2024 ASCO® ANNUAL MEETING

Datopotamab deruxtecan (Dato-DXd) vs chemotherapy in previously-treated inoperable or metastatic hormone receptor-positive, HER2-negative (HR+/HER2–) breast cancer: Patient-reported outcomes (PROs) from the TROPION-Breast01 study

Sonia Pernas,[1] Seock-Ah Im,[2] Masaya Hattori,[3] Binghe Xu,[4] Shusen Wang,[5] Yen-Shen Lu,[6] Guiliano Borges,[7] Junji Tsurutani,[8] Komal L. Jhaveri,[9,10] Qingyuan Zhang,[11] Michelino De Laurentiis,[12] Noelia Martínez Jañez,[13] Erika P. Hamilton,[14] Hope S. Rugo,[15] Kevin Kalinsky,[16] Sara M. Tolaney,[17] Lei Shi,[18] Sabrina Khan,[18] Yanyan Zhu,[18] Aditya Bardia[19]

[1]Institut Catala d'Oncologia, IDIBELL, L'Hospitalet, Barcelona, Spain; [2]Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul National University, Seoul, Republic of Korea; [3]Aichi Cancer Center, Nagoya, Japan; [4]National Cancer Center, National Clinical Research Center for Cancer, Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [5]Cancer Center of Sun Yat-sen University, Guangzhou, China; [6]National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan; [7]Catarina Pesquisa Clinica,Santa Catarina, Brazil; [8]Advanced Cancer Translational Research Institute, Showa University, Tokyo, Japan; [9]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [10]Weill Cornell Medical College, New York, NY, USA; [11]Harbin Medical University Cancer Hospital, Harbin, China; [12]Istituto Nazionale Tumori Napoli IRCCS "Fondazione Pascale", Napoli, Italy; [13]Ramon y Cajal University Hospital, Instituto Ramon y Cajal de Investigacion Sanitaria (IRYCIS), Madrid, Spain; [14]Sarah Cannon Research Institute, Nashville, TN, USA; [15]University of California San Francisco Comprehensive Cancer Center, San Francisco, CA, USA; [16]Winship Cancer Institute at Emory University, Atlanta, GA, USA; [17]Dana-Farber Cancer Institute, Boston, MA, USA; [18]AstraZeneca, Gaithersburg, MD, USA; [19]Johsonn Comprehensive Cancer Center, University of California Los Angeles, Los Angeles, CA, USA (formerly Massachusetts General Hospital Cancer Center, Boston, MA, USA)

Key takeaways

- **PRO data** from the **TROPION-Breast01 study** complemented the improvement in efficacy and manageable safety profile demonstrated with Dato-DXd vs ICC in the primary analysis
  - TTD in GHS/QoL, pain, and physical functioning were delayed in the Dato-DXd arm compared with ICC

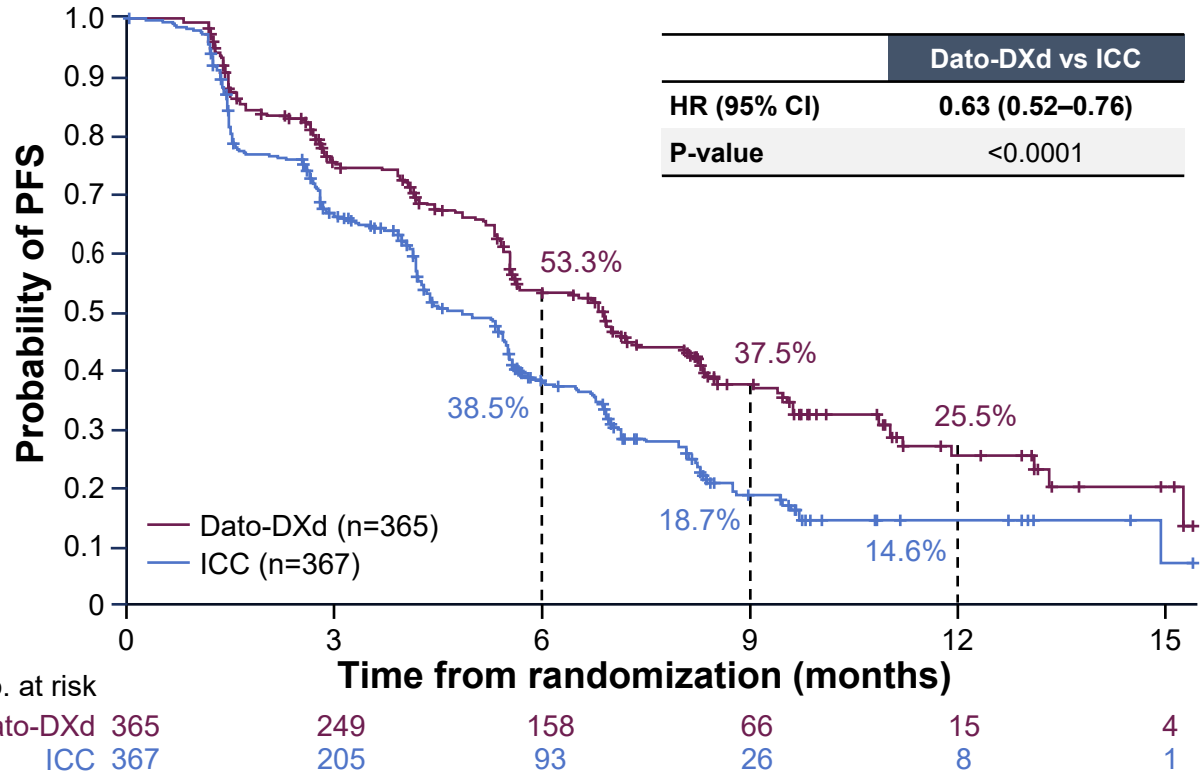
- **PRO data provided evidence directly from the patient's perspective, supporting Dato-DXd as a potential new therapeutic option for patients with metastatic HR+/HER2– breast cancer**

Dato-DXd, datopotamab deruxtecan; GHS/QoL, general health status/quality of life; HER2–, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; ICC, investigator's choice of chemotherapy; PRO, patient-reported outcome; TTD, time to deterioration.

