Poster 431P

Exposure-adjusted incidence rates (EAIRs) of adverse events from the TROPION-Breast01 study of datopotamab deruxtecan (Dato-DXd) vs investigator's choice of chemotherapy in patients with pretreated, inoperable/metastatic HR+/HER2– breast cancer

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Objective

- In the phase 3, open-label, randomized TROPION-Breast01 study, the rates of any-grade TRAEs were comparable for Dato-DXd vs ICC, yet the median duration of treatment was longer for Dato-DXd vs ICC (6.7 vs 4.1 months, respectively). The objective of this analysis was to determine if adjusting for the longer duration of exposure in the Dato-DXd arm had an impact on the comparative rates of AEs in the study.

Conclusions

- As previously presented, Dato-DXd demonstrated a manageable safety profile in TROPION-Breast01 compared with ICC,[1,2] which was consistent with that observed in previous studies of Dato-DXd.[1]
- After adjusting for the differences in treatment duration, the tolerability profile of Dato-DXd compared favorably to ICC across all categories of AEs as well as numerous individual AEs.
  - All grade and grade ≥3 TRAE rates were lower with Dato-DXd compared with ICC.
- This analysis provides additional support to the primary results of TROPION-Breast01, indicating that Dato-DXd is well tolerated and may be a novel treatment option for patients with inoperable or metastatic HR+/HER2– breast cancer who have received 1–2 prior lines of chemotherapy for advanced disease.

Plain language summary

Why did we perform this research?

- Endocrine therapy is a standard treatment for people with people with hormone receptor-positive (HR+), human epidermal growth factor receptor 2 (HER2−) inoperable or metastatic breast cancer, a type of cancer which has estrogen and/or progesterone receptors on the surface (HR+) but not HER2 (HER2−).
- If endocrine therapy stops working, then chemotherapy is given but this can have severe side effects and often does not stop the cancer from growing.
- Datopotamab deruxtecan (Dato-DXd) is an antibody-drug conjugate that consists of an antibody (datopotamab) and an anticancer drug payload (DXd), which are joined via a stable cleavable linker. Dato-DXd binds to TROP2 on the surface of cancer cells and is then internalised, where the linker detaches and releases DXd to kill the cancer cells.
- In a study called TROPION-Breast01, 732 people from around the world were treated with Dato-DXd or chemotherapy. People who received Dato-DXd had a reduced risk of their cancers growing or getting worse than people who were treated with chemotherapy.
- Some side effect rates were higher with Dato-DXd than with chemotherapy; however, this may be because people were treated for longer with Dato-DXd (median duration: 6.7 months for Dato-DXd vs 4.1 months for chemotherapy).
- In this analysis, researchers wanted to see if the number of side effects changed when they adjusted for the difference in how long people had been treated.

How did we perform this research?

- The number of people with side effects were adjusted by calculating the number of people with side-effects divided by the length of treatment for Dato-DXd and chemotherapy, these are known as exposure-adjusted incidence rates.

What were the findings of this research?

- The rate of all of the side-effect categories and most of the individual side effects were lower with Dato-DXd compared with chemotherapy.

What are the implications of this research?

- The results show that Dato-DXd had fewer side effects than chemotherapy when adjusted for length of treatment and could be a new type of treatment for people with HR+, HER2− inoperable or metastatic breast cancer whose cancers got worse while receiving endocrine therapy or who cannot receive endocrine therapy.

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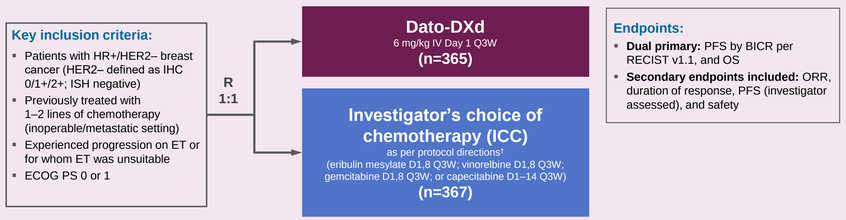
Introduction

