids, or anticancer hormonal therapy (except topical agents) • **Radiotherapy** (except for palliative radiation to areas other than the chest, after consultation with the Sponsor) • Concomitant **use of chronic systemic (IV or oral) corticosteroids or other immunosuppressive** medications except for managing AEs[b] • Concomitant **chloroquine or hydroxychloroquine** treatment[c]	• **Prophylactic/supportive stomatitis agents** (eg, dexamethasone oral solution) • **Prophylactic antiemetics**, such as 5HT3 or NK1 receptor antagonists and/or steroids (eg, dexamethasone) • **Bisphosphonates, denosumab** for treatment of bone metastasis • **Corticosteroids** if to prevent or treat hypersensitivity reactions to radiographic contrast agents; intranasal and inhaled corticosteroids or systemic corticosteroids at low doses[d] • Concomitant medications or treatments (eg, **acetaminophen or diphenhydramine**) for AE management • **Supportive care**[e]

[a]Use of tobacco products, e-cigarettes, and vaping is strongly discouraged but not prohibited. [b]Concurrent use of inhaled steroids or intra-articular steroid injections are acceptable; [c]If treatment with chloroquine or hydroxychloroquine treatment is absolutely required for COVID-19, study intervention must be interrupted. If chloroquine or hydroxychloroquine is administered, then a washout period of at least 14 days is required before restarting study intervention;
[d]At doses less than 10mg/day of prednisone or equivalent; [e]Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy, etc.]) except for those medications identified as prohibited.
In House Data, AstraZeneca Pharmaceuticals LP. CSP D9268C00001 v4.0 (Amendment 3).
Abbreviations available in slide notes.