Background

- **Datopotamab deruxtecan (Dato-DXd)** is a **TROP2-directed ADC** that delivers a potent Topo-I inhibitor payload, deruxtecan[1]
- 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 also showed a **favorable and manageable safety profile**, with no new safety signals[2,3]
  - Patients receiving **Dato-DXd had fewer grade ≥3 TRAEs and fewer TRAEs leading to dose interruption/reduction** compared with ICC[2,3]

PFS by BICR: primary endpoint[2]



ADC, antibody-drug conjugate; BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; Topo-I, topoisomerase I; TRAE, treatment-related adverse event; TROP2, trophoblast cell surface antigen 2.

1. Okajima D, et al. Mol Cancer Ther 2021;20:2329–40;
2. Bardia A, et al. Oral presentation at SABCS 2023 (Abstract GS02–01);
3. Jhaveri K, et al. Oral presentation at ESMO Breast 2024 (Abstract LBA2).

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

Randomization 1:1

Stratified by:

Lines of chemotherapy (1 vs 2)

Geographic location (US/Canada/Europe vs other geographic regions)

Previous CDK4/6 inhibitor (yes vs no)

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)

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

Endpoints:

- **Dual primary:** PFS by BICR per RECIST v1.1, and OS
- **Secondary endpoints included:** ORR, PFS (investigator assessed), TFST, safety, **PROs**
- **Exploratory PRO endpoints**

Here we report detailed results from secondary and exploratory PRO endpoints

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; ORR, overall response rate; OS, overall survival; PD, progressive disease; Q3W, every 3 weeks; RCT, randomized control trial; RECIST, Response Evaluation Criteria in Solid Tumors; TFST, time to first subsequent therapy; US, United States.

1. Bardia A, et al. Future Oncol 2023;20:423–36.

PRO endpoints in TROPION-Breast01

- PRO is an umbrella term and may include patient-reported disease- and treatment-related symptoms, functioning, and health-related quality of life (HRQoL)[1]
- In this study, **global health status/quality of life (GHS/QoL), pain,** and **physical functioning** were selected as core outcomes for **the secondary endpoints**, given the following considerations:

GHS/QoL measures overall HRQoL, which is important in evaluating the clinical benefit of cancer therapies, especially in non-curative settings[2]

Pain is a frequently reported disease symptom that can impact functioning and HRQoL in participants with HR+/HER2– advanced breast cancer[3]

Physical functioning is a core PRO of cancer therapy that evaluates the impact of disease- and treatment-related symptoms on performing daily activities[4,5]

- **Exploratory PRO endpoints** included:
  - Other patient-reported symptoms and functioning
  - Patient-reported symptomatic AEs
  - Patient-reported treatment tolerability

AE, adverse event; HRQoL, health-related quality of life.

1. Mercieca-Bebber R, et al. Patient Relat Outcome Meas 2018;9:353–67; 2. Oosting SF, et al. Ann Oncol 2023;34(4):431–9; 3. Galipeau N, et al. J Patient Rep Outcomes 2019;3:10; 4. Kleutz PG, et al. Clin Cancer Res 2016;22:1553–8; 5. FDA Core Patient-Reported Outcomes in Cancer Clinical Trials, Draft Guidance for Industry; 2021. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/core-patient-reported-outcomes-cancer-clinical-trials [Accessed May 2024].

PRO assessments

PROs were assessed at baseline and throughout the study via electronic PRO questionnaires*

Secondary PRO endpoints were measured by EORTC QLQ-C30

- **Compliance with EORTC QLQ-C30** was 82.5% at baseline in both arms and **declined but remained similar across arms** over time (80.6% vs 81.0% at Week 12 and 74.9% vs 81.4% at Week 24 for Dato-DXd and ICC, respectively)
- Time to deterioration (TTD) in **GHS/QoL, pain, and physical functioning** were defined as follows:
  - Time to **first deterioration (primary analysis**): defined as the time from date of randomization to the date of first deterioration based on derived meaningful change thresholds (16.6 for GHS/QoL and pain, and 13.3 for physical functioning)[1]
  - Time to **confirmed deterioration (sensitivity analysis):** required deterioration to be confirmed at a subsequent timepoint

