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Dato-DXd vs chemotherapy for patients with inoperable/metastatic HR+/HER2– breast cancer: TROPION-Breast01 East Asian subset analysis

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Declaration of interests

- **Junji Tsurutani** has the following disclosures:
  - Acted as an invited speaker and participated in clinical trial advisory boards for Daiichi-Sankyo, AstraZeneca, Eisai
  - Provided expert testimony on behalf of Daiichi-Sankyo
  - Received funding from Daiichi-Sankyo, Eisai, FSJD, WJOG
  - Acted as a Principal Investigator for Daiichi-Sankyo, Eisai, Seagen, Taiho, Eli Lilly, MSD, Oncotherapy

Background

- **Chemotherapy** is utilized 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 the unmet need for new therapeutic options in this setting[1–5]
- **Dato-DXd** is a **TROP2-directed ADC**, composed of a humanized anti-TROP2 IgG1 mAb attached to a Topo-I inhibitor payload via a plasma-stable, tumor-selective, tetrapeptide-based cleavable linker[6,7]
- **Primary results** from the Phase 3 **TROPION-Breast01** study presented at ESMO 2023 demonstrated:[8]
  - **Statistically significant and clinically meaningful improvement in PFS by BICR with Dato-DXd vs ICC**: median 6.9 vs 4.9 months; 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 vs 22.9% in the ICC arm
- Here, we present **efficacy** and **safety** data from patients in TROPION-Breast01 enrolled in **East Asia** (Japan, China, South Korea, and Taiwan)

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; IgG1, immunoglobulin G1; mAb: monoclonal antibody; MBC, metastatic breast cancer; ICC, investigator's choice of chemotherapy; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; 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;32:1475–95;
3. Moy B, et al. *J Clin Oncol* 2021;39:3938–58;
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. Nakada T, et al. *Chem Pharm Bull (Tokyo)* 67:173–185, 2019
8. 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

R

Dato-DXd
6 mg/kg IV D1 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

Here, we present an exploratory analysis of 273 patients recruited in East Asia:

- Dato-DXd: n=134
- ICC: n=139

Comprising patients recruited from:

- Japan: n=70
- China: n=83
- South Korea: n=82
- Taiwan: n=38

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] Total N randomized in the ITT population was 732.
*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; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; IHC, immunohistochemistry; ISH, in-situ hybridization; ITT, intention-to-treat population; IV, intravenous; PD, progressive disease; Q3W, every 3 weeks; R, randomization; RECIST, Response Evaluation Criteria In Solid Tumors; ROW, rest of world.

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

Patient disposition

Dato-DXd	ITT	East Asian subset
Randomized, n	365	**134***
Ongoing study treatment, n	93	**36**
Discontinued study treatment, n	267	**94**
Progressive disease	229	82
Adverse event	11	4
Patient decision	13	5
Death	2	0
Other	12	3

ICC	ITT	East Asian subset
Randomized, n	367	**139*†**
Ongoing study treatment, n	39	**16**
Discontinued study treatment, n	312	**119**
Progressive disease	240	94
Adverse event	10	1
Patient decision	32	18
Death	7	2
Other	23	4

- In the ITT population, 1003 patients were screened, of whom 732 were randomized
- In the East Asian subset, 343 patients were screened, of whom 273 were randomized

Data cut-off: 17 July 2023.
*In the East Asian subset, 130 and 135 patients received treatment with Dato-DXd and ICC, respectively.
†In the East Asian subset, patients received the following ICC treatments: eribulin mesylate (n=76); capecitabine (n=39); gemcitabine (n=13); vinorelbine (n=11).