- In the phase 3, open-label, randomized TROPION-Breast01 study, Dato-DXd significantly reduced the risk of disease progression or death versus ICC (hazard ratio, 0.63 [95% CI, 0.52–0.76]; p<0.0001) in patients with HR+/HER2– inoperable or metastatic breast cancer who had disease progression on endocrine therapy or for whom endocrine therapy was unsuitable and had previously received 1–2 lines of chemotherapy in the inoperable or metastatic setting.[1]
- Dato-DXd was well tolerated vs ICC, and no new safety signals were identified.[1] Additional safety analyses showed that AESIs with Dato-DXd were typically low grade and were manageable using toxicity management guidelines.[2]
- The rate of all-grade TRAEs was comparable for Dato-DXd compared with ICC (93.6% vs 86.3%); however, the median duration of treatment was longer for Dato-DXd vs ICC (6.7 months vs 4.1 months).[1]
- Due to the differences in treatment duration, we conducted a post hoc exploratory safety analysis for EAIRs.

Methods

- The study design is given in **Figure 1**. Full details of the study and primary analysis results have been published previously.[1]
- Prophylactic anti-emetic agents were highly recommended prior to infusion of Dato-DXd, and on subsequent days as needed.[1]
- As part of an AE prophylaxis plan, daily use of steroid-containing mouthwash was highly recommended. Ophthalmologic assessments were mandated for both study arms to survey for ocular surface events, and daily use of artificial tears and avoidance of contact lenses were recommended.[1,3]
- EAIR was defined as the number of patients who experienced at least one specific AE, divided by the total exposure time (patient-year of exposure in each treatment group).
- Exposure time was calculated from first dose date to first onset of an AE; if an AE did not occur this was first dose date to data cut-off (treatment ongoing) or last dose (if treatment was discontinued).

Figure 1. TROPION-Breast01. A randomized, phase 3, open-label, global study (NCT05104866).



†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.

Results and interpretation

Patients

- In total, 732 patients were randomized. Most patients had metastatic disease (98.5%) and the majority of patients (62.0%) had received one prior line of chemotherapy for inoperable or metastatic disease (**Table 1**).
- Of the 732 randomized, 5 and 16 patients did not receive Dato-DXd or ICC, respectively; consequently, 360 patients received Dato-DXd and 351 received ICC.

Table 1. Patient baseline characteristics and demographics (ITT)

Characteristic/demographic	Dato-DXd (n=365)	ICC (n=367)
Median age, years (range)[a]	56.0 (29–86)	54.0 (28–86)
Age group (years)[a], n (%)		
<65	274 (75.1)	295 (80.4)
≥65	91 (24.9)	72 (19.6)
Sex, n (%)		
Female	360 (98.6)	363 (98.9)
Male	5 (1.4)	4 (1.1)
Race, n (%)		
White	180 (49.3)	170 (46.3)
Asian	146 (40.0)	152 (41.4)
Black or African American	4 (1.1)	7 (1.9)
Other	3 (0.8)	6 (1.6)
Not reported	32 (8.8)	32 (8.7)
Ethnicity, n (%)		
Not Hispanic or Latino	322 (88.2)	318 (86.6)
Hispanic or Latino	40 (11.0)	43 (11.7)
Missing	3 (0.8)	6 (1.6)
ECOG PS, n (%)		
0	197 (54.0)	220 (59.9)
1	165 (45.2)	145 (39.5)
2	3 (0.8)	1 (0.3)
Missing	0	1 (0.3)
Type of disease, n (%)		
Metastatic	356 (97.5)	365 (99.5)
Locally advanced/inoperable	9 (2.5)	2 (0.5)
Prior lines of chemotherapy in the metastatic setting, n (%)		
1	229 (62.7)	225 (61.3)
2	135 (37.0)	141 (38.4)
3	1 (0.3)	0
4	0	1 (0.3)
Prior CDK 4/6 inhibitor, n (%)		
Yes	304 (83.3)	300 (81.7)
No	61 (16.7)	67 (18.3)
Geographic region		
US, Canada, Europe	186 (51.0)	182 (49.6)
Rest of World	179 (49.0)	185 (50.4)

[a]Age at randomization.

- At data cut-off (July 17, 2023), 267 and 312 patients had discontinued Dato-DXd and ICC, respectively (**Table 2**).
  - The most common reason for discontinuation was disease progression (Dato-DXd n=229; ICC n=240).
- At data cut-off, 93 patients were still on treatment in the Dato-DXd arm, compared with 39 in the ICC arm.