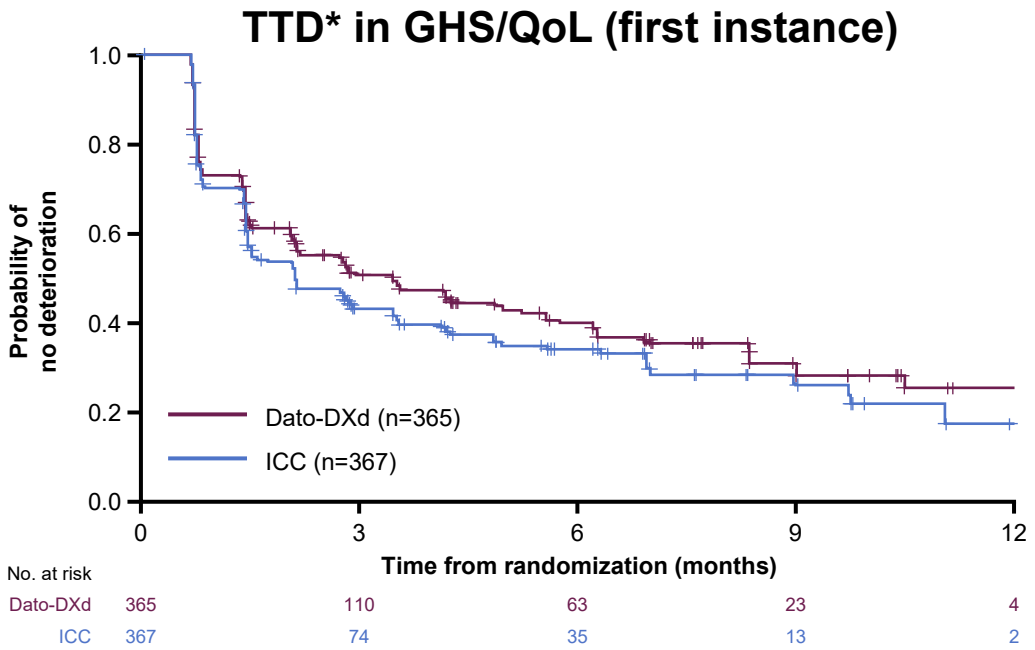
Exploratory PRO endpoints

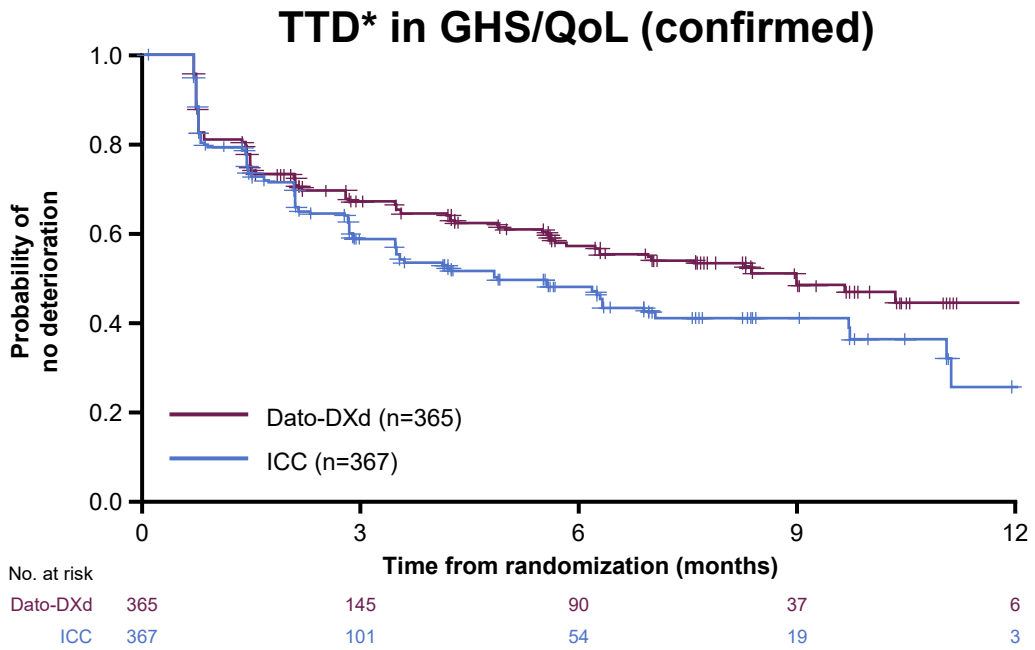
- TTD in other symptoms and functioning were measured using EORTC QLQ-C30 and IL116 (a subset of QLQ-BR45†)
- Patient-reported symptomatic AEs were measured using selected items of PRO-CTCAE and EORTC IL117
- Patient-reported treatment tolerability was measured using PGI-TT

*Schedule of assessments was as follows: On C1D1, Q3W for the first 48 weeks, Q6W until EoT, at EoT, and then Q6W until 18 weeks after disease progression for EORTC QLQ-C30/IL116, and on C1D1, weekly for the first 12 weeks, then Q3W until EoT for PRO-CTCAE, EORTC IL117 and PGI-TT; †Only arm and breast symptom scales were used from the EORTC QLQ-BR45
C1D1, Cycle 1 Day 1; EORTC, European Organisation for Research and Treatment of Cancer; EoT, end of treatment; PGI-TT, Patient's Global Impression of Treatment Tolerability; PRO-CTCAE, Patient-reported Outcomes version of the Common Terminology Criteria for Adverse Events; QLQ-BR45, 45-item quality of life questionnaire for breast cancer symptoms; QLQ-C30, 30-item core quality of life questionnaire; Q6W, every 6 weeks.

