Poster S-048

Exposure-Response analyses of datopotamab deruxtecan (Dato-DXd) in patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer

Zoey Tang[1], KyoungSoo Lim[1], Yu Jiang[1], Neelima Denduluri[2], Nana Rokutanda[2], Darlington Mapiye[3], Yuzhuo Pan[4], Ying Hong[4], Song Ren[1], Pavan Vajjah[5], Diansong Zhou[6]

[1] Clinical Pharmacology and Quantitative Pharmacology, AstraZeneca, Gaithersburg, MD, USA. [2] Clinical Development, Oncology R&D, Gaithersburg, US [3] Statistics, Oncology R&D, Cambridge, UK [4] Quantitative Clinical Pharmacology, Daiichi Sankyo Inc., Basking Ridge, NJ [5] Clinical Pharmacology and Quantitative Pharmacology, AstraZeneca, Cambridge, UK [6] Clinical Pharmacology and Quantitative Pharmacology, AstraZeneca, Waltham, MA, USA

Objective

To evaluate the relationships between Dato-DXd pharmacokinetic exposure, efficacy, and safety in patients with HR-positive/HER2-negative breast cancer.

Conclusions

In patients with HR-positive/HER2-negative breast cancer, Dato-DXd at 6 mg/kg every 3 weeks with a capped dose of 540 mg for those ≥ 90 kg demonstrates a favorable benefit–risk profile.

Plain language summary

Why did we perform this research?

This research was performed to determine the relationships between Dato-DXd pharmacokinetic exposure and efficacy and safety in the patients with HR-positive/HER2-negative breast cancer.

How did we perform this research?

We analyzed exposure–safety relationships, including Grade 3+ treatment-related adverse events, using data pooled from four clinical trials, and conducted exposure–efficacy analyses using patient data from the TROPION-Breast01 study.

What were the findings of this research?

The analyses showed that higher Dato-DXd exposure was associated with longer overall survival and progression-free survival. No exposure–response relationship was identified between PK exposure and adjudicated drug-related interstitial lung disease.

What are the implications of this research?

Dato-DXd at 6 mg/kg every three weeks (Q3W), with a capped maximum dose of 540 mg for patients with HR-positive/HER2-negative breast cancer weighing 90 kg or more, provided the optimal benefit–risk profile in clinical practice.

Where can I access more information?

Information about the medicine(s) being used in this study and the people who could participate can be found here: NCT05104866

Introduction

- Dato-DXd is a TROP2-directed antibody-drug conjugate designed to deliver a potent topoisomerase I inhibitor specifically to tumor cells, aiming to maximize anti-tumor effects while minimizing systemic toxicity[1].
- Dato-DXd has demonstrated improved efficacy compared to investigator's choice of chemotherapy in TROPION-Breast01 and was approved in 2025 in the US, EU, and Japan for adult patients with unresectable or metastatic HR-positive/HER2-negative breast cancer who have received prior endocrine and chemotherapy treatments[1].

Methods

- Exposure–efficacy analyses were conducted using data from patients in the TROPION-Breast01 study, all of whom received Dato-DXd at 6 mg/kg Q3W. Exposure–safety analyses included patients with breast or lung cancer pooled from four clinical studies (TROPION-PanTumor01, TROPION-Lung01, TROPION-Lung05, and TROPION-Breast01), with evaluated Dato-DXd dose levels ranging from 0.27 to 10 mg/kg Q3W.
- Evaluated efficacy endpoints included OS and PFS. Evaluated safety endpoints included but not limited to stomatitis and ocular surface events (OSE).
- Cox proportional hazards (CPH) models assessed exposure–efficacy relationships, and logistic regression was applied to characterize exposure–safety associations. Significant patient covariates were identified via stepwise selection processes ($p < 0.01$ for forward addition and $p < 0.001$ for backward elimination).

Results

Exposure–Efficacy Analysis

- A total of 352 patients with HR-positive/HER2-negative breast cancer from TROPION-Breast01 were included in exposure-efficacy analysis. All received Dato-DXd at 6 mg/kg every 3 weeks. The median age of patients included in the exposure-efficacy analysis dataset was 55 years (range, 29–86), and median body weight was 62 kg (range, 35.6-141). A total of 98.6% of patients were female, 50% were white, 38.1% were from Europe.
- Higher Dato-DXd exposure (First-cycle Dato-DXd AUC [AUC1]) is significantly associated with improved OS in patients with HR-positive/HER2-negative breast cancer. Patients in the higher Dato-DXd AUC1 showed longer OS (**Figure 1A and 1B**). For Dato-DXd AUC1, the 75th percentile (723 ug.d/mL) and the 25th percentile (566 ug.d/mL) showed hazard ratios of approximately 0.80 (95% CI, 0.72-0.88) and 1.3 (95% CI, 1.2 – 1.4) when compared to the median Dato-DXd AUC1 (650 ug.d/mL).
- Baseline tumor size is the most significant covariate of PFS analysis. Patients with smaller baseline tumors have notably lower PFS risk, while those with larger tumors have higher risk (**Figure 1**). For baseline tumor size, the 75th percentile (85.3 mm) and the 25th percentile (36.8 mm) showed hazard ratios of approximately 1.17 (95% CI, 1.08 – 1.25) and 0.91 (95% CI, 0.87 – 0.95) when compared to the median tumor size of 55 mm. Positive exposure-efficacy relationship with Dato-DXd AUC1 was also observed for PFS. CPH analysis suggested baseline tumor size was more significantly associated with PFS, and Dato-DXd AUC1 was removed in the backward elimination ($p = 0.0011$).