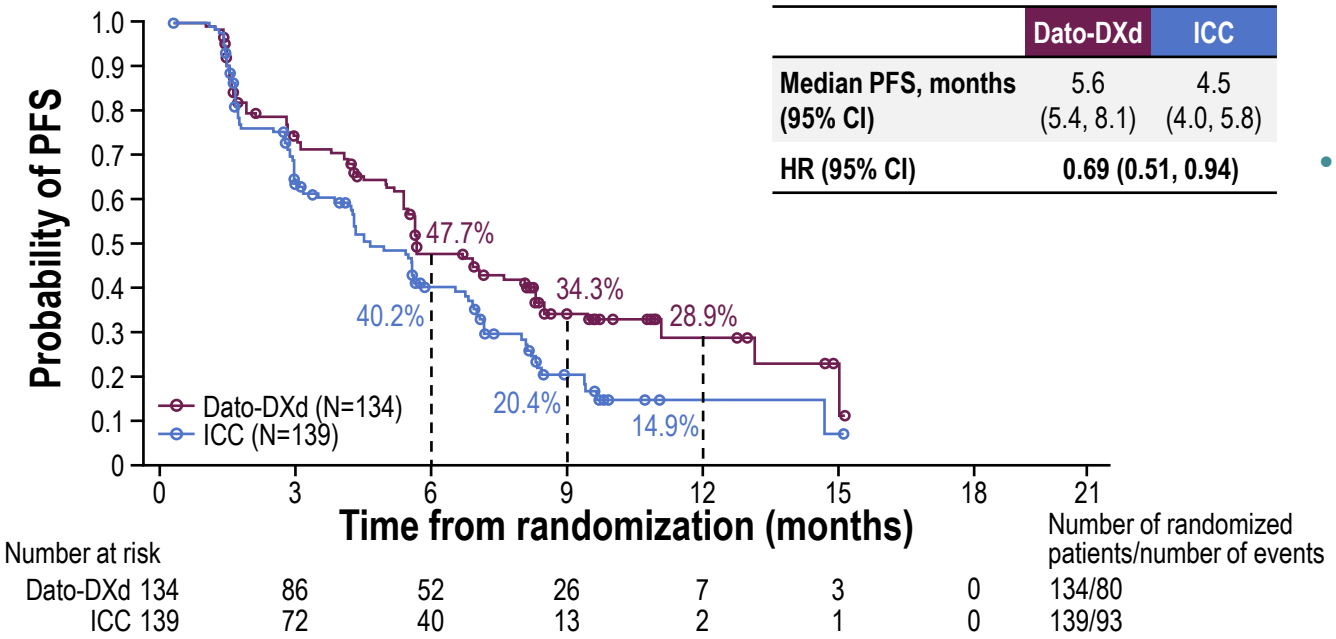
Demographics and baseline characteristics

	Dato-DXd		ICC	
	ITT (n=365)	East Asia (n=134)	ITT (n=367)	East Asia (n=139)
Age, median (range), years	56 (29–86)	54 (29–83)	54 (28–86)	52 (33–79)
Female, n (%)	360 (98.6)	134 (100)	363 (98.9)	139 (100)
Race, n (%)				
Asian	146 (40.0)	134 (100)	152 (41.4)	138 (99.3)
Other	219 (60.0)	0	215 (58.6)	1 (0.7)
Overall disease classification,* n (%)				
Locally advanced or inoperable	9 (2.5)	1 (0.7)	2 (0.5)	0
Metastatic†	356 (97.5)	133 (99.3)	365 (99.5)	139 (100)
Prior lines of chemotherapy, n (%): 1 / 2+	229 (62.7) / 135 (37.0)	87 (64.9) / 47 (35.1)	225 (61.3) / 141 (38.4)	90 (64.7) / 49 (35.3)
Prior CDK4/6 inhibitors, n (%)	304 (83.3)	108 (80.6)	300 (81.7)	111 (79.9)
Prior taxanes / anthracyclines, n (%)	295 (80.8) / 228 (62.5)	117 (87.3) / 82 (61.2)	296 (80.7) / 239 (65.1)	117 (84.2) / 87 (62.6)

Data cut-off: 17 July 2023.
*Metastatic disease is for patients with any metastatic site of disease. Locally advanced is for patients with only locally advanced sites of disease. †Of the patients with metastatic disease, most had visceral metastasis: ITT: 352/356 patients in the Dato-DXd arm, 360/365 in the ICC arm: East Asian subset: 133/133 in the Dato-DXd arm, 138/139 in the ICC arm.