1. Zhu Y, et al. ISPOR 2024. (Abstract PCR50).

TTD in GHS/QoL was longer with Dato-DXd vs ICC

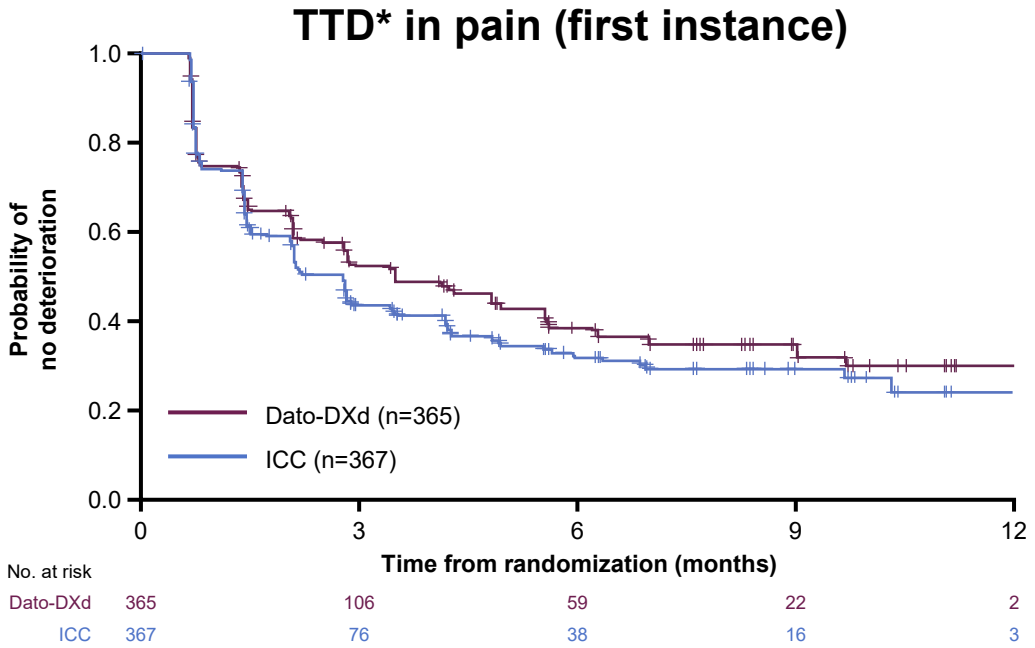


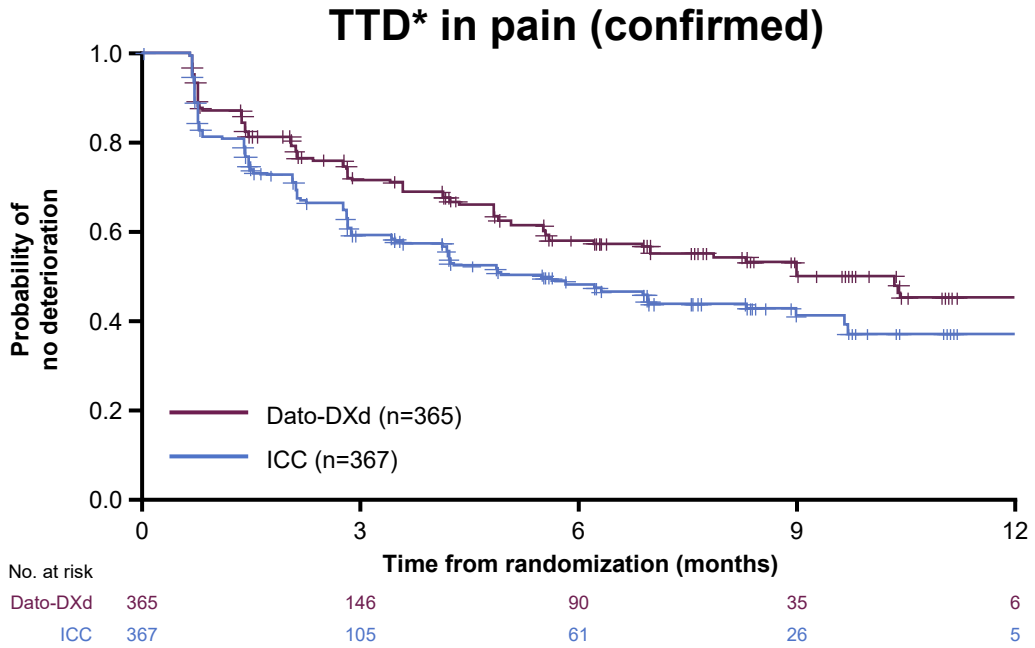


TTD*	Median TTD, months (first instance)		HR (95% CI)	Median TTD, months (confirmed)		HR (95% CI)
	Dato-DXd	ICC		Dato-DXd	ICC	
GHS/QoL	3.4	2.1	0.85 (0.68–1.06)	9.0	4.8	0.76 (0.58–0.98)

*TTD in GHS/QoL, pain, and physical functioning are secondary endpoints and were measured using EORTC QLQ-C30. Time to first deterioration (primary analysis) was defined as the time from date of randomization to date of first deterioration. Time to confirmed deterioration (sensitivity analysis) required deterioration to be confirmed at a subsequent timepoint. Deterioration was defined as a change from baseline that reached a clinically meaningful deterioration threshold of 16.6.