Figure 1. Exposure-Efficacy Relationships in Patients with HR+/HER2- BC in TROPION-Breast-01

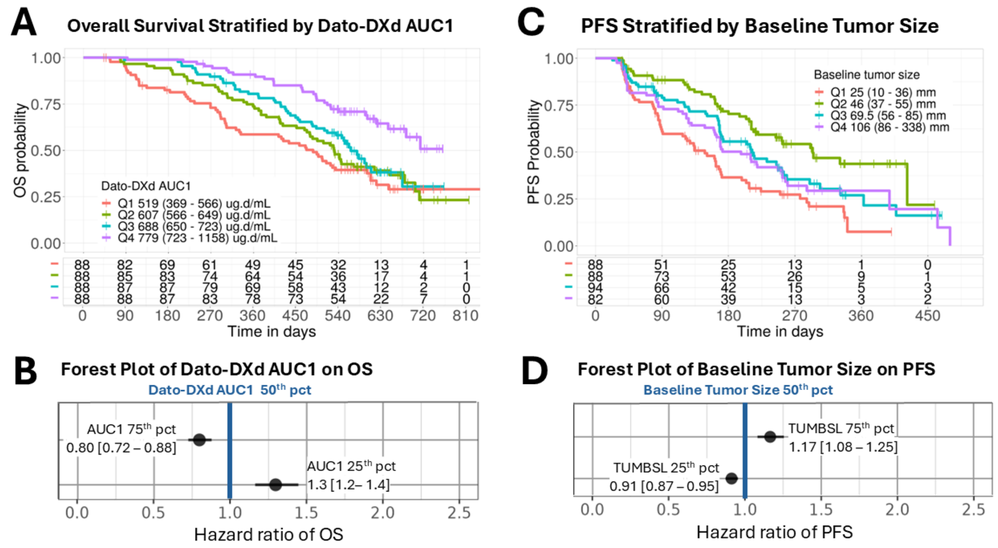

Figure 1. (A) and (C) legends represent median (min-max) of each quartile. **(B) and (D)** The points represent the median hazard ratio, while the bar represents the 95% CI; The reference value is expressed in the variable name, median for continuous variables.

Figure 2. Grade 2+ Stomatitis and Grade 2+ Ocular Surface Events (OSE)

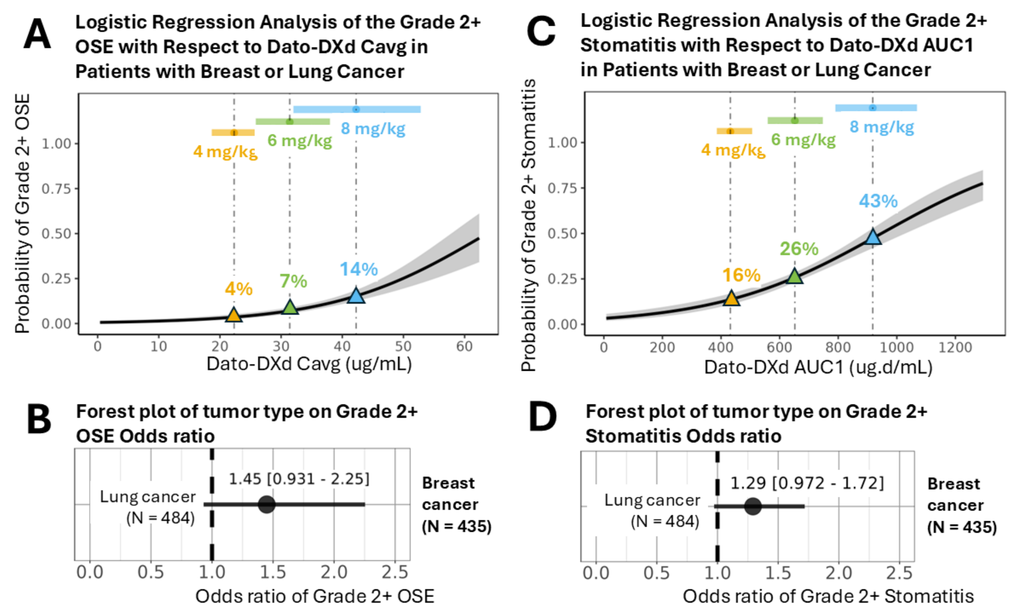

Figure 2 . (A) and (C) logistic regression analyses. Horizontal bars show the exposure at 4 mg/kg (n = 50), 6 mg/kg (n = 919), and 8 mg/kg (n = 82) in pooled population with lung or breast cancer. Lower ends, black dots, and upper ends of the horizontal bars represent the 25th percentile, median, and 75th percentile, respectively. Vertical dashed lines represent median of PK exposure at 4, 6, and 8 mg/kg. Solid back lines and shaded areas represent model predicted safety event incidences and corresponding 95% confidence interval. Triangles represent model-predicted safety% at 4,6, and 8 mg/kg. **(B) and (D)** The points represent the median hazard ratio, while the bar represents the 95% CI; The reference value is expressed in the variable name, median for continuous variables.