Progression-free survival

PFS by BICR: East Asian subset (non-stratified, exploratory analysis)



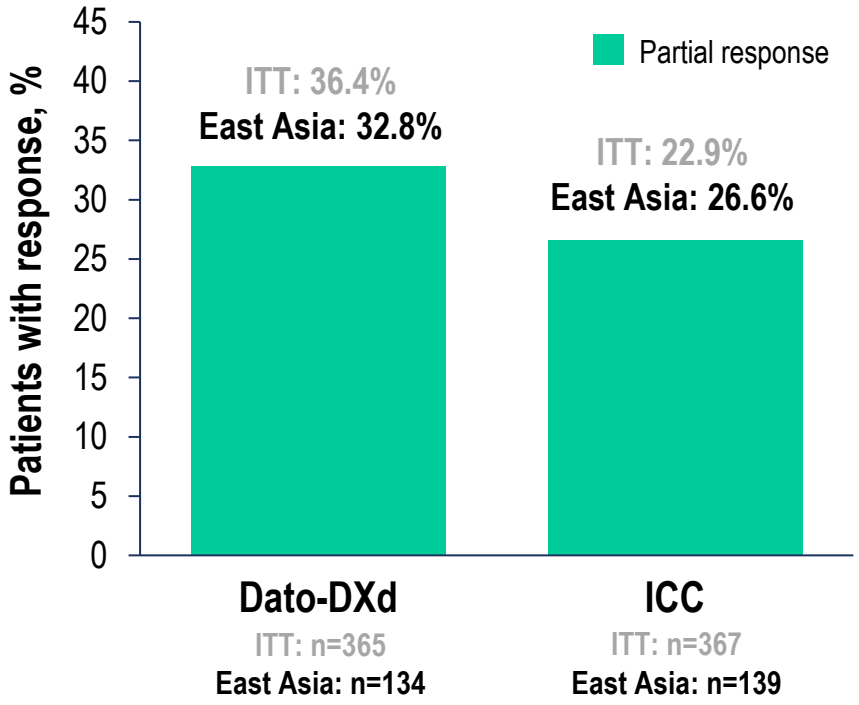
	Dato-DXd	ICC
Median PFS, months (95% CI)	5.6 (5.4, 8.1)	4.5 (4.0, 5.8)
HR (95% CI)	**0.69 (0.51, 0.94)**	

- **PFS by BICR – ITT population:** median 6.9 vs 4.9 months; HR 0.63 (95% CI: 0.52, 0.76)
- **PFS by investigator assessment – East Asian subset:** median 6.8 vs 4.5 months; HR 0.64 (95% CI: 0.48, 0.84)

Data cut-off: 17 July 2023.

Response and interim OS: East Asian subset

Confirmed ORR by BICR



OS: Dual primary endpoint

- **OS data not mature**:
  - ITT: median follow-up 9.7 months
  - East Asia: median follow-up 10.1 months
- OS at 6 months in the East Asian subset:
  - **91.5%** in the Dato-DXd arm
  - **89.6%** in the ICC arm
- The study is **continuing** to the next planned analysis for OS

Data cut-off: 17 July 2023.

Overall safety summary: East Asian subset

Events, n (%)	Dato-DXd (n=130)		ICC (n=135)	
TRAEs	124 (95.4)		114 (84.4)	
Grade ≥3	27 (20.8)		71 (52.6)	
TEAEs with outcome of:				
Death	0		0	
Discontinuation of study drug	4 (3.1)		1 (0.7)	
Dose reduction of study drug	19 (14.6)		44 (32.6)	
Dose interruption of study drug	34 (26.2)		43 (31.9)	
Serious TEAEs	14 (10.8)		21 (15.6)	
AESIs	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
ILD adjudicated as drug-related*	5 (3.8)	2 (1.5)†	0	0

