Poster 33

Datopotamab deruxtecan (Dato-DXd) vs chemotherapy in previously-treated inoperable or metastatic hormone receptor-positive, HER2-negative (HR+/HER2–) breast cancer: Primary results from the randomized Phase 3 TROPION-Breast01 trial

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Objective

- TROPION-Breast01, a randomized, Phase 3, open-label, global study, assessed efficacy and safety of Dato-DXd vs ICC in patients with inoperable or metastatic HR+/HER2- breast cancer who had received one or two prior lines of systemic chemotherapy in this setting.

Conclusions

- TROPION-Breast01 demonstrated that Dato-DXd provides both improved efficacy and safety compared with ICC for patients with HR+/HER2– disease.
- TROPION-Breast01 met its dual primary PFS endpoint, demonstrating statistically significant and clinically meaningful improvement in PFS with Dato-DXd compared with ICC.
  - Consistent PFS benefit observed across subgroups.
  - Higher ORR with Dato-DXd and a trend at interim OS favoring Dato-DXd.
- Overall, Dato-DXd demonstrated a favorable and manageable safety profile, with no new safety signals.
  - Most adverse events of special interest were Grade 1–2.
  - Patients receiving Dato-DXd had fewer Grade ≥3 TRAEs (less than half that with ICC), as well as fewer TRAEs leading to dose interruption/reduction compared with ICC.

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

Plain language summary

Why did we perform this research?

Datopotamab deruxtecan (Dato-DXd) is a drug that consists of datopotamab (an antibody) joined to a chemotherapy (deruxtecan). Datopotamab binds to a protein found on cancer cells called TROP2, where it then releases deruxtecan inside the tumor cells, which kills the tumor. The TROPION-Breast01 study involved patients with breast cancer tumors that were hormone receptor positive and classified as HER2 negative and could not be surgically removed, whose cancer continued to grow despite hormonal therapy and for whom hormonal therapy was unsuitable, and who had received previous treatment with chemotherapy. TROPION-Breast01 aims to see if Dato-DXd allows patients to live longer without their cancer getting worse, compared with patients receiving standard chemotherapy.

How did we perform this research?

732 eligible patients were randomly assigned in equal numbers to receive treatment with either Dato-DXd or a suitable chemotherapy, out of four options chosen by the treating doctor. Each patient could continue to receive their designated treatment for as long as the tumor was controlled by the drug and there were no unacceptable side effects.

What were the findings of this research?

Patients who received Dato-DXd had better progression-free survival (i.e., the time from starting treatment to the breast cancer getting worse, or death) than patients who received chemotherapy. Also, 36% of patients in the Dato-DXd group had their tumor reduce in size compared with 23% of those in the chemotherapy group. The most common side effects with Dato-DXd were feeling sick (nausea) and a sore or inflammation in the mouth (stomatitis) – these side effects are typical of Dato-DXd treatment and could be managed.

What are the implications of this research?

The results show that Dato-DXd provides meaningful benefits, with a favorable and manageable side-effect profile, and therefore represents a potential new treatment option for this type of breast cancer. The study will continue to follow patients until the question of whether treatment helps patients to live longer overall can be answered.

Where can I access more information?

This trial is listed on www.clinicaltrials.gov here: https://clinicaltrials.gov/study/NCT05104866.
The study design has been published here: https://www.futuremedicine.com/doi/10.2217/fon-2023-0188.

Poster

Infographic plain language summary

Mobile-friendly poster

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Poster presented at the 41st Annual Miami Breast Cancer Conference, Miami Beach, FL, USA; March 7–10, 2024.

Introduction

Unmet need in HR+/HER2– MBC

- HR+/HER2– breast cancer is the most common subtype of breast cancer, accounting for 60–70% of all cases.[1]
- Despite new therapeutic options becoming available, there remains an unmet need after endocrine therapy and one line of systemic therapy for patients with HR+/HER2– MBC.[2–5]
- Chemotherapy is utilized widely for management of endocrine-resistant HR+/HER2– MBC, but is associated with low response rate, poor prognosis, and significant toxicity including myelosuppression and peripheral neuropathy[6]
- TROP2-directed ADCs can have significant toxicities including diarrhea, neutropenia and thrombocytopenia.[7,8]

Dato-DXd

- Dato-DXd is a TROP2-directed ADC (**Figure 1**), that selectively delivers a potent Topo-I inhibitor payload directly into tumor cells,[9] and has several unique properties*:
  - Optimized drug to antibody ratio ≈ 4
  - Tumor-selective cleavable linker
  - Stable linker-payload
  - Bystander antitumor effect.
- Dato-DXd previously demonstrated promising antitumor activity and a manageable safety profile with a convenient Q3W schedule in pre-treated patients with metastatic HR+/HER2– breast cancer.[10]

*The clinical relevance of these features is under investigation. Based on animal data.