TTD in pain was longer with Dato-DXd vs ICC

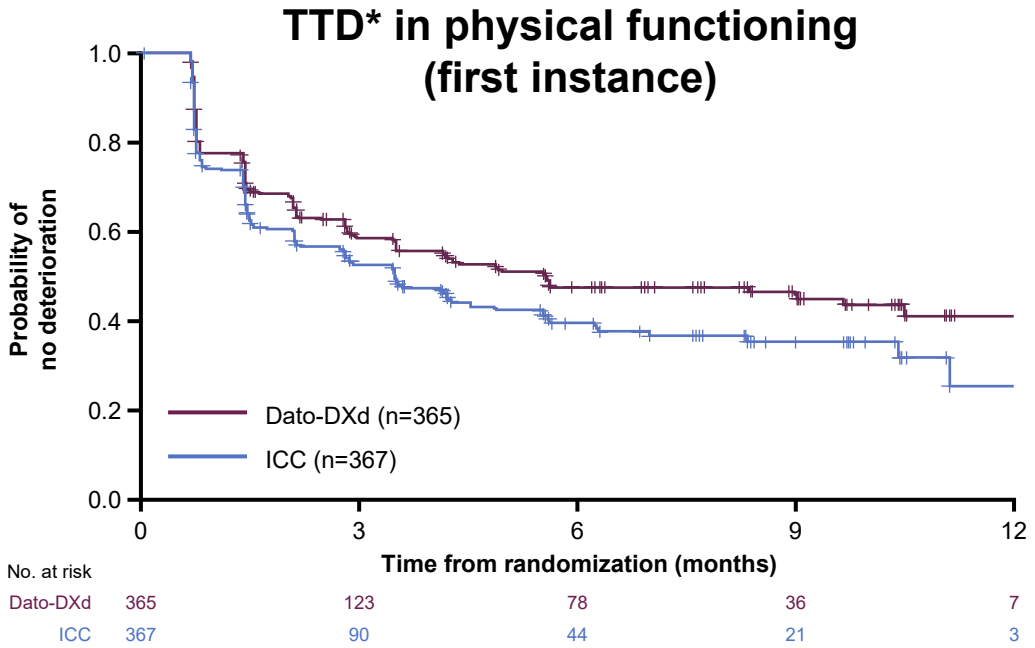


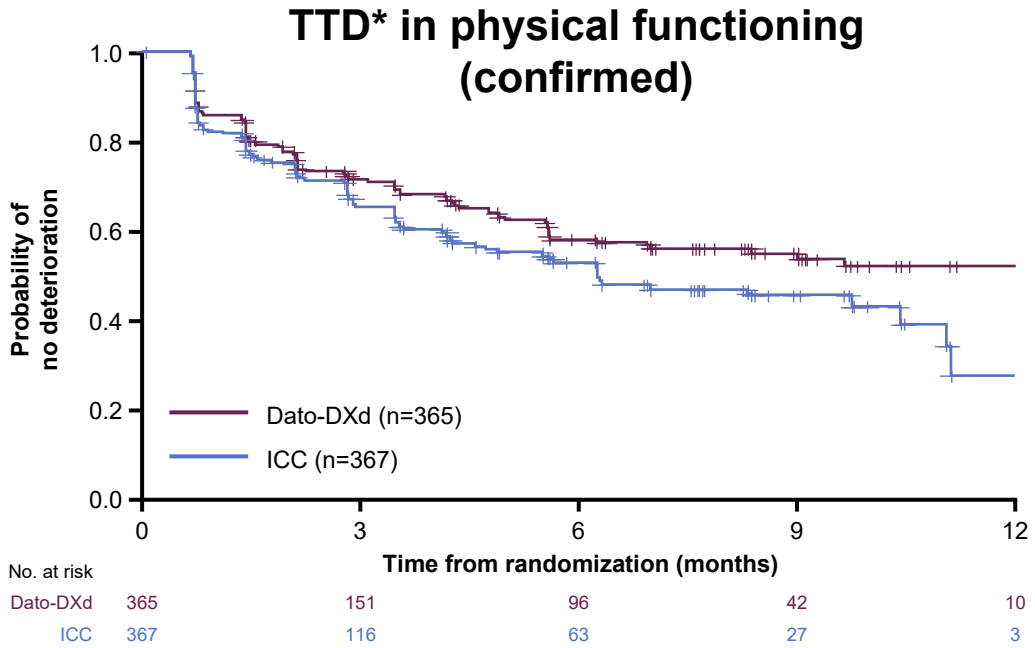


TTD*	Median TTD, months (first instance)		HR (95% CI)	Median TTD, months (confirmed)		HR (95% CI)
	Dato-DXd	ICC		Dato-DXd	ICC	
Pain	3.5	2.8	0.85 (0.68–1.07)	9.0	5.5	0.72 (0.55–0.94)

*TTD in GHS/QoL, pain, and physical functioning are secondary endpoints and were measured using EORTC QLQ-C30. Time to first deterioration (primary analysis) was defined as the time from date of randomization to date of first deterioration. Time to confirmed deterioration (sensitivity analysis) required deterioration to be confirmed at a subsequent timepoint. Deterioration was defined as a change from baseline that reached a clinically meaningful deterioration threshold of 16.6.

TTD in physical functioning was longer with Dato-DXd vs ICC





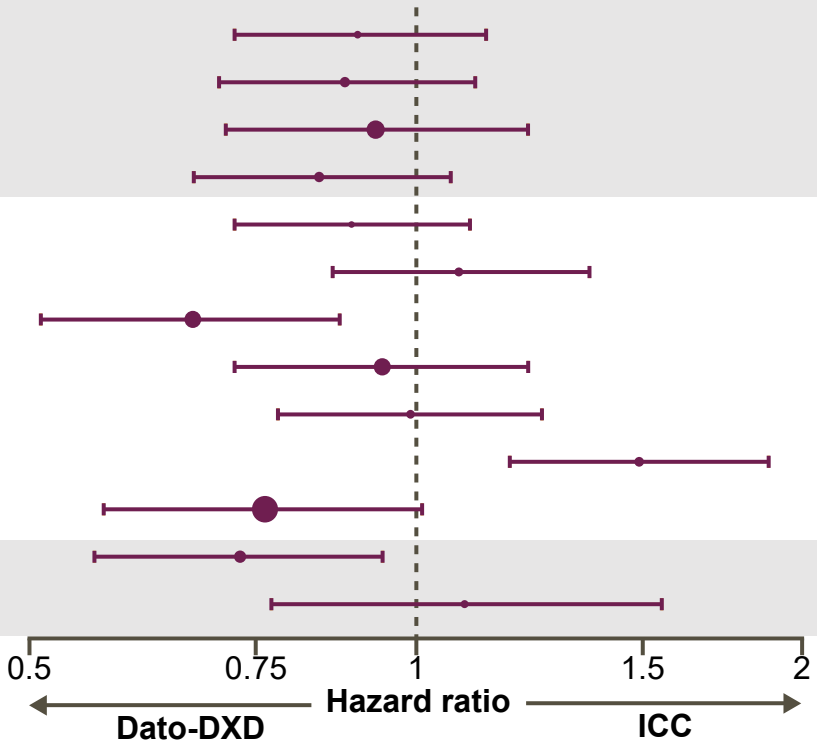
TTD*	Median TTD, months (first instance)		HR (95% CI)	Median TTD, months (confirmed)		HR (95% CI)
	Dato-DXd	ICC		Dato-DXd	ICC	
Physical functioning	5.6	3.5	0.77 (0.61–0.99)	12.5	6.2	0.77 (0.59–1.01)

*TTD in GHS/QoL, pain, and physical functioning are secondary endpoints and were measured using EORTC QLQ-C30. Time to first deterioration (primary analysis) was defined as the time from date of randomization to date of first deterioration. Time to confirmed deterioration (sensitivity analysis) required deterioration to be confirmed at a subsequent timepoint. Deterioration was defined as a change from baseline that reached a clinically meaningful deterioration threshold of 13.3.