Data cut-off: 17 July 2023.
*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 v26.0 for the narrow ILD SMQ, selected terms from the broad ILD SMQ, and PTs of respiratory failure and acute respiratory failure). †Of the two events: one adjudicated drug-related Grade 3 ILD; one adjudicated drug-related Grade 5 ILD attributed to disease progression by investigator. ‡Oral mucositis/stomatitis events included PTs of aphthous ulcer, dysphagia, glossitis, mouth ulceration, odynophagia, oral mucosal blistering, oral pain, oropharyngeal pain, pharyngeal inflammation, stomatitis, tongue ulceration. ¶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.
AESI, adverse event of special interest; ILD, interstitial lung disease; PTs, preferred terms; SMQ, standard MedDRA query; SOC, system organ class; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event

- Safety profile in the East Asian subset consistent with the ITT

Median treatment duration:

- **ITT: 6.7** months with Dato-DXd and **4.1** months with ICC
- **East Asia: 6.0** months with Dato-DXd and **4.1** months with ICC

AESIs in East Asian subset:

- No patients in the East Asian subset discontinued treatment due to oral mucositis/stomatitis‡
- Ocular events:¶ most were dry eye; one patient discontinued treatment in the Dato-DXd group due to dry eye (possibly drug-related)

TRAEs occurring in ≥15% of patients: East Asian subset

- In the ITT population, most frequent TRAEs were nausea (51.1%), stomatitis (50.0%), and alopecia (36.4%) in the Dato-DXd arm, and neutropenia (24.2%), nausea (23.6%), alopecia (20.5%), and decreased neutrophil count (20.5%) in the ICC arm

n (%)	Dato-DXd (n=134)		ICC (n=139)	
	All-grade	Grade ≥3	All-grade	Grade ≥3
Any TRAE	124 (95.4)	27 (20.8)	114 (84.4)	71 (52.6)
Nausea	71 (54.8)	3 (2.3)	29 (21.5)	0
Stomatitis	49 (37.7)	4 (3.1)	17 (12.6)	4 (3.0)
Alopecia	31 (23.8)	0	21 (15.6)	0
Vomiting	29 (22.3)	0	9 (6.7)	0
Dry eye	27 (20.8)	1 (0.8)	8 (5.9)	0
Decreased appetite	23 (17.7)	1 (0.8)	22 (16.3)	1 (0.7)
AST increased	23 (17.7)	2 (1.5)	17 (12.6)	1 (0.7)
Constipation	23 (17.7)	0	12 (8.9)	0
Fatigue	21 (16.2)	0	20 (14.8)	1 (0.7)
Decreased neutrophil count	15 (11.5)	2 (1.5)	53 (39.3)	42 (31.1)
Anemia	15 (11.5)	2 (1.5)	27 (20.0)	3 (2.2)
Decreased white blood cell count	9 (6.9)	1 (0.8)	28 (20.7)	13 (9.6)
Palmar–plantar erythrodysesthesia	1 (0.8)	0	22 (16.3)	6 (4.4)

Data cut-off: 17 July 2023.
All-grade TRAEs in ≥15% of patients with corresponding rates of Grade 3 events. AST, aspartate aminotransferase

Conclusions: East Asian subset

- Dato-DXd improved both **efficacy and safety** compared with ICC in East Asian patients enrolled in TROPION-Breast01
- In this East Asian subset, Dato-DXd demonstrated **improvement in PFS by BICR** (dual primary endpoint) compared with ICC, consistent with the overall population
  - A **higher ORR** was observed with Dato-DXd versus ICC
- Dato-DXd demonstrated a **favorable and manageable safety profile** in this East Asian subset, consistent with the overall population
  - Patients receiving Dato-DXd had fewer Grade ≥3 TRAEs, as well as fewer TEAEs leading to dose interruption/reduction than ICC

Results support Dato-DXd as a potential new therapeutic option for East Asian patients with endocrine-resistant HR+/HER2– metastatic breast cancer

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273 patients randomized from 4 countries/regions in East Asia