Figure 1. Dato-DXd: Humanized anti-TROP2 IgG1 monoclonal antibody

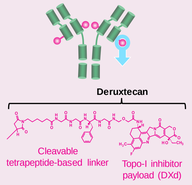


Image is for illustrative purposes only; actual drug positions may vary.

Methods

Figure 2. TROPION-Breast01 study design: Randomized, Phase 3, open-label, global study (NCT05104866)[11]

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)

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

Endpoints:

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

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).

Detailed description of the statistical methods published previously.[11] †Per ASCO/CAP guidelines. ‡ICC was administered as follows: eribulin mesylate, 1.4 mg/m² IV on Days 1 and 8, Q3W; vinorelbine, 25 mg/m² IV on Days 1 and 8, Q3W; gemcitabine, 1000 mg/m² IV on Days 1 and 8, Q3W; capecitabine, 1000 or 1250 mg/m² orally twice daily on Days 1 to 14, Q3W (dose per standard institutional practice).

Statistical methods[11]

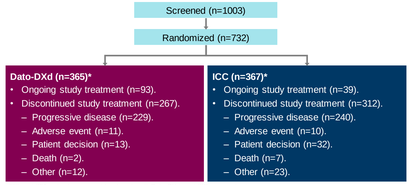
- Primary efficacy analysis performed in intention-to-treat population and analyzed by treatment group.
- Primary analysis of PFS at ~419 PFS events.
  - Interim OS analysis at the time of the primary PFS analysis.
- The final analysis of OS will be conducted at ~444 OS events.
- PFS analyzed using log-rank test utilizing stratification factors.
- Study considered positive if PFS and/or OS analysis statistically significant.

Results

Patients

- TROPION-Breast01 randomized a total of 732 patients: 365 to Dato-DXd and 367 to ICC (**Figure 3**).
- At data cut-off (17 July 2023), median study follow up was 10.8 months.
- Patient demographics and baseline characteristics are shown in **Table 1**.

Figure 3: Patient disposition



ICC:
- Eribulin mesylate: n=220.
- Vinorelbine: n=38.
- Gemcitabine: n=33.
- Capecitabine: n=76.

*360 and 351 patients received treatment with Dato-DXd and ICC, respectively.

Table 1. Demographics and baseline characteristics

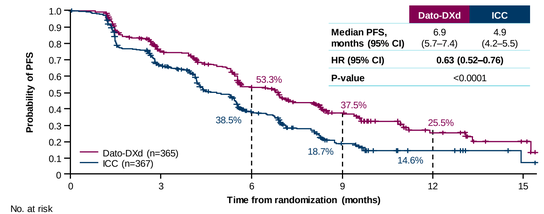
		Dato-DXd (n=365)	ICC (n=367)
Age, median (range), years		56 (29–86)	54 (28–86)
Female, n (%)		360 (99)	363 (99)
Race, n (%)	Black or African American / Asian / White / Other*	4 (1) / 146 (40) / 180 (49) / 35 (10)	7 (2) / 152 (41) / 170 (46) / 38 (10)
Ethnicity, n (%)	Hispanic or Latino / Not Hispanic or Latino†	40 (11) / 322 (88)	43 (12) / 318 (87)
Prior lines of chemotherapy,‡ n (%)	1 / 2	229 (63) / 135 (37)	225 (61) / 141 (38)
Prior CDK4/6 inhibitor, n (%)	Yes / No	304 (83) / 61 (17)	300 (82) / 67 (18)
Prior taxane and/or anthracycline, n (%)	Taxane and/or Anthracycline	330 (90)	339 (92)
	Neither	35 (10)	28 (8)

*Including not reported. †Ethnicity missing: 3 patients in Dato-DXd group; 6 patients in ICC group.
‡In the inoperable/metastatic setting: one patient in the Dato-DXd group had 3 prior lines of chemotherapy; one patient in the ICC group had 4 prior lines.

Progression-free survival

- TROPION-Breast01 met its dual primary endpoint of PFS by BICR (**Figure 4**).
- PFS by investigator assessment (secondary endpoint) was similar to PFS by BICR: median 6.9 vs 4.5 months; HR 0.64 (95% CI 0.53–0.76).

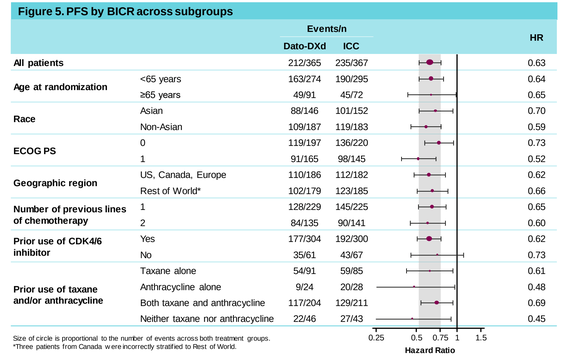
Figure 4. PFS by BICR: Primary endpoint



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

- Hazard ratios for PFS favored Dato-DXd over ICC across all prespecified patient subgroups (**Figure 5**).