Table 2. Patient disposition

Disposition	Dato-DXd (n=360)	ICC (n=351)
Discontinued treatment	267	312
Disease progression	229	240
Patient decision	13	32
Other[a]	12	23
AE	11	10
Death	2	7
Remain on treatment	93	39

[a]Includes clinical or subjective disease progression and physician decision.

Safety

- Absolute incidences and EAIRs are given in **Table 3**; all categories of AEs were lower with Dato-DXd compared with ICC by EAIR.
  - The rate of grade ≥3 TRAEs with Dato-DXd was less than half that with ICC.
  - Fewer TEAEs led to dose modification, dose reduction or interruption with Dato-DXd than with ICC.
- Absolute incidences and EAIRs are given in **Table 4** and **Figure 2**.
  - There were no differences in EAIRs between Dato-DXd and ICC for serious AEs, AEs leading to treatment discontinuation, and death due to AEs.
  - All TRAEs and grade ≥3 TRAE rates by EAIR were lower with Dato-DXd compared with ICC.
- After adjusting for exposure, most of the TEAEs had higher incidence rates in the ICC arm compared with the Dato-DXd arm (**Figure 3**).
  - Nausea and stomatitis were the most common events with Dato-DXd.
  - Nausea, neutropenia and anemia were the most common events with ICC.

Limitations

- The analysis was conducted post hoc and was not pre-defined in the statistical plan.
- EAIR assumes that the risk of an event occurring is constant over time; EAIR may not be optimal when the onset of AEs is delayed or the risk varies over time.

Table 4. Safety summary with absolute incidences and EAIR differences

	Dato-DXd (n=360)	ICC (n=351)
Any AEs, possibly treatment-related[a,b]		
n (%)	337 (93.6)	303 (86.3)
EAIR (95% CI)	1.70 (1.53–1.90)	2.16 (1.93–2.41)
EAIR difference vs ICC (95% CI)	-0.45 (-0.75 to -0.15)	
Grade ≥3 AEs, possibly treatment-related[a,b]		
n (%)	75 (20.8)	157 (44.7)
EAIR (95% CI)	0.38 (0.30–0.48)	1.12 (0.96–1.31)
EAIR difference vs ICC (95% CI)	-0.74 (-0.93 to -0.54)	
Serious AEs, possibly treatment-related[a,b]		
n (%)	21 (5.8)	32 (9.1)
EAIR (95% CI)	0.11 (0.07–0.16)	0.23 (0.16–0.32)
EAIR difference vs ICC (95% CI)	-0.12 (-0.21 to -0.03)	
AEs leading to treatment discontinuation, possibly treatment-related[a,b]		
n (%)	9 (2.5)	9 (2.6)
EAIR (95% CI)	0.05 (0.02–0.09)	0.06 (0.03–0.12)
EAIR difference vs ICC (95% CI)	-0.02 (-0.07 to 0.03)	
Deaths due to AEs, possibly treatment-related[a,b]		
n (%)	0	1 (0.3)
EAIR (95% CI)	–	0.01 (0.00–0.05)
EAIR difference vs ICC (95% CI)	0.01 (-0.01 to 0.04)	

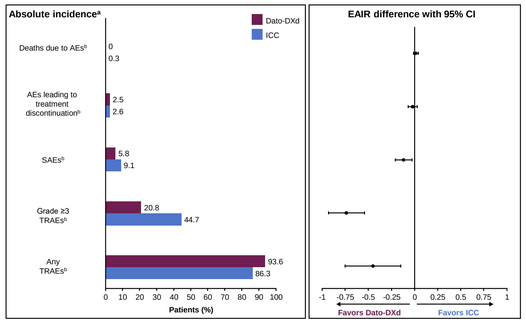
[a]Patients with multiple events in the same category are counted only once in that category; patients with events in more than one category are counted once in each of those categories. [b]As assessed by the investigator. Includes AEs with an onset date or that worsen on or after the date of first dose of study treatment up to and including date of last treatment +35 days and prior to start of any subsequent cancer therapy.