Exposure-Safety Analysis

- A total of 1081 patients across four studies were included in the exposure-safety analysis. Majority of patients received Dato-DXd at 6 mg/kg (85%, 919 of 1081). The median age of patients included in the exposure-safety analysis dataset was 60 years (range, 26 – 86), and median body weight was 64.2 kg (range, 35.6-156). A total of 67.2% of patients were female, 59.6% had lung cancer, 47.2% were white, and 29.7% were from USA.
- Model predicted a greater increase in probabilities of Grade 2+ OSE and Grade 2+ stomatitis from 6 to 8 mg/kg, compared to from 4 to 6 mg/kg (**Figure 2A and 2C**). Differences in probabilities of Grade 2+ OSE and Grade 2+ stomatitis between lung and breast cancer were not statistically meaningful (**Figure 2B and 2D**). Higher risk of any grade OSE in patients with breast cancer compared to lung cancer may be associated with frequent ophthalmologic assessments that were mandated throughout the TROPION-Breast01 study per regulatory requirement.
- Dato-DXd or DXd PK metrics were not statistical significant covariates for adjudicated drug-related ILD in patients with breast cancer (TP01 and TB01) or lung cancer (TP01, TL05, and TL-01) (**Table 1 and Figure 3**).

Figure 3. Dato-DXd PK Exposure with or without Adjudicated Drug-Related ILD

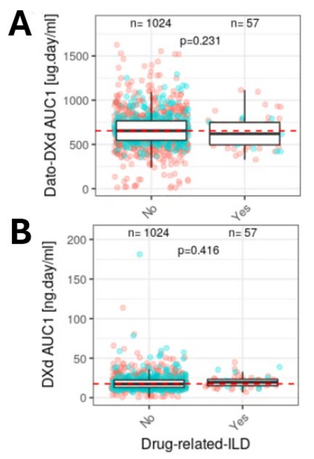

Figure 3. Boxplot of (A) Dato-DXd and (B) DXd Exposure with or without Adjudicated Drug-Related ILD. Dashed horizontal line represents the median exposure; N represents the number of samples; p values between the two boxplots indicate significant differences in the exposures between Yes and No incidence of the event. Blue and red points represent breast cancer and lung cancer. **ILD**: interstitial lung disease.

Table 1. Significant Exposure Metrics and Covariates in the Safety Logistic Regression Model in Patients with Breast Cancer (TP01 and TB01) or Lung Cancer (TP01, TL05, and TL-01)

Safety Endpoints	Significant Exposure Metrics	Significant Covariates
Grade ≥3 TEAEs	DXd C_{avg}	Region, smoke status
Serious TEAEs	DXd C_{avg}	Baseline albumin, tumor type, race
TEAE leading to dose interruption	Dato-DXd AUC1	None
TEAE leading to dose reduction	Dato-DXd AUC1	Baseline tumor size
TEAE leading to treatment discontinuation	None	Not tested
Oral mucositis/stomatitis any grade	Dato-DXd C_{avg}	None
Oral mucositis/stomatitis ≥ Grade 2	Dato-DXd AUC1	None
Adjudicated Drug-Related ILD	None	Not tested
Ocular surface event any grade	Dato-DXd C_{avg}	Tumor type (NSCLC vs BC)
Ocular surface event ≥ Grade 2	Dato-DXd C_{avg}	None

Significant covariates obtained a p-value < 0.01 when selected from forward addition, and a p value <0.001 when removed from backward elimination.

Abbreviations

PFS: Progression-Free Survival. OS: Overall Survival. OSE: Ocular Surface Events. TEAE: Treatment Emergent Adverse Events. ILD: Interstitial Lung Disease. Cavg: Average concentration. AUC1: First-cycle Area Under the Curve. Q3W: every three weeks

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Disclosures

Z. Tang, Y. Jiang, N. Denduluri, N. Rokutanda, D. Mapiye, S. Ren, P. Vajjah, and D. Zhou are current employees of and shareholders in AstraZeneca. K. Lim was previously employed by AstraZeneca, and the work presented in this article was conducted during his tenure at the company. Y. Pan, Y. Hong are current employees of Daiichi Sankyo and own stock in Daiichi Sankyo.

References

[1] Bardia A. et al. J Clin Oncol. 2025 Jan 20;43(3):285-296. doi: 10.1200/JCO.24.00920.

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Poster presented at ACoP 2025 by Zoey Tang. Corresponding author email address: zoeytang.cp.pmx@gmail.com.