TTD in other symptoms and functioning
(exploratory endpoint)

TTD* (first instance) was in favor of the Dato-DXd arm for the majority of functioning and symptoms scales

		Median TTD (months)		HR (95% CI)
		Dato-DXd (N=365)	ICC (N=367)	
Functioning (EORTC QLQ-C30)	Role	2.8	2.1	0.90 (0.72–1.13)
	Cognitive	3.0	2.8	0.88 (0.70–1.11)
	Emotional	7.0	6.3	0.93 (0.71–1.22)
	Social	3.4	2.1	0.84 (0.67–1.06)
Symptoms (EORTC QLQ-C30)	Fatigue	1.6	1.4	0.89 (0.72–1.10)
	Nausea/Vomiting	2.9	3.4	1.08 (0.86–1.36)
	Dyspnea	8.4	4.9	0.67 (0.51–0.87)
	Insomnia	7.0	6.2	0.94 (0.72–1.22)
	Appetite Loss	2.9	2.8	0.99 (0.78–1.25)
	Constipation	2.2	4.2	1.49 (1.18–1.88)
	Diarrhea	11.1	9.7	0.76 (0.57–1.01)
Symptoms (EORTC IL116†)	Arm	6.9	2.9	0.73 (0.56–0.94)
	Breast	NR	NR	1.09 (0.77–1.55)

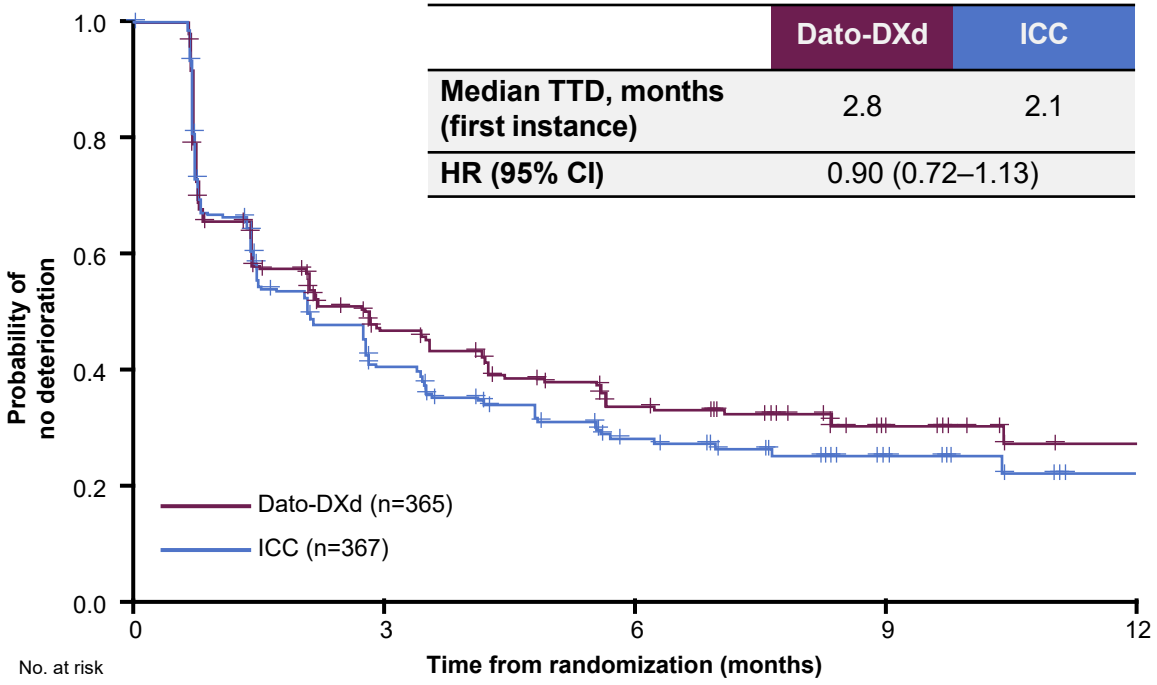


*Time to first deterioration (primary analysis) was defined as the time from date of randomization to date of first deterioration. Deterioration was defined as a change from baseline that reaches a clinically meaningful deterioration threshold;
†EORTC IL116 is a subscale of the EORTC QLQ-BR45, from which only arm and breast symptoms were used.

TTD in role functioning and fatigue

TTD* in role functioning (first instance)

	Dato-DXd	ICC
Median TTD, months (first instance)	2.8	2.1
HR (95% CI)	0.90 (0.72–1.13)	