Table 3. Safety summary with absolute incidence and EAIR for TEAEs and TRAEs

	Absolute incidence[1]		EAIR	
n (%)[a]	Dato-DXd (n=360)	ICC (n=351)	Dato-DXd	ICC
Any AEs	350 (97.2)	337 (96.0)	1.77	2.40
Any AEs, possibly treatment-related[b]	337 (93.6)	303 (86.3)	1.70	2.16
Grade ≥3 AEs	117 (32.5)	190 (54.1)	0.59	1.35
Grade ≥3 AEs, possibly treatment-related[b]	75 (20.8)	157 (44.7)	0.38	1.12
Death due to AEs	0	3 (0.9)	0.00	0.02
Death due to AEs, possibly treatment-related[b]	0	1 (0.3)	0.00	0.01
SAEs	54 (15.0)	64 (18.2)	0.27	0.46
SAEs, possibly treatment-related[b]	21 (5.8)	32 (9.1)	0.11	0.23
Grade ≥3 SAEs	47 (13.1)	60 (17.1)	0.24	0.43
Grade ≥3 SAEs, possibly treatment-related[b]	17 (4.7)	31 (8.8)	0.09	0.22
SAEs leading to treatment discontinuation	4 (1.1)	4 (1.1)	0.02	0.03
SAEs leading to treatment discontinuation, possibly treatment-related[b]	3 (0.8)	4 (1.1)	0.02	0.03
AEs leading to treatment discontinuation	11 (3.1)	10 (2.8)	0.06	0.07
AEs leading to treatment discontinuation, possibly treatment-related[b]	9 (2.5)	9 (2.6)	0.05	0.06
AEs leading to dose modification	137 (38.1)	183 (52.1)	0.69	1.30
AEs leading to dose reduction	83 (23.1)	113 (32.2)	0.42	0.80
AEs leading to dose interruption	78 (21.7)	120 (34.2)	0.39	0.85

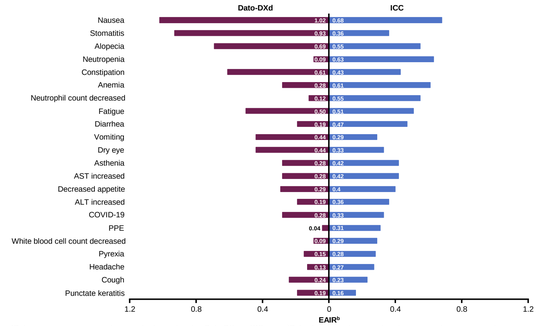
[a]Patients with multiple events in the same category are counted only once in that category; patients with events in more than one category are counted once in each of those categories. [b]As assessed by the investigator. Includes AEs with an onset date or that worsen on or after the date of first dose of study treatment up to and including date of last treatment +35 days and prior to start of any subsequent cancer therapy.

Figure 2. Forest plot for AEs with absolute incidences and EAIR differences



[a]Patients with multiple events in the same category are counted only once in that category; patients with events in more than one category are counted once in each of those categories. [b]As assessed by the investigator. Includes AEs possibly treatment-related with an onset date or that worsen on or after the date of first dose of study treatment up to and including date of last treatment +35 days and prior to start of any subsequent cancer therapy.

Figure 3. EAIRs for the most common TEAEs (≥10%) in the Dato-DXd and ICC arms[a]



[a]Data are ordered according to highest rate in either the Dato-DXd or ICC arms. [b]Patients with multiple events in the same category are counted only once in that category; patients with events in more than one category are counted once in each of those categories. Includes AEs with an onset date or that worsen on or after the date of first dose of study treatment up to and including date of last treatment +35 days and prior to start of any subsequent cancer therapy.

Abbreviations

AE, adverse event; AESI, adverse event of special interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BICR, blinded independent central review; CDK4/6, cyclin-dependent kinase 4/6; Dato-DXd, datopotamab deruxtecan;; EAIR, exposure-adjusted incidence rate; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ICC, investigator's choice of chemotherapy; ITT, intention-to-treat; IV, intravenous; ORR, objective response rate; OS, overall survival;; PFS, progression-free survival; PPE, palmar-plantar erythrodysesthesia; RECIST, Response Evaluation Criteria in Solid Tumors; Q3W, every 3 weeks; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

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