Figure 5. PFS by BICR across subgroups

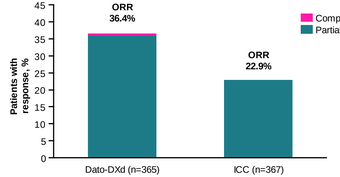


Size of circle is proportional to the number of events across both treatment groups.
*Three patients from Canada were incorrectly stratified to Rest of World.

Response

- Confirmed ORR was higher with Dato-DXd compared with ICC (**Figure 6**).

Figure 6. Response rate by BICR



Overall survival (dual primary endpoint)

- OS data were not mature (information fraction 39%): 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.

Safety summary

- Median treatment duration was 6.7 months with Dato-DXd and 4.1 months with ICC.
- Rate of Grade ≥3 TRAEs in the Dato-DXd group was less than half that in the ICC group (**Table 2**).
- Fewer TRAEs leading to dose reductions or interruptions with Dato-DXd compared with ICC (**Table 2**).
- Most TRAEs were Grade 1–2 and manageable (**Table 3**).

Table 2. Overall safety summary

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)

Table 3. TRAEs occurring in ≥15% of patients

System organ class Preferred term, n (%)	Dato-DXd (n=360)		ICC (n=351)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Blood and lymphatic system				
Anemia	40 (11)	4 (1)	69 (20)	7 (2)
Neutropenia*	39 (11)	4 (1)	149 (42)	108 (31)
Eye				
Dry eye	78 (22)	2 (0.6)	27 (8)	0
Gastrointestinal				
Nausea	184 (51)	5 (1)	83 (24)	2 (0.6)
Stomatitis	180 (50)	23 (6)	46 (13)	9 (3)
Vomiting	71 (20)	4 (1)	27 (8)	2 (0.6)
Constipation	65 (18)	0	32 (9)	0
General				
Fatigue	85 (24)	6 (2)	64 (18)	7 (2)
Skin and subcutaneous				
Alopecia	131 (36)	0	72 (21)	0

*Neutropenia included the PTs neutropenia and neutrophil count decreased.

Adverse events of special interest

- Oral mucositis/stomatitis†: led to treatment discontinuation in one patient in the Dato-DXd group.
- Ocular events‡: most were dry eye; one patient discontinued treatment in the Dato-DXd group.
- Adjudicated drug-related ILD§: rate was low; mainly Grade 1/2 (**Table 4**).

Table 4. Adjudicated drug-related ILD

	Dato-DXd	ICC
All grades, n (%)	9 (3)	0
Grade ≥3, n (%)	2 (1)¶	0

†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; all grade: 59% with Dato-DXd, 17% with ICC; Grade 3: 7% with Dato-DXd, 3% with ICC.
‡Ophthalmologic assessments were required at screening, and then every 3 cycles from Cycle 1 Day 1 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.
§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).
¶One adjudicated drug-related Grade 5 ILD event: attributed to disease progression by investigator.

Abbreviations

ADC, antibody-drug conjugate; ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CDK4/6, cyclin-dependent kinase 4/6; CI, confidence interval; Dato-DXd, datopotamab deruxtecan; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HER2–, human epidermal growth factor receptor 2-negative; HR, hazard ratio; HR+, hormone receptor-positive; ICC, investigator's choice of chemotherapy; IgG1, immunoglobulin G1; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, in-situ hybridization; IV, intravenous; MBC, metastatic breast cancer; MedDRA, Medical Dictionary for Regulatory Activities; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PTs, preferred terms; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; ROW, rest of world; SMQ, standard MedDRA query; SOC, system organ class; Topo-I, topoisomerase I; TRAEs, treatment-related adverse events; TROP2, trophoblast cell surface antigen 2.

Declaration of interests

Hope S. Rugo reports research support (to institution) from Astellas Pharma Inc., AstraZeneca, Daiichi Sankyo, Inc., F. Hoffmann-La Roche AG/Genentech, Inc., Gilead Sciences, Inc., GlaxoSmithKline, Lilly, Merck & Co., Inc., Novartis Pharmaceuticals Corporation, OBI Pharma, Pfizer, Pionyr Immunotherapeutics, Sermonix Pharmaceuticals Inc., Taiho Oncology, Inc. and Veru Inc, and consultancy/advisory support from Puma, NAPO, Blueprint, and Scorpion Therapeutics.

Acknowledgments

The authors would like to particularly thank the patients, their families and caregivers, and the 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 poster, under the direction of the authors, was provided by Helen Kitchen and Catherine Crookes of Ashfield MedComms (Macclesfield, UK), an Inizio Company, and was funded by AstraZeneca.

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