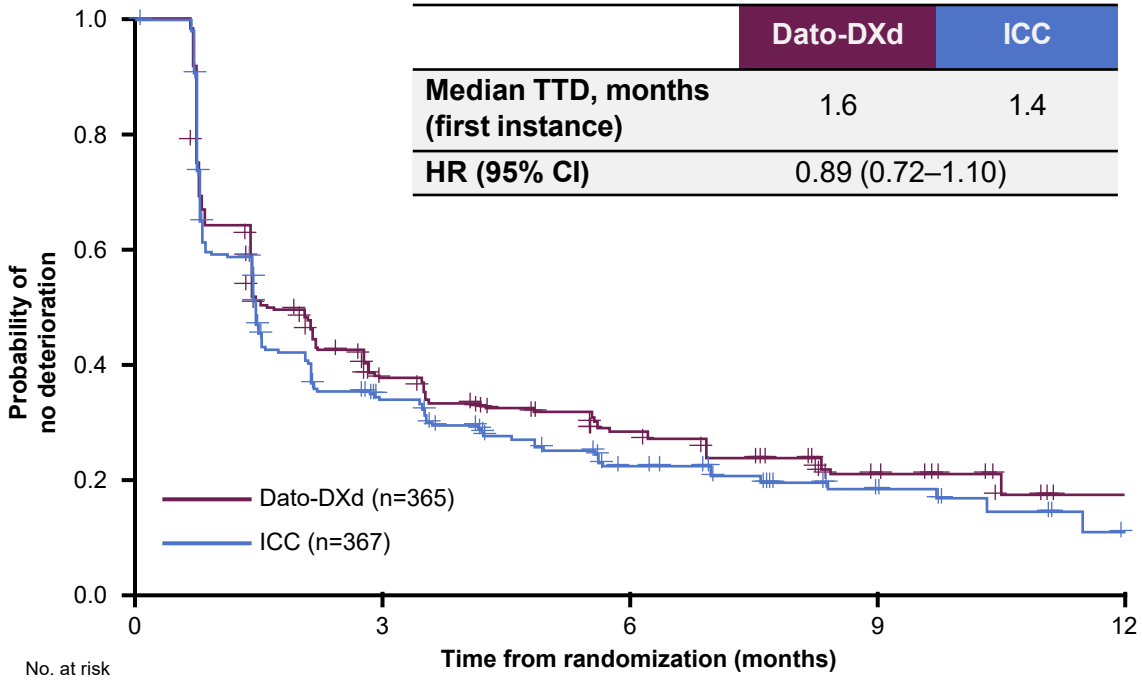


No. at risk

Dato-DXd	365	94	53	19	4
ICC	367	70	34	16	3

TTD* in fatigue (first instance)

	Dato-DXd	ICC
Median TTD, months (first instance)	1.6	1.4
HR (95% CI)	0.89 (0.72–1.10)	



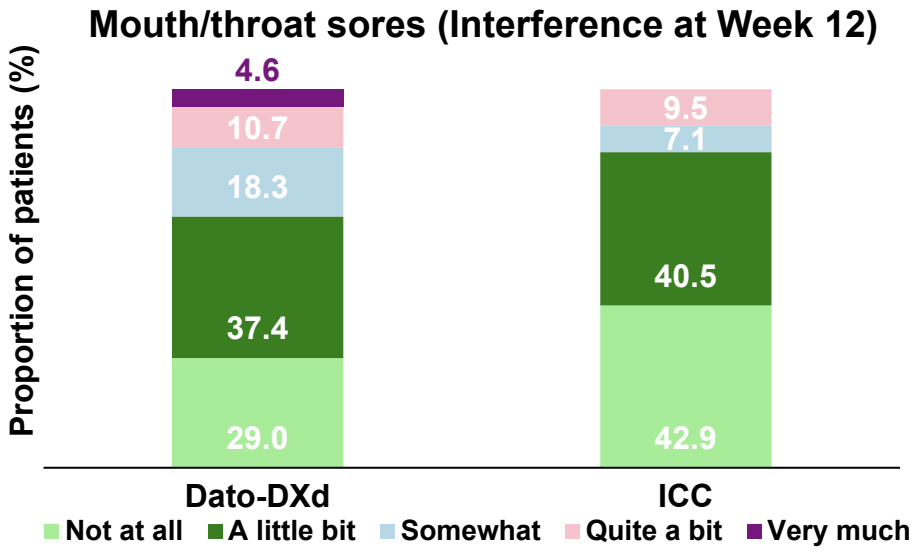
No. at risk

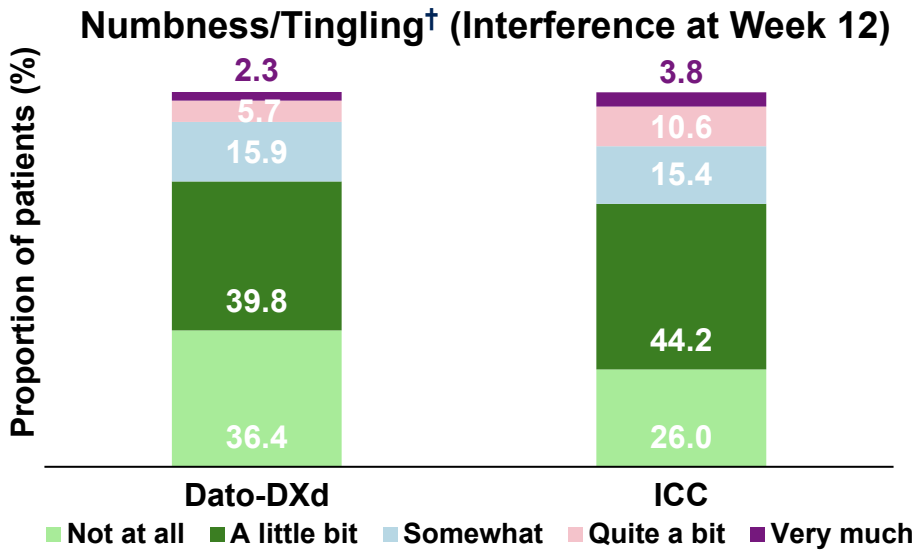
Dato-DXd	365	81	47	15	1
ICC	367	63	30	13	2

*TTD in role functioning and fatigue were exploratory endpoints and were measured using EORTC QLQ-C30. Time to first deterioration (first instance) was defined as the time from date of randomization to date of first deterioration. Deterioration was defined as a change from baseline that reached a clinically meaningful deterioration threshold.

Limited interference from patient-reported symptomatic AEs

- Interference from AEs of clinical interest was assessed; **limited interference affecting patients' daily activities** was observed among those who reported the symptoms*





- **Patient-reported symptomatic AEs‡ were generally consistent with clinician-reported safety data.** Asymptomatic AEs may not be captured by PROs
- **Additionally, patient-reported treatment tolerability** (measured by the PGI-TT questionnaire: "in the last 7 days, how bothered were you by the side effects of your cancer treatment?") showed most patients were bothered 'not at all' or 'a little bit'

*Interference was assessed for mouth/throat sores, decreased appetite, abdominal pain, shortness or breath, cough, numbness/tingling, and fatigue; †Baseline numbness and tingling causing interference was reported in both arms;
‡Patient-reported symptomatic AEs were measured using select items from PRO-CTCAE and EORTC IL117.

Conclusions

- PRO data complemented the improvement in efficacy and manageable safety profile demonstrated with Dato-DXd vs ICC in the primary analysis
  - TTD in GHS/QoL, pain, and physical functioning were delayed in the Dato-DXd arm compared with ICC
  - TTD was in favor of the Dato-DXd arm for the majority of functioning and symptoms scales
  - Patient-reported symptomatic AEs were generally consistent with clinician-reported safety data, without showing major impact on patients' functioning and HRQoL
- Despite the possibility of potential bias in an open-label trial there is no evidence of significant bias for PROs

In conclusion, PRO data provided evidence directly from the patient's perspective, supporting Dato-DXd as a potential new therapeutic option for patients with metastatic HR+/HER2– breast cancer

Future directions

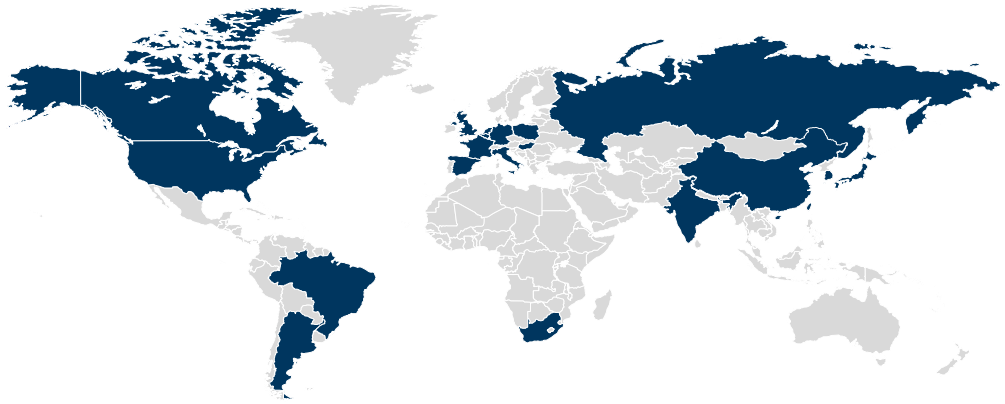
- PRO data will continue to be analyzed based on future data-cut offs with **longer follow-up periods,** including **time to confirmed deterioration for exploratory endpoints**
- **Long-term safety data** for TROPION-Breast01 will continue to be monitored
- Further phase 3 studies are now in progress evaluating Dato-DXd in **other breast cancer settings**, including **early and metastatic triple-negative breast cancer**, either **as monotherapy or in combination** with durvalumab

Acknowledgements

- The authors would like to particularly thank:
  - Patients
  - Families and caregivers
  - TROPION-Breast01 investigators and site personnel

- TROPION-Breast01 (NCT05104866) is sponsored by AstraZeneca. In July 2020, Daiichi-Sankyo entered into a global development and commercialization collaboration with AstraZeneca for Dato-DXd

- Medical writing support for the development of this presentation, under the direction of the authors, was provided by Ella Spencer and Helen Kitchen of Ashfield MedComms (Macclesfield, UK), an Inizio Company, and was funded by AstraZeneca



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

Scan the QR code or visit the link:

- To obtain a copy of these slides
- To access a plain language summary

https://bit.ly/4aPJzPb

Datopotamab deruxtecan (Dato-DXd) vs chemotherapy in previously-treated inoperable or metastatic hormone receptor-positive, HER2-negative (HR+/HER2–) breast cancer: Patient-reported outcomes (PROs) from the TROPION-Breast01 study

Plain Language Summary

Why did we perform this research?

- TROPION-Breast01 was a phase 3 clinical research study in which a new treatment, called Datopotamab deruxtecan (Dato-DXd), was studied. Dato-DXd is a drug that consists of datopotamab (an antibody) joined to an anticancer drug (deruxtecan)
- Patients in the TROPION-Breast01 study had a specific type of breast cancer, with tumors that were hormone receptor positive and classified as HER2 negative (HR+/HER2–) and could not be removed with surgery. Patients included in the study also:
  - Had previous treatment with chemotherapy
  - Had cancer that continued to grow despite hormonal therapy
  - Were not able to take hormonal therapy again
- Previous results from TROPION-Breast01 showed that the time from starting treatment to the cancer getting worse or death (progression-free survival) was longer in patients who received Dato-DXd than in patients who received chemotherapy. They also showed that the type of side effects seen were typical of Dato-DXd treatment and could be managed[1]
- It was also important to understand how the patients in the study felt and functioned by asking them directly. This summary focuses on the patient-reported outcomes (PROs) questionnaire results from TROPION-Breast01

How did we perform this research?

- Patients in the TROPION-Breast01 study completed electronic PRO questionnaires before the start of the study treatments and throughout the study
- The PRO questionnaires asked about things such as quality of life, what symptoms they had, and how they were finding doing daily activities
- The information collected from the PRO questionnaires were summarized to help understand the effect of the different treatments on patients' quality of life

What were the findings of this research?

- The TROPION-Breast01 research team looked at time to deterioration (TTD) in quality of life/global health status, pain, physical functioning, and other symptoms and functioning
- Time to deterioration (TTD) means the amount of time it takes something to worsen
  - Overall quality of life decreased more slowly for patients who received Dato-DXd treatment when compared with the patients who received chemotherapy treatment
  - Specifically, it took a longer time for quality of life/global health status, pain, physical functioning, and other symptoms and functioning to get worse
  - Side effects of the treatments in TROPION-Breast01 that were described by patients were similar to the side effect profile reported by doctors
  - Patients' perspectives of how much they were bothered by the side effects were also similar for patients who received Dato-DXd and patients who received chemotherapy

What are the implications of this research?

- The TROPION-Breast01 PRO questionnaire results provide direct information about the perspectives of the patients who received the treatments in this study
- These results support the use of Dato-DXd as a potential new treatment option with a manageable safety profile for patients with HR+/HER2– breast cancer

1. Bardia A, et al. Ann Oncol 2023;34(suppl_2):S1264–5.